

Communicable Disease Control in New South Wales and globally

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Originality statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at ANU or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at NSW Health or elsewhere, is explicitly acknowledged 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.....

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Thesis Abstract

Effective communicable disease control calls for a wide range of core public health competencies. In fulfilling the requirements of the Masters of Philosophy in Applied Epidemiology (MAE), I conducted projects in my placement at Health Protection New South Wales (NSW) between March 2014 and October 2015 which highlight some of these competencies.

In May 2014, the Communicable Diseases Branch was notified of hepatitis E virus (HEV) infection in two men who had not recently travelled overseas, but had both shared a meal with seven other work colleagues at a single Sydney restaurant. We conducted an investigation to assess the source and extent of the outbreak. We found a further 15 HEV cases linked to the restaurant. Pork pate was consumed by all 17 diners. Pork livers used to make pate were traced back to a single Australian farm. This is the first reported outbreak of locally-acquired HEV in Australia and has important clinical and public health implications. We recommend that clinicians consider locally-acquired HEV infection in patients with unexplained acute hepatitis regardless of travel history and that the public cook pork products thoroughly.

An outbreak was also the basis for my epidemiological project which involved a case-control study assessing risk factors for acquisition of a novel strain of Methicillin-resistant *Staphylococcal aureus* (MRSA) in a local health district (LHD) in NSW. Despite this new strain replacing endemic MRSA strains in nine hospitals in the LHD, we found no significant differences in clinical infection, admission to an intensive care unit or mortality when compared to people infected with endemic strains. Whole genome sequencing was used to describe transmission pathways. This modality may play a role in better characterising MRSA outbreaks in future.

In November 2014, I volunteered to assist in the Ebola virus disease (EVD) epidemic that affected three countries in West Africa. I worked in Monrovia, Liberia as a clinician at a Medecins sans Frontieres Ebola transit centre. At this centre, we admitted and tested patients with signs and symptoms of EVD. I analysed clinical and demographic data of patients who presented to the centre in our first month of opening and found that almost half did not have a measured temperature greater than 37.5°C. This has important implications for screening procedures in EVD-affected countries and elsewhere.

Acute Rheumatic Fever (ARF) and its sequelae, Rheumatic Heart Disease (RHD) are conditions thought to be rare in NSW. With an aim of improving cardiac outcomes in Aboriginal and Torres Strait Islander people, NSW Health committed to establishing a register-based control program for these diseases. In establishing this program, my work included quantifying the burden of disease, engaging with stakeholders and designing a system for notification and registration of cases. Both conditions were made notifiable in NSW in October 2015.

This thesis documents the investigation of Australia's first reported locally-acquired hepatitis E outbreak, the assessment of a novel strain of MRSA, the establishment of a system for notification of two important public health conditions in Australia and the public health response to a global health emergency. Findings from these projects will contribute to the body of knowledge and provide important information to guide public health policy and stimulate ongoing research.

Chapter 1:

Overview of placement at Health Protection New South Wales and Summary of Masters of Philosophy in Applied Epidemiology course requirements

“I like the scientific spirit—the holding off, the being sure but not too sure, the willingness to surrender ideas when the evidence is against them: this is ultimately fine—it always keeps the way beyond open—always gives life, thought, affection, the whole man, a chance to try over again after a mistake—after a wrong guess”

Walt Whitman, American poet

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Abbreviations

ARF	Acute Rheumatic Fever
BBVAP	Blood-borne virus Advisory Panel
CDB	Communicable Diseases Branch
CDC	United States Centre for Disease Control and Prevention
EHB	Environmental Health Branch
ETU	Ebola Transit Unit
EVD	Ebola virus disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human Immunodeficiency virus
IF	Immunofluorescence
LHD	Local Health District
MAE	Masters of Philosophy in Applied Epidemiology
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSF	Medecins sans Frontieres
NSW	New South Wales
PCR	Polymerase chain reaction
PHU	Public Health Unit
RHD	Rheumatic Heart Disease
TB	Tuberculosis
WGS	Whole genome sequencing

Getting into the Masters of Philosophy in Applied Epidemiology

I was interviewed for the MAE program while working at a camp for Syrian refugees in northern Iraq with Medecins sans Frontieres (MSF). I worked as the Medical Team Leader on the project and encountered several challenges that I had no previous experience facing. In the first few weeks of arrival, an increase in cases of jaundice had us concerned about an outbreak of hepatitis E. A few months later, as a result of the worsening crisis in Syria, the number of refugees arriving at the camp more than tripled in four months, without a proportionate increase in living space. Water and sanitation conditions were below the minimum emergency threshold of 15 to 20 litres per person per day and one latrine per 20 individuals (1). Given this situation and with cholera being endemic to northern Iraq, we were worried about the possibility of a cholera outbreak. I had to develop a cholera preparedness plan that could be implemented in the event this happened.

I had no formal training in public health and wasn't always comfortable with some of the situations I found myself in (although common sense often prevailed). Discussing future plans with an MSF colleague, he suggested I apply for the Masters of Philosophy in Applied Epidemiology (MAE) program. He said that it would be a great way to learn about public health systems in the developed world so that these lessons could be applied in less-resourced settings. I'm glad I took his advice.

The opportunity to pursue the MAE program at Health Protection New South Wales (NSW) has been an educational, nurturing and fun experience. It has taught me the importance of research and evidence in informing policy. It has taught me of the daily functions and operations of a government health department. It has allowed me to consolidate lessons learnt in MSF and learn completely new ones. Working in a resource-rich environment with experts in their field has given me an appreciation for the standard of public health care that every individual in the world has the right to receive.

About Health Protection New South Wales

Health Protection NSW is an organisation that reports to the Chief Health Officer in the NSW Ministry of Health. The duties of Health Protection NSW are to monitor the incidence of notifiable infectious diseases, take appropriate action to control the spread of disease, provide public health advice and respond to environmental issues that affect human health.

There are two main branches within Health Protection NSW. The Communicable Diseases Branch (CDB), which cover areas of immunisation, vaccine preventable diseases, enteric diseases, respiratory and vector-borne diseases, blood-borne viruses and sexually-transmitted infections and tuberculosis. The Environmental Health Branch (EHB) is sub-divided into the water unit, general environmental health, policy and risk assessment and Aboriginal environmental health. The CDB and EHB are headed by directors who report to the Director of Health Protection.

There are 15 local health districts (LHDs) in NSW – eight which cover the greater Sydney metropolitan region and seven which cover rural and regional NSW (2). In addition, there are separate networks for Justice Health and the Sydney Children's Hospital Network (2). Each LHD is served by a public health unit (PHU) headed by a PHU Director. The PHUs are responsible for carrying out the daily public health work in their district related to communicable diseases, environmental health and immunisation. Public Health Unit Directors meet with Directors of Health Protection to discuss current public health issues on a monthly teleconference and a quarterly face-to-face meeting as part of the Health Protection Leadership Team.

Summary of public health experience

This has been the first time Health Protection NSW have had an MAE student in over ten years. Therefore, it has been a learning experience for both the placement and myself, regarding the MAE learning requirements. Over the course of my placement, I was mainly involved in the activities of the CDB and I participated in the Branch's routine and emergency activities. I was on call for 'CD Oncall' once a week in my first year which involved taking calls from PHUs regarding infectious disease notifications, participating in daily 'Wrap' meetings where a summary of all daily notified diseases were discussed and attending weekly surveillance meetings where trends in notified conditions were discussed.

I organised journal club for Health Protection staff on a monthly basis. This was initially organised for the NSW public health network, but due to a lack of participation from the network, we made it an internal meeting. Running and attending journal club was a good way to further my understanding of critical appraisal of the literature and learning of different study types used in public health research.

I regularly contributed to the *Health Protection Report* - a newsletter produced by Health Protection NSW aimed at sharing experiences, research and providing educational resources for the NSW public health network. I wrote the 'Epi Corner' section of the *Report*, which was a question-and-answer article that highlighted and discussed basic epidemiological concepts (Appendix 1). This was another good learning opportunity to read up on, understand and write about core epidemiological principles.

I was also involved in Health Protection's response to public health emergencies across the state. These comprised communicable disease and environmental health issues. Some of the major issues were: a leak in a main water pipe which supplies a filtration plant that delivers water to over 250, 000 Sydney residents, an incident involving inadequate temperature monitoring of a vaccine fridge at a major public hospital in Sydney affecting more than 750 newborn babies, the possible microbial contamination of an enteral feeding system requiring an alert to all health departments across the country, an outbreak of *Salmonella Bovismorbificans* across 10 aged care facilities in the

Illawarra, Canberra and Southeast Sydney localities with deaths in two residents and finally, breaches in infection control at four dental clinics that resulted in a retrospective investigation which identified more than 11,000 patients at risk of acquiring a blood-borne virus infection. As part of the management of these public health incidents, I attended meetings, wrote up minutes of meetings, wrote briefs to the Chief Health Officer, interviewed patients (in the *Salmonella Bovismorbificans* outbreak), conducted literature reviews and wrote an investigation protocol that public health units could use to investigate patients affected by the dental infection control incident (Appendix 2). In addition to these public health threats, I also sat in on desktop exercises conducted for the network in the event of a public health emergency, such as an Ebola virus disease or Middle East respiratory syndrome coronavirus (MERS Co-V) case in NSW, the public health consequences of a power outage in a local health district or a bushfire affecting a coal mine.

Another task that I was given while at the CDB was to address concerns raised by a general practitioner regarding an increasing trend of positive laboratory results of the parasites *Blastocystis hominis* and *Dientamoeba fragilis* and a link to the application of biosolids on agricultural land. I did a literature review of the parasites and biosolids, spoke to leading researchers in the area from around the country and convened an expert panel to address issues raised. This issue brought together members from the Environmental Health Branch and Communicable Diseases Branch as well as other government regulatory authorities. I learned important lessons from this experience – mainly regarding the confusion created by the use of culture independent diagnostic testing in detecting pathogens of unknown clinical significance. I was reminded of principles in pathology such as Koch's postulates which require fulfilment of certain criteria to establish a causative relationship between a microorganism and disease. The principles of the Hippocratic Oath and 'to first do no harm' also came into mind in thinking about the adverse effects caused by using antibiotics to treat infections caused by these organisms compared to the benefit that such treatment might confer.

I was fortunate to work closely with the Director of Health Protection and participate in the various meetings he attended, some at a national level. Many of these were completely unrelated to my MAE projects and it was great to be exposed to the breadth of subject areas covered by public health. Some of the issues covered in these meetings related to the regulation of electronic cigarettes, point of care testing for the human immunodeficiency virus (HIV), blood-borne virus panels investigating risk to healthcare workers, and multi-drug resistant tuberculosis expert group

meetings among others. I also observed media trainings and live interviews conducted on a range of health issues that were made public or were raised by media. Some of these included providing advice on the preparation of pork products after a link to locally acquired hepatitis E virus infections, advice around wild mushroom picking after several hospitalisations from mushroom poisoning, clarifying confusion around a case of Creutzfeldt-Jakob disease and alerting the public of poor infection control at four dental clinics that may have put some at risk of acquiring a blood-borne virus infection.

I went on several field trips to witness what happens every day in public health. I visited the Western Sydney public health unit to gain insight into the 'coal-face' of public health work, visited the refugee health service at Liverpool to understand what services are available for refugees in NSW, visited the Warragamba Dam and Prospect reservoir to see how Sydney's water is managed at the source and before delivery to households and I went on a bus tour of the new WestConnex road-tunnel infrastructure to learn of the potential environmental health impacts this might have on local residents.

I also had the opportunity to attend various conferences and forums related to communicable disease control. I attended the NSW tuberculosis (TB) conference in 2014 which focused on current topics in TB prevention and control, the HIV Support Program workshops in 2014 and 2015 looking at ways in which the system could better support HIV-diagnosing physicians and I participated in a three day workshop and colloquium organised by Rheumatic Heart Disease Australia and NSW Health, which aimed to educate and raise awareness of the new acute rheumatic fever and rheumatic heart disease control register in NSW. I also attended and presented at the Communicable Disease Control conference in Brisbane in June 2015 (organised by the Public Health Association of Australia) and attended and presented at the International Conference on Emerging Infectious Diseases held in Atlanta, Georgia in August 2015 organised by the United States Centre for Disease Control and Prevention (CDC).

These activities are in addition to the work that I did for the requirements of the MAE program; these are discussed in detail in the next chapters and outlined in the table below (Table 1). Briefly, I was involved in the investigation of a cluster of hepatitis E virus (HEV) infections in individuals without a travel history. I organised expert panel teleconferences, designed a food history

questionnaire, conducted an investigative study, analysed data, wrote up the findings for publication and presented the investigation at various meetings. My surveillance system project was to establish a register-based control program for acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in NSW in which I analysed data, engaged stakeholders and wrote a plan for notification and registration of cases. My epidemiological project involved conducting a case-control study aiming to find risk factors for acquisition of a novel strain of Methicillin-resistant *Staphylococcus aureus* (MRSA) in a local health district. For this study, I designed the data collection forms, extracted information from hospital medical records, mapped out descriptive data from whole genome sequencing results and wrote a report. I also undertook a couple of data analysis projects, one of which is included in the bound volume. The first was an analysis of 81 laboratory samples of measles where both immunofluorescence (IF) and polymerase chain reaction (PCR) tests were conducted. My job was to correlate these laboratory results to epidemiological and clinical findings to determine the sensitivity and specificity of each test. The second data analysis project, included in this bound volume, is on the outcomes of patients who presented to an Ebola transit unit (ETU) in Monrovia, Liberia between November and December 2014, while working there as a medical doctor with MSF. My role at the ETU was to triage patients and determine whether they met the suspect or probable case definition for Ebola virus disease.

Summary of public health impact

The locally acquired HEV outbreak was the first reported in Australia and therefore has important implications for Australian medical practitioners. HEV has typically been thought to occur in returned travellers from HEV-endemic countries. However with a link established to local pork products, we were able to show that there is a risk of acquiring the infection locally in people who consume undercooked pork products, particularly pork liver. We recommended that Australian clinicians should consider the diagnosis of HEV in patients with an unexplained acute hepatitis regardless of a history of overseas travel where no alternative diagnosis has been made. HEV factsheets have been changed and national control guidelines are under review to reflect this recommendation. Previously, certain reference laboratories had only tested for HEV when the clinician requesting the test had indicated a history of overseas travel. These laboratories may also have to change practice so that they test all HEV requests made. The findings also have an impact on the food service industry and public who should ensure that pork products are cooked thoroughly.

Establishing a register for ARF and RHD in NSW will have a significant impact on the way these conditions are managed. These diseases were thought to be rare in the state but after assessing hospitalisation data over a 10 year period, we found that cases do occur in NSW and may be more frequent than previously thought. Registers have proven to be a useful and cost-effective mechanism of delivering monthly penicillin injections to patients with ARF to prevent progression to RHD (3). The system that we have established to do this will involve various staff members from public health units, local health districts and organisations within the Ministry of Health. Rheumatic heart disease is not notifiable anywhere in the country and by making it a notifiable condition in NSW in October 2015, we hope that other states and territories will follow suit. In setting up this system, there will be increased awareness and initiative to address and eliminate two conditions which should not exist in a country like Australia.

The findings of the measles data analysis showed that immunofluorescence (IF) had poor sensitivity and specificity when compared to a PCR-based test. Australia has achieved measles elimination status making it increasingly important that suspected measles cases are detected and confirmed early. This allows appropriate public health action to be taken in a timely manner and does not

waste resources on false positive cases or allow false negative cases to cause further infection. The findings of the study helped in providing evidence to the main reference laboratory in NSW to stop using IF as a first line test for measles. These results were published in the *Journal of Clinical Virology* of which I am an author (Appendix 3).

The expert panel group that was convened to address concerns relating to *Blastocystis hominis* and *Dientamoeba fragilis* determined that increased detection of these organisms was due to a new, more sensitive diagnostic test and was unlikely to represent a true increase in the incidence of infection. I produced factsheets on these organisms which appear on the NSW Health website (Appendix 4).

The case control study examining a novel strain of MRSA did not identify any unique risk factors for acquisition of the bacterium or adverse outcomes related to the new strain. It was reassuring to find that enhanced control measures in the hospitals affected may have contributed to a reduction in incidence of both endemic MRSA strains and the novel strain. This was the first time whole genome sequencing (WGS) was used in the state to track the spread of MRSA and we learnt important lessons in how WGS results should be analysed and reported. This may assist others who will use these methods in future outbreak investigations. Understanding the epidemiology of new multi-resistant organisms is important given that antimicrobial resistance has been recognised as an increasing threat to global public health (4).

The 2014/15 Ebola virus disease (EVD) epidemic affected some of the poorest communities in the world in the countries of Liberia, Sierra Leone and Guinea. Many lives were unnecessarily lost and the international community had a role to play in the delayed response that led to this. I was grateful for the opportunity to have been a part of the response and to have worked as a clinician with MSF. The transit unit that we set up was useful in providing an alternative place for EVD-testing in a community that had been a 'hotspot' since the beginning of the outbreak. Our model of care based on affiliation with a large public hospital and rigorous triage is one that can be adapted in other healthcare facilities in countries affected by EVD.

Table 1: Overview of my Masters of Philosophy in Applied Epidemiology course requirements, February 2014 – November 2015

	Chapter 1: Overview of field placement	Chapter 2: Register for Acute Rheumatic Fever and Rheumatic Heart Disease in NSW	Chapter 3: Locally-acquired hepatitis E virus outbreak	Chapter 4: Outcomes of an Ebola transit unit	Chapter 5: A case control study of a novel strain of MRSA in a NSW local health district	Chapter 6: Teaching and lessons from the field
Analyse a public health dataset	X	X	X	X		
Epidemiological study			X		X	
Establish a surveillance system		X				
Literature review and critical appraisal	X	X	X			
Oral conference presentation			X		X	
Scientific article for a peer-review journal	X	X	X	X	X	
Summary for a lay person	X		X			
Lessons from the field and teaching	X					X

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4. World Health Organization., editor WHO'S first global report on antibiotic resistance reveals serious, worldwide threat to public health. Antimicrobial resistance–global surveillance report2014: Virtual Press Conference.

Appendices

Appendix 1: Health Protection Report – Epi Corner – as published on the NSW Health website, August 2014 – June 2015

Epi Corner August 2014

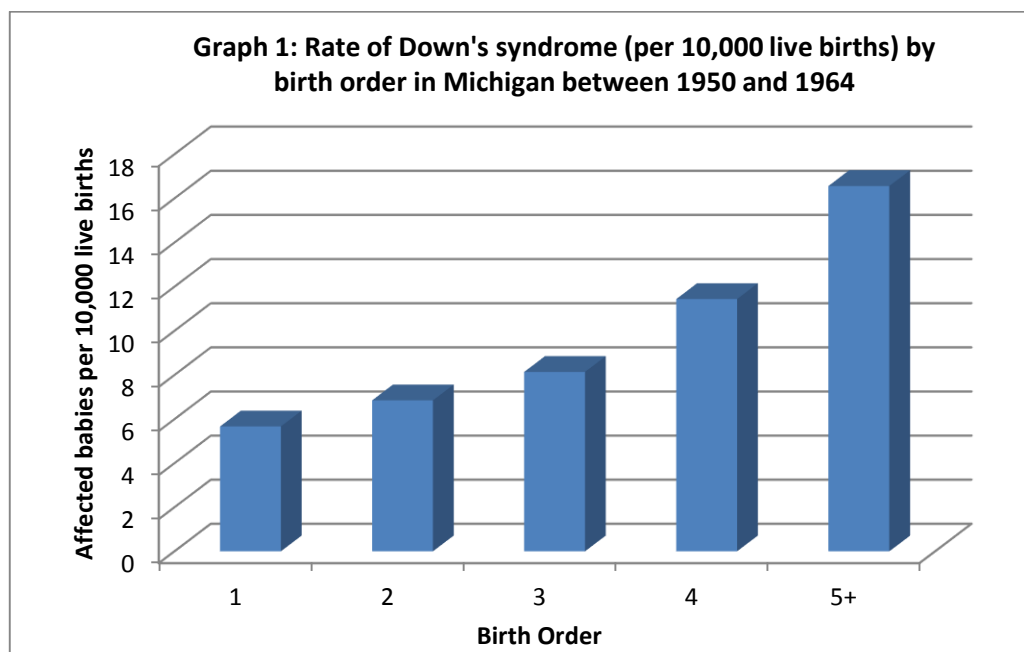
In the 1960s, researchers were keenly investigating the potential causes of Down's syndrome. The aetiology of Down's syndrome was largely unknown and there were different hypotheses as to the cause of this condition. Some of the hypotheses related to the geographical distribution of cases – higher rates being seen in urban areas compared to rural areas, other theories looked at the influence of intrauterine infections such as cytomegalovirus, rubella and toxoplasma, and yet other considerations included factors such as birth order and maternal/paternal age.

A study done by Stark and Mantel in 1966 aimed to examine in more depth, the apparent association between maternal age and birth order with the risk of Down's syndrome.

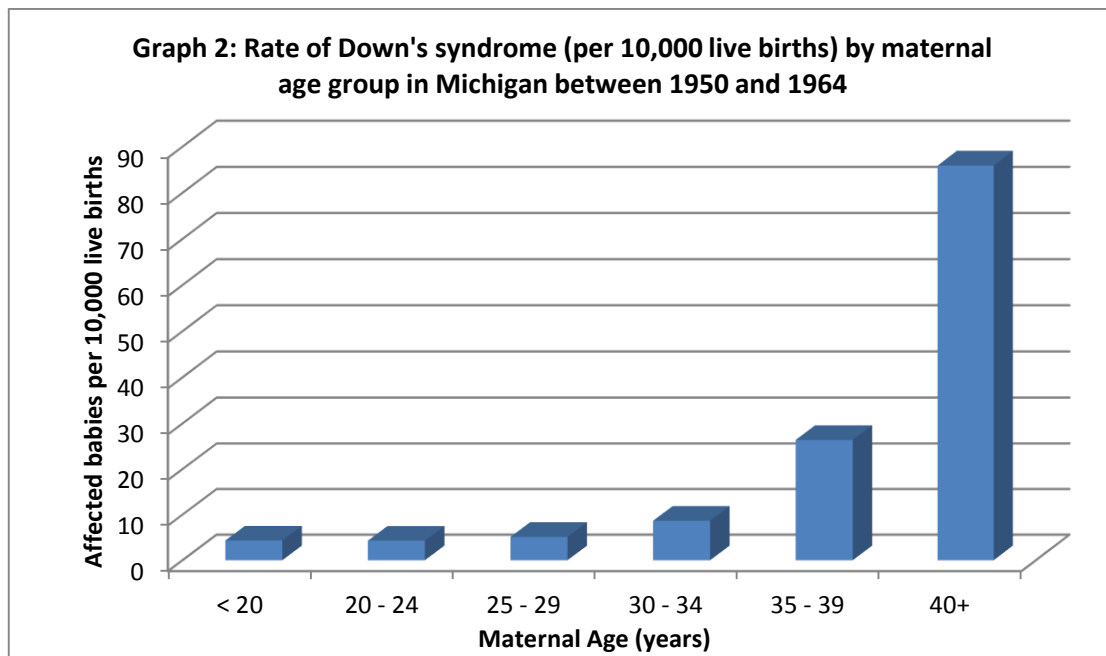
The graphs below show some of their results (reproduced from the original study).

Graph 1 shows the trend between the prevalence of Down's syndrome and birth order.

There appears to be an association between increasing birth order and the risk of Down's Syndrome – a 5th- born child appears to have almost a 4-fold increase in the risk of being born with Down's syndrome, compared to a 1st-born child.



However, consider also that the order in which a woman's children are born is also linked to her age at the time of child birth. When Stark and Mantel examined the relationship between maternal age at birth and risk of the child having Down's syndrome, they observed the relationship shown in the graph below.



Graph 2 above, shows a striking relationship between maternal age at birth and the child's risk of being born with Down's syndrome.

It would be reasonable to assume that a woman giving birth to her fifth child would be, on average, older than a woman giving birth to her first child. It appears that the two factors – birth order of children and maternal age when a child is born – are inter-related.

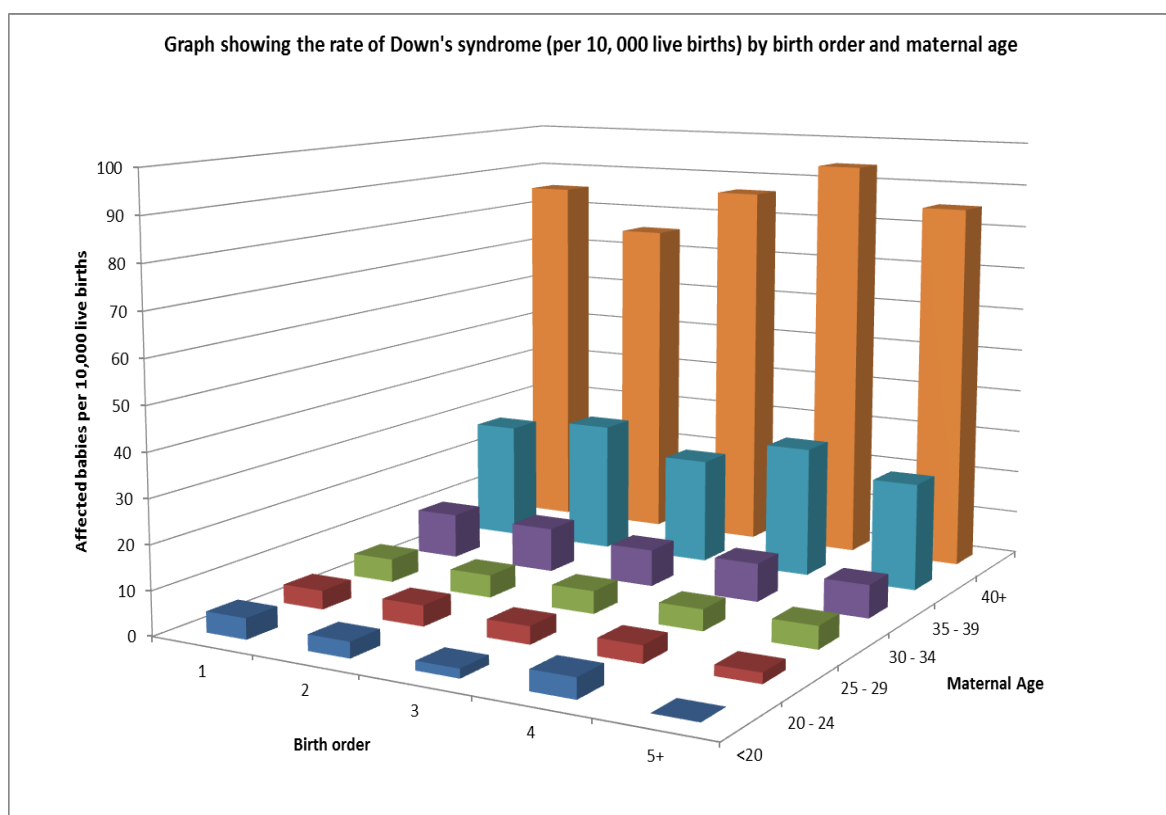
Questions:

- 1) How might Stark and Mantel further evaluate the true association between the two variables and the risk of Down's syndrome?
- 2) What is this mixing of effects called in epidemiology?

Answers:

- 1) To further evaluate the independent effect of each of the variables - birth order and maternal age - on the outcome - risk of Down's syndrome, Stark and Mantel can stratify their data.

Stratification is a method in epidemiology that allows two different exposures to be analyzed at the same time. The graph below stratifies the prevalence of Down's syndrome by both birth order and maternal age.



If we look at how prevalence changes within any particular maternal age, going from left to right, it is clear that increasing birth order does not correlate with the prevalence of Down's syndrome.

However, if we look at the prevalence within each of the birth order groups, by going from front to back, it becomes clear that the prevalence of Down's syndrome increases as maternal age increases, in each of the levels of birth order.

- 2) This kind of association between factors is called *confounding*. Confounding is a form of bias and occurs when the primary exposure of interest is mixed-up with some other factor that is associated with the outcome.

In this example, the relationship between birth order and the prevalence of Down's syndrome is confounded by maternal age.

References:

1. Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. *Journal of the National Cancer Institute*, 1966 vol 37 (5); pp 687-698
2. Stern H, Microbial causes of mental retardation. The role of prenatal infections with cytomegalovirus, rubella virus, and toxoplasma. *Lancet*, 1969 vol 2 (7618), pp. 443-448
3. Rothman KJ, Greenland S, Lash T, 2008, *Modern Epidemiology: Third edition*, Lippincott, Williams & Wilkins, Philadelphia, USA

Epi Corner – September 2014

The flu season has hit states and territories throughout Australia exceptionally hard this year, with more than 42,300 laboratory confirmed cases recorded at the end of August. This compares to approximately 14,000 lab-confirmed cases at the same time last year.

These kinds of numbers are able to be determined at a local and state level because of the application of a standardized case definition, which allows public health professionals to classify and count cases consistently across reporting jurisdictions

Imagine that you are a public health officer investigating an influenza outbreak in an aged care facility (ACF X) in your local health district. The experienced nurse in charge, in anticipation of your visit, has attempted to help in the investigation by developing some case definitions and creating a line list of cases as shown in the table below.

Case definitions:

Probable: Resident of ACF X with symptoms suggestive of influenza (measured fever of greater than 38.0°C AND at least 1 of the following 2 respiratory symptoms: cough or sore throat) where symptoms started after August 25th 2014.

Confirmed: Resident of ACF X with symptoms suggestive of influenza (as above) where symptoms started after August 25th 2014 AND with a throat swab positive for influenza.

Table showing residents of ACF X with reported symptoms and available laboratory results for Influenza

Case ID	Date symptom onset	Cough	Measured fever >38.0°C	Sore throat	Throat swab taken	Throat swab positive for influenza
1	26/8/2014	Y	Y	Y	Y	Y
2	28/8/2014	Y	Y	N	Y	Y
3	29/8/2014	N	Y	N	Y	Waiting for result
4	29/8/2014	Y	Y	Y	N	
5	1/9/2014	Y	Y	Y	N	
6	1/9/2014	Y	Y	N	Y	Y
7	2/9/2014	N	Y	N	N	
8	2/9/2014	N	Y	Y	Y	Waiting for result

Questions:

- 1) According to the line list of cases, how many **probable** and **confirmed** cases are there at this time?
- 2) What are some important elements to consider when developing a case definition for an outbreak investigation?
- 3) How do the concepts of 'sensitivity' and 'specificity' apply to a case definition?

Answers:

1. According to the case definition, there are 3 probable cases (cases 4, 5 and 8) and 3 confirmed cases (cases 1, 2 and 6).
2. A case definition should be simple, objective and easily applied. It can be broad to begin with and refined as the investigation continues.

A good case definition will include characteristics that relate to time, place and person. In this example, we are looking at residents of ACF X (person and place) after August 25th (time).

The case definition should also include clinical aspects that are well accepted and typical of the particular disease that you are investigating. If the diagnosis can be easily and quickly confirmed by laboratory testing, the confirmation criteria can be used to define a *confirmed* case. Patients with symptoms but without lab confirmation can be referred to as *probable* cases.

3. The sensitivity and specificity of a case definition may vary according to the purpose of case identification. The sensitivity of a case definition refers to the proportion of individuals in the population who actually have the disease and are correctly identified by the case definition. For a severe disease with epidemic potential like SARS, epidemiologists will want to choose a very sensitive case definition which ensures that no cases are missed. However, a very sensitive case definition may mean that individuals who do not have the disease are also captured.

A specific case definition will try to make sure that individuals who truly do not have the disease are excluded by not meeting the requirements of the case definition.

A highly specific case definition however, may mean that some individuals who do have the disease may be excluded.

References:

1. Australian Influenza Surveillance Report No. 5 2014, Australian Government Department of Health, accessed 5th Sept 2014. Available from:
[http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/\\$File/Australian-Influenza-Surveillance-Report.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/Australian-Influenza-Surveillance-Report.pdf)
2. Gregg, M.B (2008) Field Epidemiology 3rd edition, Oxford University Press, New York
3. Guy R, Lambert S, Kelly H. Estimating influenza vaccine effectiveness in an outbreak when anti-viral medications were used as a control measure. *Australian & New Zealand Journal of Public Health* 2005; 29: 540-3

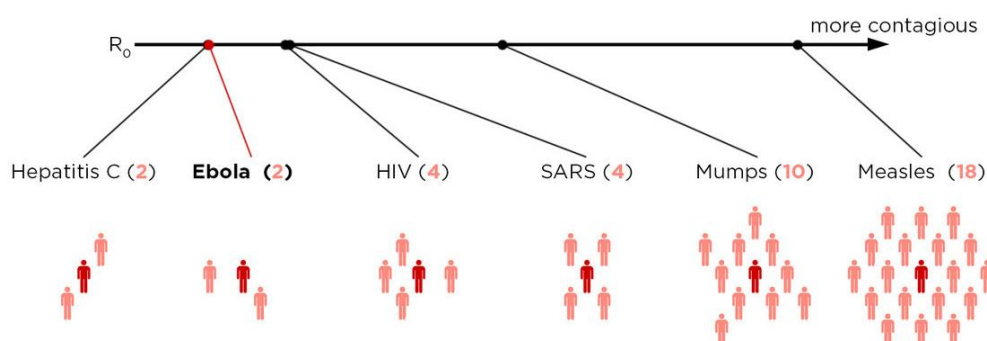
Epi Corner October 2014

At present, the countries of Guinea, Sierra Leone and Liberia in West Africa are experiencing the largest outbreak of Ebola virus disease (EVD) that has occurred in history. While efforts are being made to implement public health measures in the affected regions, each week there is an upward trend in the number of newly confirmed cases and deaths from the disease.

In an epidemic such as that occurring in West Africa, epidemiologists can measure the spread of infection by calculating a number called the basic reproduction number, also called R_0 . The basic reproduction number is defined as the number of secondary infections generated by an infected index case in the absence of control interventions in a population that is completely susceptible to the disease.

R_0 is used to measure the transmission potential of a disease, and for an epidemic to occur in a susceptible population, the value of R_0 must be greater than 1.

The basic reproductive number has been calculated for the current EVD epidemic using mathematical models¹ and is estimated to be at 2. This means that every infectious case has the potential to produce 2 new secondary cases. The diagram below compares the R_0 for EVD and for other more well-known diseases such as measles and HIV (in a completely susceptible population)².



Questions:

- 1) What value must R_0 be, for an epidemic to stop?
- 2) What factors might affect the basic reproduction number?
- 3) What measures can be taken to reduce R_0 ?

Answers:

- 1) The basic reproductive number must be less than 1 for an epidemic to stop. When R_0 is less than 1, each infected case doesn't produce enough cases to replace itself. If R_0 equals 1, then each primary case replaces itself and the disease will continue to persist in the population endemically.
- 2) The basic reproductive rate is affected by several factors:
 - the rate of contacts in the population
 - the probability of infection being transmitted during contact
 - the duration of infectiousness

As the epidemic continues and the pathogen becomes established in the population, previously infected individuals will either die or develop natural or acquired immunity to the disease. When this occurs, the average number of secondary cases per infectious case will decrease as there are fewer numbers of susceptible individuals in the population. A different kind of measurement is used to describe this situation, and it is called the effective reproductive rate (R_e).

- 3) Given that R_0 is affected by the size of the *susceptible* population and the rate of contacts by an infected case, public health measures such as isolation and treatment of cases will have an effect on reducing the reproduction number.

Vaccination will also reduce R_0 by reducing the number of susceptible individuals in a population. Vaccination provides direct protection against the disease at an individual level but it also provides indirect protection at a population level through the concept of herd immunity.

References:

1. Althaus CL. Estimating the Reproduction Number of Ebola Virus (EBOV) During the 2014 Outbreak in West Africa. PLOS Currents Outbreaks. 2014 Sep 2. Edition 1, doi: 10.1371/currents.outbreaks.91afb5e0f279e7f29e7056095255b288.
2. Doucleff M, No, seriously how contagious is ebola, Accessed 08th October 2014. Available from: <http://www.npr.org/blogs/health/2014/10/02/352983774/no-seriously-how-contagious-is-ebola>
3. Public Health Action Support Team CIC, Health Knowledge, Epidemic theory (effective and basic reproduction numbers, epidemic thresholds). Accessed 10th October 2014. Available from: <http://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/epidemic-theory>

Epi Corner November 2014

A case-control study is a useful epidemiological study type that tries to determine whether an exposure is associated with an outcome. In theory, the case-control study can be described simply. It requires that cases are identified - a group known to have the outcome - as well as controls - a group known to be free of the outcome. Researchers can then look back in time to find out which subjects in each group had the exposure(s) and compare the frequency of the exposure in the case group to the control group.

Here we discuss a case-control study made famous for all the wrong reasons.

In 1981, an eminent Harvard professor of epidemiology published a paper in the New England Journal of Medicine investigating the association between drinking coffee and the occurrence of pancreatic cancer. The conclusions of the study were that there was a 'strong association between coffee consumption and pancreatic cancer'. They found that the risk associated with drinking up to two cups of coffee per day was 1.8, and that with three or more cups per day, the risk was 2.7.

In conducting the study, the researches enrolled cases with histologically confirmed pancreatic cancer from 11 large hospitals in the Boston and Rhode Island area over a 5 year time period. The controls were patients who were under the care of the same physician in the same hospital at the time of an interview with a patient with pancreatic cancer.

The idea was to make the process of selecting the cases and control as similar as possible.

However, what the study group failed to understand at the time of recruitment, was that patients often seen by physicians who treated pancreatic cancer were those with other gastrointestinal disorders. These 'control' patients were often advised not to drink coffee or had chosen to reduce coffee drinking on their own accord. This in turn, led to the selection of controls with a higher prevalence of gastrointestinal disorders who had unusually low odds of exposure, that is, intake of coffee.

The results of this study could not be reproduced by other researchers and led to some questioning of the study methods.

Questions:

- 1) In this study, what is the term given to the form of bias that is evident in the recruitment of controls?
- 2) How might choosing controls with lower odds of exposure affect the strength of association between the exposure and outcome?
- 3) What are the advantages and disadvantages of conducting a case-control study for a study like this?

Answers:

- 1) This type of bias is a form of selection bias – more specifically it is known as Berkson's bias. Selection bias in a case-control study can occur when controls are not recruited from the source population that gives rise to the study's cases. A general rule of thumb is that cases and controls should be similar enough that a control could be labelled a case if they had the disease or condition of interest.

Berkson's bias is a special type of bias that applies to controls selected from a hospital in-patient population. According to the Oxford Reference Dictionary of Public Health, it occurs when hospital cases and hospital controls are systematically different from one another because the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to hospital. In this study, controls happened to be a group with higher prevalence of gastrointestinal disorders (and therefore reduced coffee consumption) that led to increased hospital admissions.

- 2) The fact that the control group were people with a higher prevalence of gastrointestinal disorders with reduced coffee intake compared to cases, led to a spurious positive association between coffee intake and pancreatic cancer.

In other words, the association between coffee intake and pancreatic cancer was skewed away from the null.

- 3) The advantages of a case-control study are that they are efficient at investigating rare conditions, multiple exposures can be studied at the same time and findings can be obtained relatively quickly with minimal funding.

Some of the disadvantages are that they can be subject to bias in the recruitment process – i.e. in the selection of controls, and in gathering data – if record keeping is inadequate or unreliable.

Case control studies also don't estimate risk directly. All they can tell is whether the odds of developing an outcome is higher or lower in a group of people who have the outcome compared to a group of people who don't.

References:

1. McMahon B, Yen S, Trichopoulos D, et al. Coffee and cancer of the pancreas, *New England Journal of Medicine* 1981; 304 (11) 630 – 633
2. Pai M, Kaufman J. Case studies of bias in real life epidemiologic studies - Should we stop drinking coffee? The story of coffee and pancreatic cancer, accessed 25th October, 2014; available from:
http://www.teachepi.org/documents/courses/bfiles/The%20B%20Files_File2_Coffee_Final_Complete.pdf
3. Gregg, M.B (2008) *Field Epidemiology* 3rd edition, Oxford University Press, New York
4. Oxford Reference Dictionary of Public Health. Berkson's bias, accessed 27th October 2014; available from:
<http://www.oxfordreference.com/view/10.1093/oi/authority.20110803095500748>

Epi Corner May 2015

For months, researchers have been working on a vaccine against Ebola Virus Disease (EVD) as part of continuing efforts to prevent the transmission of the virus in West Africa. Just this month (April 2015), the US Centre for Disease Control in collaboration with the Sierra Leone Ministry of Health and the Sierra Leone College of Medicine and Allied Health Sciences have launched the STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola) trial. This study aims to carry out a combined Phase 2 and 3 clinical trial to assess the safety and *efficacy* of a recombinant Vesicular Stomatitis Virus-Zaire Ebolavirus vaccine (rVSV-ZEBOV).

Phase 1 trials have already been conducted in Canada, Gabon, Germany, Kenya, Switzerland and the United States. These studies found that the vaccine did not produce any serious side effects in those who were vaccinated and scientists were able to determine a safe dose of the vaccine. However, they could not tell how much protection the vaccine would confer. The STRIVE trial will therefore help to answer this latter question by studying the vaccine in groups of people in various parts of Sierra Leone that have been affected by Ebola, thereby giving some guidance on the *effectiveness* of the vaccine.

For more information on the STRIVE trial, go to the following link:

<http://www.cdc.gov/vhf/ebola/strive/qa.html>

Questions:

- 1) Regarding vaccines in general, what is the difference between vaccine efficacy and vaccine effectiveness?
- 2) What are the types of epidemiological studies that are conducted to determine vaccine efficacy and effectiveness?
- 3) Vaccine trials are conducted in different phases. What are the different phases in a clinical trial and what is their purpose?

Answers:

1 & 2) The concepts of vaccine efficacy and effectiveness are important to differentiate.

Vaccine efficacy relates to the “best case scenario” of vaccine protectiveness under controlled conditions. They are best measured by double-blinded, randomized controlled clinical trials. In this type of study, individuals are randomly assigned to either a group that is given the vaccine or to a second group that is given a placebo, and researchers and participants are not aware of which they receive. Vaccine efficacy trials are commonly required before a new vaccine is licensed by a regulatory authority, such as the Therapeutic Goods Administration (TGA) of Australia.

Vaccine effectiveness, on the other hand, relates to the “real world” view of how a vaccine (which may already have proved to have high vaccine efficacy) reduces disease in a population. It is a useful way to assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under more natural field conditions rather than in a controlled clinical trial.

One of the commonest ways of measuring this is by conducting a retrospective case control study, where the rates of vaccination among a set of infected cases are compared to appropriate uninfected controls, and an odds ratio for developing infection despite vaccination, is calculated.

3) Clinical trials, including vaccine trials are conducted in a series of steps, called phases and each phase is designed to answer a separate research question.

- **Phase I:** These are usually small-scale trials (approximately 10 – 100 participants) to assess whether the vaccine is safe in humans and see what immune response it evokes. A safe dosing range and possible side-effects can also be determined.
- **Phase II:** The vaccine is given to a larger group of people to see if it is effective and to further evaluate its safety.
- **Phase III:** The vaccine is studied on an even larger scale (1000 – 10,000 participants) across several sites to confirm its effectiveness, monitor side effects, and collect information that will allow the vaccine to be used safely. If the vaccine retains safety and efficacy over a defined period, the manufacturer will be able to apply to the regulatory authorities for a license to market the product for human use.

- **Phase IV:** These studies are done after the vaccine has been licensed and introduced for use. This stage aims to detect rare adverse effects and assess any side effects associated with long-term use.

References:

- 1) Weinberg GA and Szilagyi PG, Vaccine Epidemiology: Efficacy, Effectiveness and the Translational Research Roadmap. *Journal of Infectious Diseases* 2010; 201: 1607 - 1610
- 2) Comstock GW, Evaluating vaccination effectiveness and vaccine efficacy by means of case-control studies. *Epidemiological Reviews* 1994; 16 (1): 77-89
- 3) WHO Vaccine safety basics – Pre licensure vaccine safety, accessed 20th April 2015; available from: <http://vaccine-safety-training.org/pre-licensure-vaccine-safety.html>

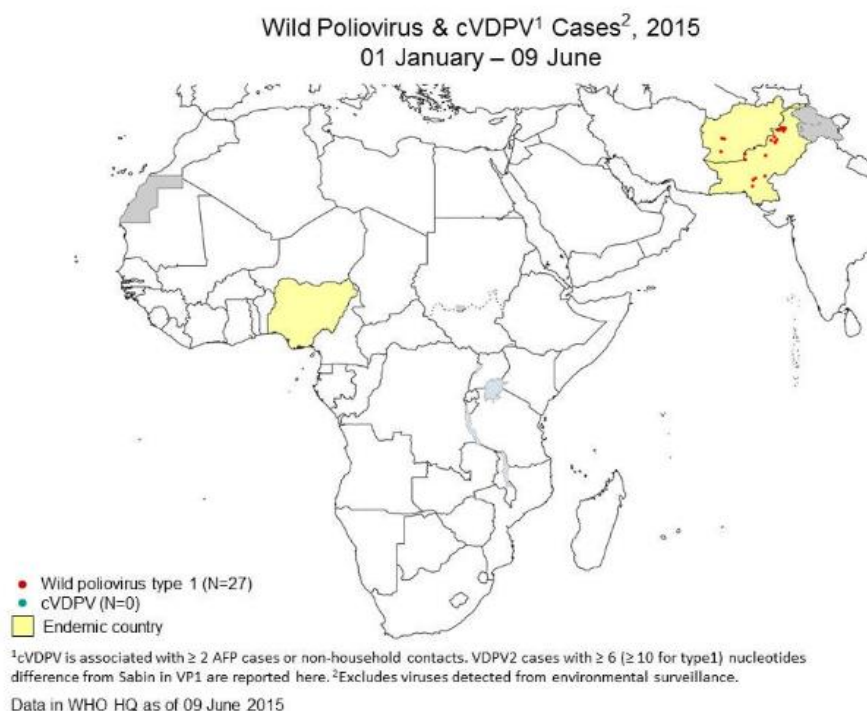
Epi Corner June 2015

The eradication of disease is the ultimate goal of public health. In 1977, Somalia reported the last case of naturally occurring smallpox, effectively marking global eradication of this disease. Since then, the World Health Assembly – the policy-making body of the World Health Organization – declared the goals of eradicating dracunculiasis (guinea worm disease) in 1986 and poliomyelitis in 1988.

Both diseases are very close to eradication and currently poliomyelitis cases are only recorded in 3 countries – Nigeria, Pakistan and Afghanistan (figure 1). However, after more than 20 years of interventions, this target is yet to be achieved, eluding to the complex interaction between biological, social, political and economic factors underpinning disease control.

Figure 1: Map showing countries with ongoing cases of poliomyelitis up to 9th June 2015 Source: Global polio eradication initiative, accessed 22nd June 2015

source: <http://www.polioeradication.org/Dataandmonitoring.aspx>



There are certain biological features of an organism and technical factors of dealing with them that make a disease more or less likely to be eradicated.

The three essential criteria for eradicability of an infectious disease are:

- 1) availability of an effective intervention for interrupting transmission of the agent
- 2) practical diagnostic tools with sufficient sensitivity and specificity to detect infection
- 3) the necessity for humans to be implicated in the life-cycle of the agent without any other vertebrate reservoir and without amplification in the environment.

Questions:

1. The terms elimination and eradication are often confused when it comes to infectious diseases. What is the difference between disease elimination and eradication?
2. What are some other diseases that have been considered for global eradication?
3. In addition to the biological and disease-specific criteria relevant to eradication, what are some examples of the economic, social and political considerations that should be considered?

Answers:

- 1) Eradication of a disease refers to the permanent reduction of the worldwide prevalence to zero. In this case, intervention measures are no longer needed. Smallpox is the only example of an eradicated disease.

Elimination, on the other hand, is defined as the reduction of prevalence of a disease in a defined *area* to zero or the reduction of global prevalence to a negligible amount.

Continued measures are required to prevent re-establishment of transmission. Poliomyelitis and measles are examples of eliminated infections in some parts of the world.

- 2) Eradication programs for yaws and malaria were initiated in the mid-1950s but terminated in the 1970s. There were multiple reasons for the failure of these programs, but two important ones were the lack of a pilot program to demonstrate the feasibility of eradication and the lack of adequate global surveillance.

The elimination of yellow fever from Cuba and controlling it in Panama in the early 1900s raised hopes for eradication of this disease. However, the existence of animal reservoirs for this virus makes eradication a particularly challenging goal.

An International Task Force for Disease Eradication was formed in 1988 and in addition to dracunculiasis and poliomyelitis, public health experts have identified five other diseases that have the potential to be eradicated. These diseases are measles, mumps, rubella, lymphatic filariasis and cysticercosis.

- 3) Important considerations economically are the costs and benefits in embarking on an elimination or eradication program. Decisions have to be made as to whether the use of resources on such a program is preferable to their use in non-health projects or in alternative health interventions. This is especially so in resource-poor settings.

Societal and political commitment are needed from beginning to end at all levels – regional, national and global. A clear commitment of resources, effective alliances with all potential collaborators and partners and support to broader health infrastructure are examples of some of the considerations in making an eradication program successful.

References:

1. Dowdle WR The principles of disease elimination and eradication, *MMWR Supplements* (1999); 48 (SU01); 23 – 27
2. Hopkins DR Disease Eradication, *New England Journal of Medicine* (2013); 368: 54 – 63

Appendix 2: Protocol to investigate potential blood borne virus transmission at four dental clinics

Purpose:

The purpose of this document is to outline a framework for evaluating the likelihood of blood borne virus (BBV) transmission in notifications of patients from four dental clinics with breaches in infection control.

Background:

In late 2014, a public health investigation was initiated by two public health units in Sydney to investigate reports from the Dental Council of poor infection control practices at four dental clinics – Clinics A, B, C and D.

The breaches in infection control included:

- Inadequate cleaning and washing of dental instruments
- Inadequate re-processing of dental instruments
- Re-use of single use equipment
- Sterilising autoclaves that were non-functional or had serious defects

The NSW Health Blood Borne Viruses Advisory Panel (BBVAP) convened in February and March 2015 and agreed that there may be a low risk of BBV transmission to an individual patient at these four clinics as a result of these breaches. Specifically, the risk was for patients who underwent a high risk or invasive procedure. The BBVAP recommended that all patients be contacted and advised to seek testing for human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C virus (HCV).

On 2 July 2015, a media conference was held to alert the public. A letter was also written to all of Clinic A's patients (769 patients) and Clinic B's patients who underwent a high risk procedure (11, 251 of 40, 000 total patients).

Aim of the investigation:

To identify whether notified HBV, HCV or HIV infections in patients of Clinic A and Clinic B can be attributed to exposure at one of these dental practices.

Rationale for investigation methods:

Disease characteristics and modes of transmission have to be considered separately for each BBV. In this investigation, if the BBV was acquired at one of the dental practices, the most likely mode of transmission would be from patient to patient via contaminated instruments. Where similar incidents have occurred in NSW and overseas in the past, there has been no evidence to suggest that HBV, HCV or HIV was acquired from breaches in infection control at a dental clinic.

The most common and less common risk factors for each of the BBVs in Australia are presented in the table below (information extracted from the respective draft or finalised version of the Series of National Guidelines (SoNGs)).

Infection	Common	Uncommon
Hepatitis C virus	-Injecting drug use -Receipt of donated blood, blood products and organs in Australia before 1990 - Receipt of donated blood, blood products and organs in low-resourced countries - Skin penetration procedures (e.g. tattooing) where there is poor infection control (e.g. prisons) - Perinatal exposure, especially if from high prevalent regions such as Egypt, Pakistan, Central Asia, Eastern Europe	-Heterosexual unprotected sex -Sharing of household equipment (razors, toothbrushes) -Blood transfusions

	- HIV infection, especially men who have sex with men (MSM)	
HIV	-Unprotected sexual contact , especially anal sex in MSM - Percutaneous exposure to blood, blood products or tissue from a HIV-positive person e.g. injecting drug use	- Maternal to child transmission -Blood transfusions
Acute hepatitis B virus	-Sexual contact of people with hepatitis, including MSM -Sexual contact with a person who is an injecting drug user - Sharing needles, syringes, injecting fluids	-Renal dialysis -Tattooing, body piercing or acupuncture without adequate infection control -Needlestick injuries -Accidental exposure of eyes, mucus membranes or wound to blood of another person -Blood transfusions -Solid organ donation
Chronic hepatitis B virus	-Perinatal or early childhood infection (increased risk in people born in an intermediate or high hepatitis B prevalence country and born to mothers with chronic hepatitis B, esp. if not vaccinated at birth) - Increased risk in people who have ever been incarcerated in a custodial setting	

Case definition:

A case considered for further investigation is a person on the list of patients of Clinic A from 1990 to December 2014 and Clinic B from 2005 to April 2015:

- who has tested positive for a BBV from 1st July 2015 OR
- was previously notified in NSW as a case of newly-acquired hepatitis B or hepatitis C infection

Methods:

All those meeting the case definition should be referred to the incident investigation team, which will comprise of representatives from Sydney and Southeast Sydney PHUs, CDB, a virologist (most likely Bill Rawlinson) and the Director of Health Protection. A dentist may be invited on an as-needs basis.

It is proposed that the investigation progress in 2 stages:

Stage 1 – Assessment of single notifications

Stage 2 – Cluster Analysis

Stage 1: Assessing a single BBV notification

1. Timing of infection and dental procedure

a) For each notification check whether they are already on the NSW Notifiable Conditions Information Management System (NCIMS)

b) If there has been a previous diagnosis:

Check the date of the dental procedure(s)

➔ If the date of BBV diagnosis is before the dental procedure(s), then dental exposure can be ruled OUT as a source of infection

- ➔ If the date of diagnosis is after the dental procedure(s), the case should be further investigated

2. Considering known risk factors

Given what is already known about the risk of transmission of each of these BBVs, we can assign a level of likelihood that a case's infection may have been acquired through a known risk factor that is higher than the risk of transmission from a dental procedure.

Risk factors can be classified as 'High' or 'Low' for each BBV as follows:

Infection	High risk factors	Low risk factors
Hepatitis C virus	Injecting/snorting drug user	History of needlestick injury
	Received blood/blood products/tissue/organ transplantation overseas	Tattooing at home/overseas/registered practice
	Received blood/blood products/tissue in Australia prior to 1990	Unprotected sex with multiple sexual contacts
	History of imprisonment	Unprotected sex with a sex worker
	Born overseas and confirmed that mother is positive for BBV	Born overseas with no previous positive results
	Renal dialysis	Sharing razors/toothbrushes
HIV	MSM	History of needlestick injury
	Received blood/blood products/tissue/organ transplantation overseas	Tattooing overseas/unregistered practice
	Injecting drug user	Unprotected sex with multiple sexual contacts
	Unprotected sex in a country with a high prevalence of HIV infection	Unprotected sex with a sex worker

	Unprotected sex with someone known to have HIV infection	Sharing razors/toothbrushes
	Unprotected sex with a person from a country with high HIV prevalence	
Hepatitis B virus	Born overseas with evidence of previous viral infection (previous blood test results available and able to be verified)	History of needlestick injury
	Born in high prevalent country, mother's status unknown and case did not receive birth vaccine	History of imprisonment
	Born overseas and confirmed that mother is positive for HBV	Tattooing at home/overseas/registered practice
	Received blood/blood products/tissue/organ transplantation overseas	Unprotected sex with a sex worker
	Received blood/blood products/tissue in Australia prior to 1990	Sharing razors/toothbrushes
	Injecting drug user	Born overseas with no previous positive results
	Renal dialysis	
	Unprotected sex with multiple sexual contacts	

- a) For each notification, check the risk factor history on the questionnaire.

If a case has had any of the high risk factors for the particular BBV concerned, then it is most likely that they acquired their infection from this exposure/source and not from the dental clinic. No additional public health follow up is required at this stage of the investigation.

- b) If there are no high risk factors but there are low or no risk factors identified, the case should be put forward for the next stage of investigation.

Stage 2: Cluster investigation

Stage 2 will consider cases whose dental procedure precedes their BBV diagnosis and who have no identifiable high risk factors for acquisition of the infection.

Steps in Stage 2 are a guide only and should be further informed by response rates, results and experience.

1. Summarise the information on notified cases by compiling a line list. The line list should include (and is not limited to) information on:

- Age
- Country of birth
- Parent's country of birth
- Occupation
- Risk factor history
- Lab test results (further tests may need to be requested if incomplete)
- Type of dental procedure (high risk versus medium risk versus low risk)
- Gender
- Dental practice
- Dentist (if possible to determine)
- Number of dental procedures
- Date of dental appointment

2. Identify all patients notified on NCIMS (and dental clinic patients now diagnosed with a high risk factor) with the same BBV as the case who had an appointment on the day of, or the two days before, the date/s of the case's appointment/s at the relevant practice

3. Draw a graph of the number of cases by date of dental appointment for the day of, and the two days before the day of the case's appointment/s.

Two types of clusters can be defined:

One-day clusters: ≥ 2 patients with the same BBV (HBV, HCV, HIV) who have had a procedure on the same day

Three-day clusters: ≥ 2 patients with the same BBV (HBV, HCV, HIV) who had a procedure within three days of one another.

4. For each BBV and dental practice, conduct a statistical assessment of transmission risk. The purpose of this analysis is to assess whether the observed clusters are greater than could be expected by chance alone, based on the underlying prevalence of HBV, HCV and HIV in the cohort.

The steps involved are:

- Step 1 Calculate the expected rate of attendance of a case of BBV per day using the cohort prevalence rate
- Step 2 Calculate the expected probability of attendance of ≥ 2 cases of the BBV in a single day using the Poisson distribution
- Step 3 Observe the number of days in which ≥ 2 cases of the BBV are seen in a single day
- Step 4 Record the total number of days observed
- Step 5 Calculate the probability of seeing the observed number of days with ≥ 2 presentations by chance alone using the binomial distribution and inputting a "success" day in the trial as a day with ≥ 2 or more cases of the BBV, the number of trials as the total number of days observed, and the Poisson probability from Step 2 as the probability of success
 - a) If there is a cluster identified that is greater than can be expected by chance, sera from each case that has an active infection in the cluster should be further tested. Sequencing and genotyping should be done to determine whether there is any genetic relatedness between cases.

- b) To further investigate the 1-day and 3-day clusters, get a record from the dental practice of all the patients who had dental procedures on the same day (or 3-days) as the cluster-cases. Check to see whether any of these names appear on NCIMS or the HIV database and are already known to have a BBV.
- c) Evidence of nosocomial transmission will be identified where there are 2 or more cases of a single BBV where there is no other potential source of transmission identified, and is supported by molecular testing.

Stage 3: Further investigations to consider if nosocomial transmission found

If there is evidence of nosocomial transmission, consider whether other untested patients who may have had procedures on the same day, 3 days before and after (or longer) the cluster may be at risk.

Consider factors such as the number of high risk procedures done that day/week, how instruments were used/shared, the flow of patients, etc.

To be considered in detail if the situation arises.

Appendix 3: Publication of a Measles study comparing Immunofluorescence (IF) to a new Polymerase Chain Reaction (PCR) assay

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What assay is optimal for the diagnosis of measles virus infection? An evaluation of the performance of a measles virus real-time reverse transcriptase PCR using the Cepheid SmartCycler® and antigen detection by immunofluorescence

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ABSTRACT

Background: Despite the World Health Organization (WHO)-reported elimination of measles in Australia, importation of cases especially in travellers from Asia continues in Sydney, Australia's largest city. Laboratory confirmation supports clinico-epidemiological evidence of measles virus infection, and is needed to establish elimination.

Objectives: To evaluate the performance of a random access real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay using the moderate complexity SmartCycler® platform, and measles antigen detection by immunofluorescence (IFA), for the detection of measles virus in patient samples.

Study design: One hundred samples comprising nose and throat swabs, nasopharyngeal aspirates and urine, collected from patients with suspected measles were tested in parallel using IFA and nucleic acid testing using the SmartCycler® and LightCycler® RT-PCR platforms. The LightCycler® RT-PCR was used as the reference assay against which the SmartCycler® RT-PCR and IFA were compared.

Results: Using the LightCycler® RT-PCR, measles virus was detected in 35 clinical samples. There was 100% concordance between the results of the SmartCycler® and the LightCycler®-based RT-PCR. Measles genotypes detected included B3, D8, and D9. Testing urine in addition to NTS did not improve diagnostic yield. In contrast, the sensitivity and specificity of IFA compared to the reference LightCycler® RT-PCR was 34.3% and 96.7%, respectively.

Conclusion: The performance of the SmartCycler® is comparable to the LightCycler® for the detection of measles virus. However, IFA had poor sensitivity and should not be used to confirm measles virus infection where nucleic acid testing is available.

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1. Background

In March 2014, the World Health Organization (WHO) announced that measles elimination had been achieved in Australia

[22]. However, the importation of measles by foreign visitors or returned travelers from areas of high prevalence continues to result in multiple localized outbreaks [3,11,18,19]. Laboratory confirmation is essential to accurately monitor the epidemiology of measles and to implement effective control strategies. Detection of measles virus-specific IgM antibody on acute-phase sera is the most widely available test, but is not without limitations. Testing sera collected <72 h after rash onset has a false negative rate of 33% [7]. Measles virus-specific IgM testing in a highly vaccinated low prevalence population has a 4% false positive rate; cross-reactivity

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from other viruses including human parvovirus, rubella and human herpesvirus 6 has been described [1,21]. The IgM response in measles vaccine failures may also be absent [8].

Due to these limitations with measles virus-specific serology, detection of measles virus antigen by immunofluorescence (IFA) or by nucleic acid testing (NAT) is increasingly used. In our laboratory, an immunofluorescent monoclonal antibody against measles virus hemagglutinin and matrix protein (EMD Millipore Corp, Temecula, CA, USA) is used as the first line test for direct detection of measles. The in-house real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the LightCycler® 480 System (LightCycler: Roche Diagnostics, Mannheim, Germany) is not generally performed, unless there is a strong clinical suspicion for infection despite a negative IFA. However, the acquisition of measles in non-travellers within the local community suggested that not all index patients with measles infection were being identified using this diagnostic algorithm.

We therefore developed and evaluated a Taqman-based RT-PCR on the SmartCycler® (SmartCycler: Cepheid, Sunnyvale, CA, USA) platform for the detection of measles virus. The SmartCycler platform was chosen because it allows for random access and the assay is categorized as moderate complexity in terms of test performance and result interpretation. Non-molecular biology trained staff at our 24 h, 7 day a week laboratory were already familiar with the SmartCycler.

2. Objectives

To evaluate the performance of a random access real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay using the SmartCycler® platform and measles antigen detection by immunofluorescence for the detection of measles virus. Each assay was compared against the LightCycler NAT as the reference assay.

3. Study design

3.1. Samples used to determine the analytical sensitivity and specificity of the SmartCycler NAT

For analysis of the lower limit of detection (LoD) of the SmartCycler assay, RNA extracted from 5 µL of the M-M-R11 vaccine (CSL Limited/Merck & Co., Inc., Parkville, Victoria, Australia). Each 0.5 mL vial of M-M-R11 vaccine contains $\geq 10^3$ 50% tissue culture infectious dose (TCID₅₀) of the Edmonston strain of measles [5]. A solitary vial was tested, and the amount of RNA extracted from the vaccine was not quantified. Serial dilutions (neat to 10^{-7}) of RNA extracted were then used as template nucleic acid extract for the RT-PCR. Experiments were performed in duplicate to determine the LoD of the assay. To determine specificity of the RT-PCR assay, nucleic acid extracts of stored clinical samples of enterovirus/rhinovirus, varicella zoster virus, herpes simplex virus-1 and -2, human herpesvirus 6, human parvovirus, adenovirus, influenza A, influenza B, respiratory syncytial virus, human metapneumovirus, and parainfluenza viruses 1–3 were tested. To determine specificity against mumps and rubella, commercially sourced mumps and rubella RNA (Viracell AmpliRun Mumps RNA control and Viracell AmpliRun Rubella RNA control, Abacus Diagnostics, Granada, Spain) were also tested on the measles RT-PCR assay.

3.2. Patient specimens

One hundred specimens (combined nose and throat swabs [NTS], $n=48$; nasopharyngeal aspirate [NPA], $n=7$; and urine, $n=45$) from 86 patients, previously submitted for measles antigen detection by IFA over a 20-month period from August 2012 to

March 2014 were retrieved from storage at -80°C . Included in this collection were five archived pediatric specimens where measles antigen was detected by IFA but no corresponding epidemiological information was available. The age of patients ranged from 4 months to 73 years. Where available, all specimens from different sites for each patient were tested. In 14 patients, NTS and urine samples were tested concurrently. NTS samples were collected and submitted to the laboratory in viral transport media (Copan Italia, Brescia, Italy).

3.3. RNA extraction

RNA was extracted using the BioRobot EZ1 and EZ1 Virus Mini Kit v2.0 according to the manufacturer's instructions (Qiagen, Valencia, CA, USA). For NTS samples, swabs were vortexed in 1 mL of HBSS (Gibco, Life Technologies, Grand Island, NY, USA). For all samples, 200 µL of specimen was used for RNA extraction.

3.4. SmartCycler and LightCycler assays

The primers and probes against measles virus N-gene were designed based on previously published assays [9], with minor modifications, with the inclusion of degenerate nucleotides at positions 585, 590, 599, 600 and 606 (forward primer): 687 (reverse primer) and 657 (probe). The sequences were as follows: forward primer MVF2, 5'YCCTGGMGGGATTCARYATGATYCT; reverse primer MVR2, 5'ATCCACCTTCTWAGCTCCGAATC; Taqman probe, 5'FAM (TCTTGCTCGCAAAGCGGTACKG) BHQ-1. This produced a 114bp product. An internal positive control to detect the human β -globin gene (BGL) was used: forward primer, 5'ACAACTGTGTTCCTAGC; reverse primer, 5'CAACTTCATCCACGTTCCAC; Taqman probe 5'Quasar (TCAAACAGACACCATGGTGACCTGA) BHQ-2. The PCR master mix contained 0.4 µM of each measles primer, 0.2 µM of each BGL primer, 0.32 µM of measles probe MeaP, 0.16 µM of BGL probe, AgPath-ID enzyme mix (Ambion, Applied Biosystems, Foster City, CA, USA), AgPath-ID buffer, and 5 µL of nucleic acid template in a final 25 µL reaction. The PCR cycling conditions on the SmartCycler were as follows: reverse transcription, 50°C for 30 min; followed by 95°C for 15 min; followed by 3 cycles of 95°C for 30 s, 60°C for 30 s, 72°C for 40 s; followed by 40 cycles of 95°C for 15 s, 60°C for 15 s, 72°C for 20 s.

3.5. Measles virus genotyping

Amplification and sequencing of the measles virus N gene was used to genotype the RT-PCR positive RNA extracts at the Measles Reference Laboratory, Victorian Infectious Diseases Reference Laboratory, Australia [4]. Specimens were referred for genotyping as directed by local public health unit investigations. All specimens from sporadic cases of measles infection and at least one case from any documented chain of transmission were genotyped.

3.6. Measles immunofluorescence antigen test

Briefly, NTS were vortexed in 1 mL of HBSS and then centrifuged at 2000 rpm for 10 min. The supernatant was removed, and the cell pellet resuspended in phosphate-buffered saline with 10% fetal calf serum. This suspension was then placed onto a slide, fixed in acetone and stained using mouse anti-measles monoclonal antibody directed against measles hemagglutinin and matrix protein (EMD Millipore Corp). Anti-mouse IgG:FITC conjugate was added to the slide, and incubated at 37°C for 30 min. Slides were then read using a fluorescence microscope. Urines were processed in a similar manner, but the cell pellet was obtained without the addition of HBSS.

Table 1
Comparison of detection of measles virus by SmartCycler® in comparison to LightCycler® 480 system.

		Measles virus RT-PCR on LightCycler® platform		
		Detected	Not detected	Indeterminate
Measles virus RT-PCR on SmartCycler® platform	Detected	35	0	0
	Not detected	0	62	0
	Indeterminate	0	2	1

Table 2
Comparison of detection of detection of measles virus antigen by immunofluorescence (IFA) versus reference LightCycler® RT-PCR.

		Measles virus RT-PCR reference assay		
		Detected	Not detected	Indeterminate
Measles virus antigen detection by IFA	Detected	12	2	0
	Not detected	23	59	1
	Indeterminate	0	3	0

3.7. Measles virus-specific serology

Where available, data on measles virus-specific IgG and IgM detection were collected. Various serology platforms were used, including the WHO LabNet recommended Enzygnost® anti-measles virus IgG and IgM (Siemens, Erlangen, Germany) [13] in our laboratory, and the BioPlex™ 2200 (Biorad, Berkeley, CA, USA) and LIAISON® (DiaSorin, Stillwater, MN, USA) assays in laboratories that referred specimens for IFA and/or NAT.

3.8. Public health unit investigations

In the state of New South Wales (NSW), Australia, measles virus infection is notifiable by doctors and laboratories to the local public health unit. Notified cases were assessed against the national case definition and investigated in accordance with national guidelines [12].

4. Results

4.1. Limit of detection of measles virus and analytical specificity on the SmartCycler RT-PCR

The mean cycle threshold (Ct) values of RNA extracted from the M-M-R II vaccine tested neat, 10^{-1} , 10^{-2} , 10^{-3} and 10^{-4} was 22.7, 26.3, 30.3, 34.3 and 40.9, respectively. For clinical samples tested, the Ct values were noted to be marginally higher on the SmartCycler compared to the LightCycler with a mean difference of 0.89 cycles (range –1.88 to 3.38). No PCR products were obtained when nucleic acid extracts of other non-measles viruses were tested on both the SmartCycler and LightCycler RT-PCR platforms.

4.2. The SmartCycler RT-PCR was concordant with the LightCycler RT-PCR

As shown in Table 1, there was 100% concordance between positive and negative SmartCycler and LightCycler NAT results. However, using the SmartCycler, there were nine indeterminate results, defined as failure to amplify the human β -globin gene (BGL) internal control due to the presence of RT-PCR inhibitors, or insufficient human cellular material. Of these nine specimens, five were also indeterminate using the LightCycler. All of these specimens were urine. Nucleic acid extracts were therefore diluted 1:10 and the assay repeated. This resulted in amplification of the BGL internal control for six of the nine indeterminate samples on the SmartCycler assay, suggesting that the reason for non-amplification for the remaining three samples was insufficient extracted nucleic acid due to inadequate specimen quality. This also resolved four of the

five indeterminate results on the LightCycler assay. Measles antigen was not detected by immunofluorescence in any specimens with indeterminate results, and none of these patients had a clinical syndrome compatible with measles. When the indeterminate results were excluded, the sensitivity and specificity of the SmartCycler compared to the LightCycler RT-PCR were both 100% (Table 1). The mean Ct value for positives on the SmartCycler was 29.6 (range 23.8–40.2).

4.3. Testing urine in addition to NTS or NPA by RT-PCR did not improve laboratory diagnosis of measles infection

There were 14 patients who had both NTS and urine tested; in six of these patients, measles RNA was not detected by NAT in both specimens; in seven patients, measles RNA was detected in both specimens; and in one patient, measles RNA was detected in NTS but not in urine. For seven samples where measles RNA was detected in both samples, the Ct values for NTS were lower than the urine samples (mean Ct difference –4.6, range –16.2 to 2.7), indicating a higher viral burden in the upper respiratory tract specimens.

4.4. Positive RT-PCR results were clinically significant

All patients apart from one patient ($n=27$), with samples that were measles virus RT-PCR positive, had a clinico-epidemiological syndrome compatible with measles (Table 3). The solitary patient where measles virus was detected by RT-PCR but not IFA had exudative tonsillitis. This patient had been vaccinated against measles 93 days prior to NTS collection. Measles virus genotyping demonstrated genotype A, consistent with the vaccine genotype.

4.5. Genotyping supports clinical and epidemiological investigations by public health units

Thirteen samples where measles virus was detected by RT-PCR were genotyped for epidemiological purposes. Genotypes B3 ($n=10$), D8 ($n=2$), and D9 ($n=1$) were identified. Public health investigations identified four distinct epidemiological clusters linking patients where measles virus was detected (Table 3). Outbreak 1 (O1) was associated with an imported case of measles from the Philippines who attended a large music festival during the incubation period. Local secondary transmission to 15 others occurred—eight are reported here. Outbreak 2 (O2) occurred in a family where the index case acquired infection during interstate travel outside NSW. Outbreak 3 (O3) was in a high school group resulting in seven cases, four of which are included here. The single case in Outbreak 4 (O4) was part of a larger cluster in which

Table 3

Clinical and epidemiological characteristics of patients with measles RNA detected by nucleic acid testing.

Case	Age (years, except where otherwise stated)/Sex	Day of collection of specimens after rash onset	Clinical specimen	Measles virus nucleic acid testing (NAT)	Measles virus antigen detection by immunofluorescence (IFA)	Measles virus-specific IgG	Measles virus-specific IgM	Genotype	Clinical criteria met	Epidemiological information	Vaccination status	Outbreak number (O#) or sporadic (S) case
1	19/M	Unknown	NTS	+	–	+	–	B3	Y	Attended music festival	Unknown	O1
2	19/M	0	NTS	+	–	+	–	B3	Y	Attended music festival	Fully vaccinated	O1
3	19/M	1	NTS and U	+	–	+	+	NP	Y	Attended music festival	Unvaccinated	O1
4	21/M	1	NTS	+	–	–	+	NP	Y	Attended music festival	Unvaccinated	O1
5	20/M	0	U	+	–	+	–	B3	Y	Attended music festival	Partially vaccinated	O1
6	18/M	3	U	+	–	NP	NP	NP	Y	Attended music festival	Unknown	O1
7	23/M	1	NTS and U	+	+	–	+	NP	Y	Attended music festival	Unvaccinated	O1
8	20/F	Serum collected on day 3; NTS and U collected on day 4	NTS and U	+	+	–	+	NP	Partial (Fever and rash only)	Attended music festival	Unvaccinated	O1
9	23/F	3	U	+	–	–	+	NP	Y	Infection acquired interstate; index case	Partially vaccinated	O2
10	18/M	1	NTS and U	+	NTS was +; U was –	–	–	B3	Y	Household contact of case 9	Unvaccinated	O2
11	13/M	0	NTS and U	+	–	–	–	B3	Y	High school cluster; index case	Unvaccinated	O3
12	13/F	Serum collected on day 2; NTS collected on day 3	NTS	+	–	+	+	NP	Y	High school cluster, contact of case 11	Unvaccinated	O3
13	30/F	0	U	+	+	–	+	B3	Y	Contact of case 12—attended the same birthday party	Partially vaccinated	O3

Table 3 (Continued)

Case	Age (years, except where otherwise stated)/Sex	Day of collection of specimens after rash onset	Clinical specimen	Measles virus nucleic acid testing (NAT)	Measles virus antigen detection by immunofluorescence (IFA)	Measles virus-specific IgG	Measles virus-specific IgM	Genotype	Clinical criteria met	Epidemiological information	Vaccination status	Outbreak number (O#) or sporadic (S) case
14	2/M	2	NTS	+	–	–	–	B3	Y	Contact of case 13—attended the same birthday party	Fully vaccinated	O3
15	30/F	7	U	+	–	Equivocal	+	D8	Y	Infection acquired interstate; part of a large outbreak	Unknown	O4
16	32/M	1	NTS and U	NTS was +; U was –	–	+	+	B3	Y	Exposed to a measles case at a medical practice	Fully vaccinated	O5
17	1/F	0	NTS	+	–	–	Equivocal	F	Y	Infection acquired overseas; Philippines	Unvaccinated	S
18	8/F	1	U	+	–	–	+	F	Y	Infection acquired overseas; Indonesia	Unvaccinated	S
19	20/F	2	U	+	–	–	+	D8	Y	Infection acquired overseas; United Kingdom	Unknown	S
20	19/M	Serum collected on day 3; NTS and U collected on day 1	NTS and U	+	–	+	+	B3	Y	Infection acquired overseas; Philippines	Fully vaccinated	S
21	20/F	1	NTS and U	+	NTS was +; U was –	–	+	B3	Y	Locally acquired	Unknown	S
22	34/M	2	NTS	+	–	–	+	D9	Y	Locally acquired	Unvaccinated	S
23	15 months/M	Unknown	NTS	+	–	NP	NP	A	N	No epidemiological links	Vaccinated 93 days prior to testing	NR
24	<16/Unknown	Unknown	NTS	+	+	NP	NP	NP	Y	Unknown	Unknown	Unknown
25	<16/Unknown	Unknown	NPA	+	+	–	Equivocal	NP	Y	Unknown	Unknown	Unknown
26	<16/Unknown	Unknown	NPA	+	+	NP	+	NP	Y	Unknown	Unknown	Unknown
27	<16/Unknown	Unknown	NPA	+	+	–	+	NP	Y	Unknown	Unknown	Unknown
28	<16/Unknown	Unknown	NPA	+	+	NP	NP	NP	Y	Unknown	Unknown	Unknown

Note: M—male; F—female; NTS—combined nose and throat swabs; U—urine; +—detected; –—not detected; NP—not performed; F—genotyping failed or unsuccessful due to low viral load or insufficient specimen; Y—yes; N—no; O—outbreak; S—sporadic; NR—not relevant. Where both combined nose and throat swabs and urine specimens are collected in the one patient and, results of testing for NAT and IFA are concordant, results are presented as detected (+) or not detected (–).

acquisition of infection occurred interstate. Genotyping from at least one of the cases from outbreaks O1, O2, O3 and O5 identified the responsible genotype as B3; the genotype of O4 was D8.

In addition to the clusters, six sporadic cases were identified. Four were imported from overseas—two from the Philippines and one each from Indonesia and the United Kingdom. No epidemiological links could be determined in two locally acquired sporadic cases (cases 21 and 22). Where successfully performed, genotypes B3, D8, and D9 were identified in the sporadic cases.

Only laboratory diagnostic data was available on the patients who provided the five archived specimens (Cases 24–28).

4.6. Measles virus antigen detection by immunofluorescence

Results of measles virus detection by IFA are shown in Table 2. An indeterminate IFA result was reported when there was a paucity of cells visualized on the slide. There were 23 specimens (from 20 patients) where measles virus was detected by RT-PCR but not by IFA. The Ct values for these specimens on the reference LightCycler RT-PCR ranged between 23.9 and 40. Measles virus was detected in two specimens by IFA but not by RT-PCR. Neither of these patients was measles virus-specific IgM seropositive, nor did they have clinico-epidemiological features consistent with measles. When the indeterminate results were excluded from analysis, the sensitivity and specificity of IFA versus RT-PCR was 34.3% and 96.7%, respectively. The positive and negative predictive value of IFA was 85.7% and 72%, respectively.

4.7. Measles virus-specific serology

Only 43 out of 86 patients had serology performed, perhaps reflecting the many pediatric patients in this cohort where it is less convenient to obtain a serum sample. Of the 28 patients where measles virus was detected by RT-PCR, 24 had measles virus-specific serology performed (Table 3). Of these, 16 had measles-specific IgM detected, two had an equivocal IgM result, and six were negative. In these six patients where measles-specific IgM was not detected, 5 serum specimens were collected <72 h after rash onset; in one patient, information to determine the timing of the serological test in relation to rash onset was unavailable.

Clinical information was available on all 17 patients where measles virus-specific IgM was detected. Sixteen patients had clinical and epidemiological features consistent with measles infection. The remaining patient was diagnosed with parvovirus infection and had been vaccinated with the first dose of a measles-containing vaccine 3 weeks prior to presentation, likely accounting for IgM detection. No measles RNA was detected by RT-PCR in this patient.

When all these diagnostic modalities were assessed in combination, there were five patients where measles virus was detected by NAT, but who were measles-specific IgM and IFA not detected. Laboratory confirmation of measles infection was missed in four of these patients until this study was performed (Table 3).

5. Discussion

In the present study, the SmartCycler NAT performed comparably with the reference LightCycler RT-PCR to detect measles virus in a range of clinical samples. Additional advantages of the SmartCycler NAT platform include random access and a modest level of training required for usage and interpretation of results.

One patient without clinical measles infection had measles RNA detected by RT-PCR in NTS due to recent vaccination with a measles-containing vaccine. Our diagnostic RT-PCR does not distinguish between wild-type and vaccine measles virus [9]. In a series of 18 immunocompetent and immunocompromised children who were followed after measles virus infection, measles virus RNA was

detected for up to 118 days after rash onset by nested RT-PCR [15]. Given that vaccination with the live attenuated virus simulates natural infection, the prolonged duration of RNA detection in our patient is perhaps unsurprising.

Although only 14 patients in our study had samples collected from multiple sites submitted for testing, our findings would support the use of NTS as the specimen of choice for the diagnosis of measles [11,14,17,20]. Our results also indicate that testing urine in addition to NTS is unnecessary when NAT is used as the diagnostic method. Although some guidelines recommend collection of both NTS and urine to increase diagnostic yield, this may be based on findings from studies that have used methods of lower diagnostic sensitivity than RT-PCR such as cell culture or IFA [2]. In our study, an additional limitation of urine as a diagnostic sample was the presence of RT-PCR inhibitors or insufficient cellular material in this sample type that led to a higher rate of indeterminate results in both RT-PCR assays compared to NTS and NPA.

In contrast to the performance of the SmartCycler NAT, our existing first line assay, the IFA, performed poorly, with both false negative and false positive results. Other authors have also reported a similar poor performance using this assay with test sensitivity reported to be 46.2–54.4% [11]. The poor sensitivity of IFA should preclude its use as a first line diagnostic test to prevent transmission of measles. The use of molecular methods to detect measles virus also facilitates genetic characterization of circulating measles virus strains to inform local and global epidemiology, and determine the success of control strategies [16,17]. Genotypes previously associated with importation into Australia include D4, D5, D8, D9 and H1 but not B3 [11,16].

The major limitation to the routine introduction of RT-PCR as a first line assay is cost. We estimate that the cost for measles RT-PCR is approximately AUD \$65 per sample. Although the cost of measles virus antigen detection by IFA is lower (approximately AUD \$43), we have demonstrated that the lack of sensitivity with this assay will result in cases being missed. In comparison, the cost to public health units for containing a measles outbreak following a single confirmed case was estimated at AUD \$2433 per contact [6]. This excluded the cost of measles-containing vaccine and normal human immunoglobulin. Arguably, the cost of performing measles NAT is offset by the benefits of a rapid and accurate test result that allows for timely public health interventions.

In the present study, the SmartCycler assay was developed using the M–M–R II vaccine as a positive control in the absence of cell cultures. Other investigators have developed RT-PCR assays for the detection of measles virus using synthetic measles virus generated from recombinant plasmids, clinical material or viral culture supernatant [9,10]. Although the vaccine contains both attenuated mumps and rubella virus strains, these viruses are unlikely to have affected the LoD of measles virus as the assay was shown to be measles virus specific when extracts of mumps and rubella viruses were tested.

In conclusion, this study provides compelling reasons for laboratories to use NAT for the detection of measles virus. The accurate diagnosis of measles virus infection is critical in facilitating prompt and appropriate public health responses to prevent further transmission.

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None.

Conflict of interest

None.

Ethical approval

The investigation of individual cases of measles infection was conducted as part of public health investigations of suspected or confirmed cases of measles notified under the legal authority conferred by the New South Wales Public Health Act 2010. Research ethics approval was not required.

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Appendix 4: Factsheets on *Blastocystis hominis* and *Dientamoeba fragilis* – as published on the NSW Health website

Factsheet *Blastocystis hominis*

What is *Blastocystis hominis*?

Blastocystis hominis is a species of one of the most common human intestinal parasites. *Blastocystis* species are found throughout the world and higher numbers are reported in developing countries. *Blastocystis* has also been found in a wide range of animals including mammals, birds and amphibians.

What are the symptoms?

Many people infected with *Blastocystis hominis* have no symptoms at all. However, in those that do report symptoms, the most common ones are diarrhoea, abdominal pain and vomiting. Other reported symptoms are anal itching, weight loss, constipation and excess gas.

How is it spread?

It's not certain how *Blastocystis* is spread. Higher rates of infection have been reported in areas of poor sanitation. Given that the organism is found in the gastrointestinal tract, transmission is most likely to occur via the faecal-oral route. This means that infection might occur if you bring something to your mouth that has touched the stool of a person infected with *Blastocystis* or if you swallow food or water contaminated with the organism.

Who is at risk?

Blastocystis is found in the intestines of many people, some without ever having symptoms.

There is still debate about whether *Blastocystis* species really causes disease in humans, as the parasite can be found in both well and unwell individuals. New research suggests that some types of *Blastocystis* may be more likely to be associated with symptoms.

Some studies have shown that people with poor immune systems have higher rates of *Blastocystis* infection. People who travel to areas of poor sanitary condition are also more likely to be infected.

How is it prevented?

As *Blastocystis* infections seem to be more common in places with poor sanitation, it is important to practice good hand hygiene, especially after using the toilet and before handling food.

Some general precautionary measures that should be taken are:

- Wash hands thoroughly using soap for at least 10 seconds and dry them with a clean towel after using the toilet, before preparing food and after handling nappies.
- Avoid food or water that may be contaminated by sewage
- Wash and peel all raw vegetables and fruits before eating
- When traveling in countries where the water supply may be unsafe, avoid drinking unboiled tap water.

How is it diagnosed?

Diagnosis is based on symptoms and on finding the *Blastocystis* parasite from a stool sample.

How is it treated?

Due to the uncertainty of whether this parasite is a pathogen or not, it is difficult for doctors to decide whether to treat the infection.

There are medications available to treat *Blastocystis* infections. However, these are not always effective and it may be necessary for the doctor to look for other possible causes of a patient's symptoms.

What is the public health response?

Blastocystis hominis is not a notifiable condition in New South Wales and there is no public health response for individual infections.

Factsheet *Dientamoeba fragilis*

What is *Dientamoeba fragilis*?

Dientamoeba fragilis is a parasite that is commonly found in the gastrointestinal tract of humans. It is found in human populations around the world and is increasingly recognised as a parasite with the potential to cause illness in humans.

What are the symptoms?

Many people who are infected with *Dientamoeba fragilis* do not have any symptoms. In those that do show symptoms, these include loose stools, diarrhea and abdominal pain. Other reported symptoms are weight loss, loss of appetite, nausea and fatigue.

How is it spread?

The way *Dientamoeba fragilis* is spread is not yet clear. Given that the parasite is found in the gastrointestinal tract, transmission is most likely to occur via the fecal-oral route. This means that infection might occur if you bring something to your mouth that has touched the stool of a person infected with *Dientamoeba fragilis* or if you swallow food or water contaminated with the parasite.

Who is at risk?

Dientamoeba fragilis is found in the intestines of many people, some without ever having symptoms. People who travel to regions with poor sanitation are at higher risk of infection.

How is it prevented?

As infections seem to be more common in places with poor sanitation, it is important to practice good hand hygiene, especially after using the toilet and before handling food.

Some general precautionary measures that should be taken are:

- Wash hands thoroughly using soap for at least 10 seconds and dry them with a clean towel after using the toilet, before preparing food and after handling nappies
- Avoid food or water that may be contaminated by sewage
- Wash and peel all raw vegetables and fruits before eating
- When traveling in countries where the water supply may be unsafe, avoid drinking unboiled tap water.

How is it diagnosed?

Diagnosis of a *Dientamoeba fragilis* infection is based on symptoms and on finding the parasite from one or more stool samples.

How is it treated?

There are medications available to treat *Dientamoeba fragilis* infections. However, these are not always effective and it may be necessary for the doctor to look for other possible causes of a patient's symptoms.

What is the public health response?

Dientamoeba fragilis is not a notifiable condition in New South Wales and there is no public health response for individual infections.

Chapter 2:

Establishing a register for Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

“It is important that government resources for surveillance are not wasted on infections or diseases that are unimportant from a public health perspective.”

- Anonymous

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Abbreviations

ACI	Agency for Clinical Innovation
AHMRC	Aboriginal Health and Medical Research Council
APDC	Admitted Patient Data Collection
APSU	Australian Paediatric Surveillance Unit
ARF	Acute Rheumatic Fever
CDC	Centre for Disease Control and Prevention
CDNA	Communicable Diseases Network Australia
CHeReL	Centre for Health Record Linkage
EOC	Episode of Care
GAS	Group A <i>Streptococcus</i>
ICD-10 AM	International Classification of Diseases, 10 th edition, Australian Modified
LHD	Local Health District
NCIMS	Notifiable Conditions Information Management System
NSW	New South Wales
NT	Northern Territory
PHU	Public Health Unit
RHD	Rheumatic Heart Disease
SA	South Australia
WA	Western Australia
WHO	World Health Organization

Chapter Prelude

My role

Being involved in the establishment of a register for Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) in New South Wales (NSW) has been one of the highlights of my time at NSW Health. Having trained as a medical doctor in Auckland, New Zealand, I was always taught to consider the diagnosis of ARF in young adults, especially in Maori and Pacific Islander populations, as they have particularly high rates of disease. After completing my training, I worked in some of the Aboriginal communities around Alice Springs and with the Cardiology service at Royal Darwin Hospital. Here, I witnessed first-hand acute presentations of ARF and the severe and completely preventable complications of RHD. What struck me at that time was that these conditions affected Aboriginal and Torres Strait Islander youth at a prime time in their lives, with medical ramifications that could last them a lifetime and potentially lead to their lives being significantly shortened. What I also observed was the cost to the health system of treating a single case of ARF or RHD in hospital. Therefore, when I was given the opportunity to be involved in setting up a register for these conditions in NSW, it was a task that I was keen to take on.

Public health officer trainees had previously worked on this project and in particular had attempted to quantify the burden of disease of ARF and RHD in NSW using linked hospitalisation data. However, the results that were obtained were inconsistent with what is generally known about ARF. I re-examined this data, and with the immense help of a biostatistician, we were able to validate some of these results and use them to communicate to stakeholders.

The next task was to understand how existing register-based systems worked in other states and territories. I talked to RHD Coordinators in the Northern Territory, Western Australia, South Australia and Queensland to understand how their systems worked. I also spoke with the commonwealth-funded coordinating body for ARF and RHD in Australia - RHD Australia. I then scoped out the local situation by talking to stakeholders in NSW. I had discussions with general practitioners, cardiologists, infectious disease specialists, and government authorities such as the Agency for Clinical Innovation and the Office of the Chief Health Officer. I also undertook 'field trips'

to visit the director of the Australian Paediatric Surveillance Unit, the principal investigator of the 'RHD in pregnancy' study and a leading cardiologist at Prince of Wales Hospital. By doing this, I developed a better sense of what a surveillance system for ARF and RHD in NSW might look like and importantly, it was reassuring to know that stakeholders were interested and motivated to tackle these conditions in NSW.

I then drafted a document that outlined the problem and in collaboration with others at the Communicable Diseases Branch (CDB), came up with a plan for how the diagnosis, notification and follow up of people with ARF and RHD might work in NSW. We presented this plan to the NSW Chief Health Officer and once approved, it was circulated among the chief executives of the local health districts and public health units for comment. I also drafted a document outlining reasons for why ARF and RHD should be made notifiable in NSW for the Legal Branch to work with.

I investigated funding sources for the register through the Commonwealth and RHD Australia. After funding was secured for a coordinator position in NSW Health, I helped to write the job description for the RHD Coordinator.

After the Coordinator came on board, I played a much lesser role. However, I still attended fortnightly meetings and drafted a patient consent form, helped with the preparation of factsheets and control guidelines for use by public health units. I also attended jurisdictional teleconference meetings organised by RHD Australia and was on a national panel established by Telethon Kids Institute in Perth to estimate the burden of RHD in Australia using data linkage.

I presented the proposed system at a meeting for general practitioners of Aboriginal Medical Services, which was organised by the Aboriginal Health and Medical Research Council (AHMRC). I also presented on ARF and RHD at the monthly infectious diseases forum at the NSW Ministry of Health – Bug Breakfast.

Lessons learned

The lessons learned in the process of setting up this system have been many. One of the most important ones is that in order to create long term and sustainable policy changes, there need to be individuals with 'high influence' to push for change and individuals with 'high interest' concerned enough about the issue at hand to make the change happen. Examples of this with regard to ARF and RHD are its inclusion as a priority area in the '*Better Cardiac Care for Aboriginal and Torres Strait Islander people*' – an initiative of the Australian Health Ministers Advisory Council which has been endorsed by the Australian Health Protection Principal Committee and for which the NSW Chief Health Officer is the chair. By having this level of political will and interest in addressing the discrepancy in morbidity and mortality caused by cardiovascular disease between Aboriginal and Torres Strait Islander and non-Aboriginal and Torres Strait Islander people, ARF and RHD have been brought to the attention of policy-makers minds. To illustrate this point even further, in my discussions with clinicians, I came across some who had been championing this cause for years but despite their 'high interest', their 'low influence' meant that change was not so easy to make happen.

Another key lesson I learned was the importance of having burden of disease data to justify the need for establishing a system. Data is a major driving force behind policy-making and also provides a valuable tool to communicate with stakeholders. Knowing how big or small a problem is helps to allocate resources accordingly and gets people interested.

I also learned of the importance of consultation with various stakeholders and how iterative the process can be. Different people will have different agendas and priorities so I learned that it was important to make each person feel heard and understood before coming to a compromise that best fit with the overall objectives of the system. I also learned that in a government system progress can take time. Flexibility and ongoing discussions are essential to the consultative process.

Public health implications

Having a register for ARF and RHD will inevitably have an impact on the way these conditions are managed in NSW. A register will allow information to be collected on all patients notified with these conditions. It will give clinicians and public health staff an additional resource to better follow up patients diagnosed with these conditions.

Better management of individuals with ARF and RHD will help in preventing recurrent cases of ARF and halt the progression of RHD, which will play some part in reducing the gap in cardiovascular-related morbidity and mortality between Aboriginal and Torres Strait Islander people and non-Aboriginal and Torres Strait Islander people.

As surveillance can directly measure the health status of individuals and the behaviour of a population, a well-functioning register will allow public health professionals and stakeholders to have a better understanding of the epidemiology of ARF and RHD in NSW. It will prove useful in assessing the true burden of disease in an area where these conditions have been thought to be rare.

ARF and RHD in individuals under 35 years were made notifiable conditions in NSW in October 2015. While ARF is notifiable or in the process of being made notifiable in other states and territories where register programs exist, RHD is not. Having RHD made a notifiable condition in NSW may set a precedent for other states and territories to follow. At the *'Better Cardiac Care for Aboriginal people'* forum in Sydney in March 2014 – a meeting attended by policy makers, clinicians, public health professionals and others from around the country, there was a strong push for national notification of ARF and RHD. The experience in NSW can help guide the direction of other states on this matter.

Abstract

Background

Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) are conditions of public health importance in Australia. Register data from the Northern Territory, Western Australia and Queensland indicate that these parts of Australia have some of the highest global incidence rates of ARF and prevalence rates of RHD and that Aboriginal and Torres Strait Islander people are disproportionately affected. In New South Wales (NSW), the epidemiology of ARF and RHD remains largely unknown, despite having the largest population of Aboriginal and Torres Strait Islander people in Australia. The progression of ARF into RHD is largely preventable through the monthly administration of a penicillin injection. One of the most cost-efficient methods for organising care around prophylaxis is a register-based control program. We aimed to estimate the number of individuals hospitalised with ARF in NSW. We used the data gathered to inform the establishment of a register-based control program for ARF and RHD in NSW.

Methods

We used the NSW Admitted Patient Data Collection to analyse hospital separations in NSW residents between 2003 and 2012. We limited our search to primary diagnoses of ARF using ICD10-AM codes I00 – I02. In establishing the register-based control program, we engaged with key stakeholders, investigated resources required to operate the system, determined the most appropriate method for flow of information and legal authority for data collection, outlined case definitions to be used and evaluated the necessary attributes of the system.

Results

Between 2003 and 2012, there were 238 hospital admissions with ARF as a primary diagnosis, an average of 24 per year, at a rate of 0.3 per 100, 000 population per year. The highest number of hospitalisations was in the 10 to 14 year old age group with 61 cases over the year 10 year period - an age-specific rate of 13.6 per 100, 000 over the 10 year period. Almost one third (33%; 51 of 155)

of ARF diagnoses were made in Aboriginal and Torres Strait Islander people under the age of 30. Local health districts with the most number of ARF cases were Western Sydney with 40 (17%), Southwest Sydney with 37 (16%) and Hunter New England with 34 (14%). Local health districts with the highest age-standardised hospitalisation rates for ARF in five to 14 years old children were Far West (350 per 100, 000 over 10 years), Western NSW (208 per 100, 000 over 10 years) and Northern NSW (116 per 100, 000 over 10 years). Interviews with stakeholders resulted in the development of a system for notification that involved clinicians, public health units, a local health district coordinator and a rheumatic heart disease coordinator. Acute rheumatic fever and rheumatic heart disease in individuals under 35 years of age were made notifiable conditions in NSW in October 2015.

Conclusion

While the rate of hospital admissions for ARF in NSW is not large, cases of ARF do occur in NSW. Children aged five to 14 years and local health districts with higher proportions of Aboriginal and Torres Strait Islander people are most affected. To address these conditions, a register-based control program for ARF and RHD in individuals under the age of 35 years has been established in NSW following an extensive consultation process.

Background

Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) are conditions which have largely been eliminated from many industrialised countries around the world. However, in Australia, these disease entities continue to be important clinical and public health problems (1). Some of the highest global rates of ARF incidence and RHD prevalence are recorded in parts of Australia where they cause significant morbidity, potentially preventable hospitalisations and death in the paediatric and young adult population (1) (2). In addition, these conditions disproportionately affect Indigenous Australians and migrant groups from high-prevalence countries, leading to an issue of equity in healthcare access and outcomes (3) (4).

1) Clinical Manifestations of Acute Rheumatic Fever and Rheumatic Heart Disease

Acute Rheumatic Fever is an immune mediated response to an untreated bacterial infection of the throat and possibly the skin, caused by the bacterium Group A *Streptococcus* (GAS). Group A *Streptococcus* infections account for up to 30% of throat infections in children and young adults (1). If left untreated, the risk of developing ARF in these individuals is between 0.3-3%, depending on the endemicity of the bacterium in the affected community (5) (6). Individuals who have had one episode of ARF are much more likely than the wider community to have subsequent episodes of ARF (1).

The clinical presentation of ARF is characterised by an acute, generalised inflammatory response which affects certain parts of the body including the heart, joints, brain and skin. Individuals with ARF are often severely unwell and require hospitalisation (1, 2, 7). In Australia, the diagnosis of ARF is based on the modified Jones criteria which has been adapted from the original diagnostic criteria to increase sensitivity in high risk populations (1). These criteria ask that clinicians consider numerous clinical signs, blood tests and electrocardiographic changes to make the diagnosis of ARF (Appendix 1).

Although ARF results in no lasting damage to the brain, joints or skin, the most devastating result of recurrent ARF is the cumulative damage caused to the heart valves (1). Chronic inflammation of the heart valves as a sequelae of recurrent episodes of ARF is known as Rheumatic Heart Disease (1). It is estimated that approximately 60% of people with ARF will subsequently develop RHD, the risk being greater in individuals where carditis (i.e. inflammation of the heart valves) was a clinical feature of their ARF episode (1) (8). A diagnosis of RHD is based on echocardiographic evidence of rheumatic heart valve lesions, therefore requiring access to specialist radiology and cardiology services (9).

The permanent damage caused to one or more of the four heart valves in RHD manifests as valvular stenosis or regurgitation. As valvular disease progresses, secondary health complications such as congestive heart failure, infective endocarditis and atrial fibrillation can ensue (10). These conditions often necessitate the need for more advanced cardiac care such as heart valve surgery (1). In addition, women with RHD are at an increased risk of complications during pregnancy and labour due to the natural physiological changes that occur during pregnancy (1) .

2) Global Epidemiology of Acute Rheumatic Fever and Rheumatic Heart Disease

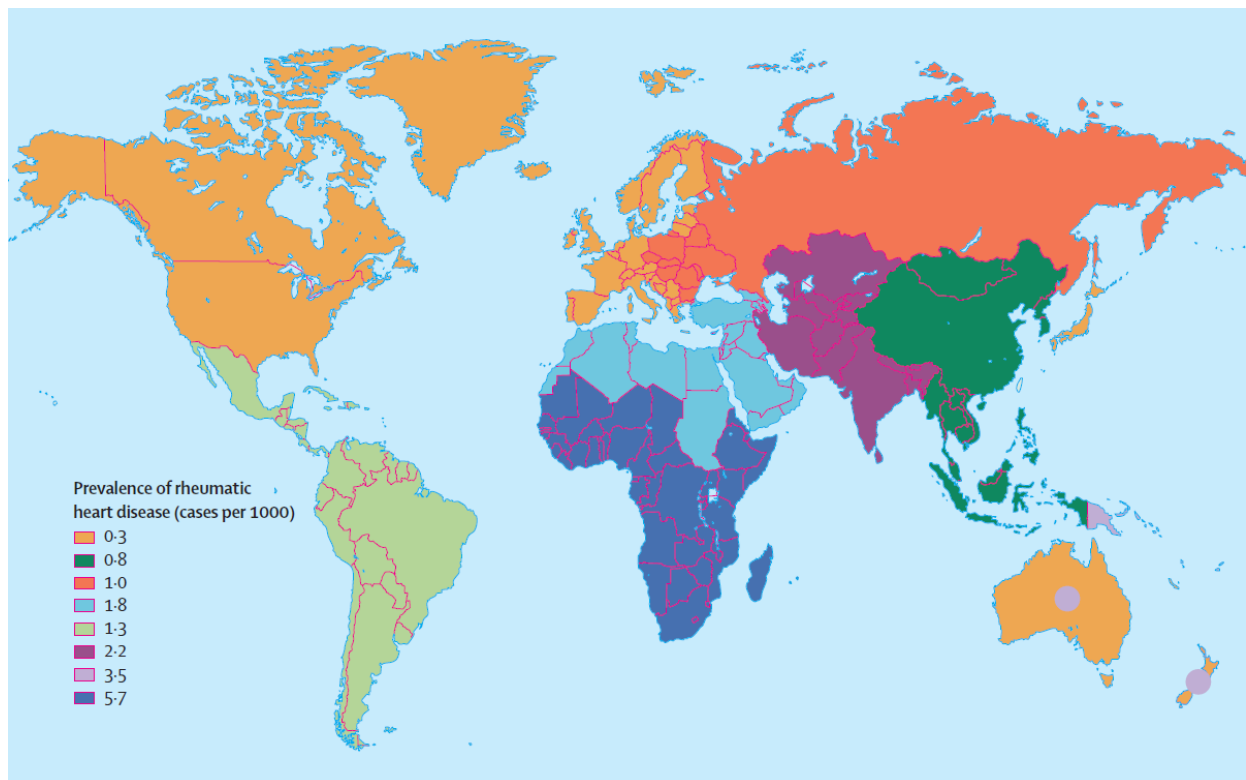
According to the World Health Organization (WHO), at least 15·6 million people worldwide have RHD and 233, 000 deaths annually are directly attributable to ARF or RHD (4) . It is estimated that more than 75% of RHD occurs in resource-poor countries where a prevalence rate between 2.5 to 3.2 cases per 1000 population exists (4). In these settings, RHD is a leading cause of paediatric mortality (2) (4) (7). The estimated prevalence of RHD in children aged 5–14 years is highest in sub-Saharan Africa (5·7 cases per 1000 population), the Pacific and Indigenous populations of Australia and New Zealand (3·5 cases per 1000 population), and south-central Asia (2·2 cases per 1000 population) (4)(Figure 1).

In more developed countries, many clinicians may never have seen a patient with ARF or RHD. The burden of these two conditions has declined dramatically in developed countries over the 20th century largely due to the reduced transmission of the Group A *Streptococcus* bacterium (1) . In Australia, the age-standardised mortality rate from chronic RHD fell from 56·4 per 100, 000 persons in 1931 to 1·2 per 100, 000 persons in 2000 (11). Improvements in living conditions, increased

hygiene standards, better access to primary and secondary health care services and an increased availability of penicillin antibiotics have contributed to this decline (1).

Figure 1: Prevalence of rheumatic heart disease in children aged 5 – 14 years #

(The circles within Australia and New Zealand represent indigenous populations, and also Pacific Islanders in New Zealand).



3) Epidemiology of Acute Rheumatic Fever and Rheumatic Heart Disease in Australia

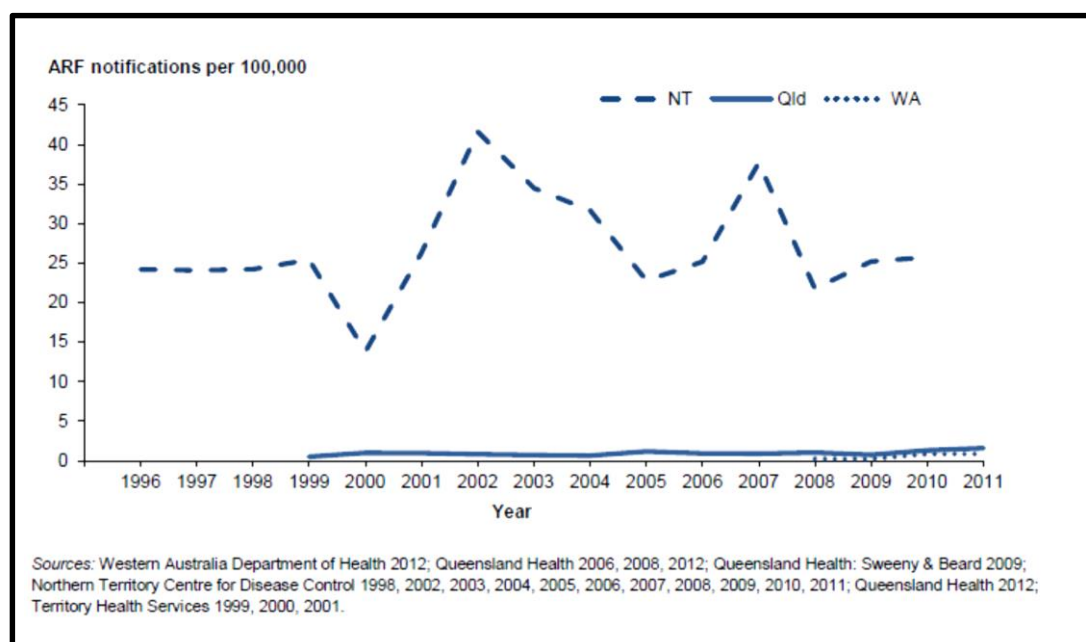
Our understanding of the burden of disease of ARF and RHD in Australia is gathered largely from jurisdictions where surveillance systems have been established at various points in time. Acute Rheumatic Fever became notifiable and a register-based control program set up in the Northern Territory (NT) in 1994, in Queensland in 1999 and in Western Australia (WA) in 2007 (1). Although a control program exists in South Australia (SA), ARF is not currently notifiable in this state (personal

Adapted from Carapetis, J.R., et al., *The global burden of group A streptococcal diseases*. The Lancet Infectious Diseases, 2005. 5(11): p. 685-694.

communication, RHD Coordinator, South Australia). Prior to the establishment of the register-based program in NSW, RHD was not a notifiable condition anywhere in Australia (1).

Notification rates for ARF vary considerably around the country. The highest reported rates are in the NT with an average of 26 notifications per 100, 000 population per year (over a 15 year period), to 1.0 notification per 100,000 population per year in Queensland and an average of 0.6 notifications per 100,000 population per year in WA (Figure 2) (12) . Data from these regions reveal that notifications of ARF are highest in the 5-14 year old age group and it is rarely reported in children under 5 years or adults over 40 years of age (1, 2).

Figure 2: Acute Rheumatic Fever notifications in the Northern Territory, Queensland and Western Australia, 1996 – 2011 #



Although there is a pre-dominance in the early years of life, recurrent episodes of ARF may continue well into the fourth decade of life. Since RHD represents the cumulative damage to the heart of previous ARF episodes, the prevalence of RHD peaks in the third and fourth decade of life and

Adapted from Australian Institute of Health and Welfare. *Rheumatic heart disease and acute rheumatic fever in Australia: 1996-2012* 2013 [cited 2015 September]; Available from: <http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129542747>.

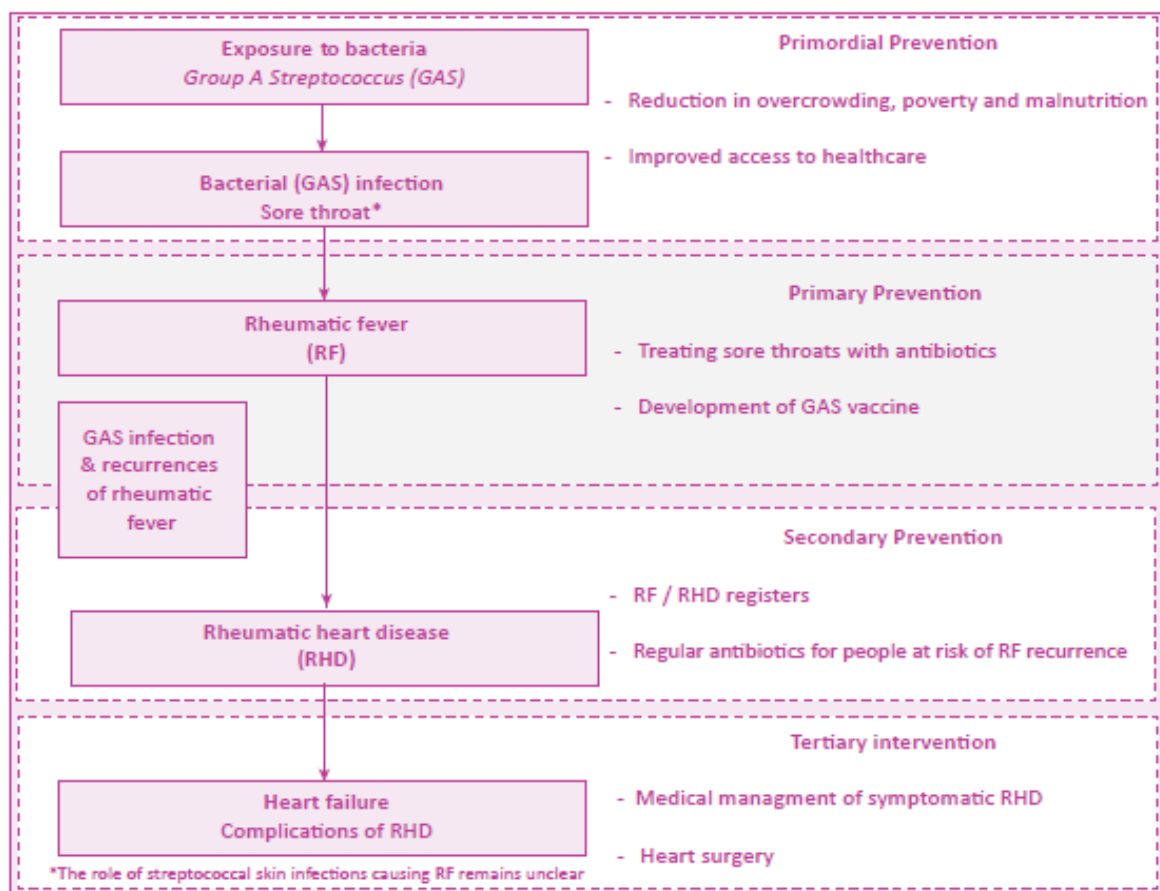
increases with age (1, 10). Register data from the NT suggests that the age-standardised prevalence rate for RHD has been increasing over time (12). In 2004, the rate was 555 cases per 100,000 population and in 2010 this increased by 17% to 647 cases per 100,000 population (12). This increase is thought to reflect improved diagnosis and data collection rather than a true rise in the prevalence of disease (12). In Queensland there were 939 patients with RHD on the register by August 2012, and 158 on the WA register as of June 2011 (12). The prevalence of RHD is highest in individuals aged 35-39 years in all three jurisdictions (1).

There is currently very little known about the epidemiology of ARF and RHD in NSW. The few published studies that have reported on cases of ARF in NSW have been when ARF was made a notifiable condition through the Australian Paediatric Surveillance Unit (APSU). The APSU is a surveillance system established by paediatricians to monitor rare childhood conditions (13). It relies on paediatricians from around the country returning a questionnaire with information on a range of rare notifiable conditions, pre-determined by the APSU. An APSU surveillance report in 2009 documented nine notifications of ARF in NSW between October 2007 and December 2008 (14) and 18 notifications between 1 October 2007 and 31 December 2010 (13). A further retrospective review of medical records at the Children's Hospital Westmead in Sydney between 1 January 2000 and 30 December 2008 identified 26 children under the age of 15 years who met the diagnostic criteria for ARF (15). These data suggest that while case numbers of ARF are relatively low in the state, cases do occur.

4) Approaches to prevention of Acute Rheumatic Fever and Rheumatic Heart Disease

Prevention of ARF and RHD can occur at multiple levels and interventions can be implemented at each of these stages (Figure 3) (8).

Figure 3: Causal pathway of Acute Rheumatic Fever and Rheumatic Heart Disease and possible levels of prevention ⁵



The primordial level of prevention takes into account the broad social, economic, behavioural and environmental factors that are known to increase GAS infections (1). The main risk factors described in the literature are those pertaining to socio-economic disadvantage and relative poverty (16, 17). Living in overcrowded housing with limited infrastructure to maintain hygiene, poor nutrition and lower levels of education are often cited as being the predominant drivers of ARF and RHD (1, 16,

⁵ Adapted from Wyber, R., et al., *Tools for Implementing RHD Control Programmes, Quick TIPS Summary*. World Heart Federation and RhEACH. 2014: Perth, Australia.

17). However, there is a lack of evidence currently to support specific environmental or social interventions to address the acquisition of risk factors for ARF and RHD (1).

Primary prevention refers to the reduction in transmission, acquisition and colonisation of GAS infections to prevent the development of ARF (1). These measures should be targeted at populations at elevated risk for ARF and include using protocols such as empirical antibiotic use for the management of pharyngitis. However, the current evidence does not advocate for the administration of antibiotic prophylaxis to reduce GAS pharyngeal colonisation. The Australian guidelines for prevention, diagnosis and management of ARF and RHD do suggest that “in high-risk populations where clinical follow up may be difficult, empirical management of pharyngitis with antibiotics in those at greatest risk of ARF may be warranted.” However, they go on to say that “focused programs of early GAS pharyngitis diagnosis and management in populations at high risk of ARF have not yet been shown to translate to a significant reduction in ARF incidence” (1). A GAS vaccine would offer a longer-term solution, however this is currently not available (1).

Secondary prevention refers to the early detection of disease and implementation of measures to prevent recurrent and worsening disease. The regular administration of a 28-day intramuscular antibiotic (Benzathine Penicillin G) to prevent recurrent episodes of ARF remains the mainstay of prevention against the development of RHD (1, 4, 10, 18). The duration of prophylaxis is set at a minimum of 10 years or until age 21 (whichever is longer) in all individuals with ARF or RHD. It can be up to age 35 or 40 or lifelong in individuals with moderate to severe RHD (1). Secondary prophylaxis has been shown to significantly reduce the recurrence of ARF, reduce the severity of RHD, is associated with the regression of heart disease in more than half of those with adequate adherence over a decade and is shown to reduce mortality (1, 4, 10).

A register-based control program has existed in New Zealand since the 1980s (1). This program has been attributed to successfully reducing the recurrence rate of ARF from 22% between 1972 and 1981 to only 6% between 1982 and 1992 (19). Australia’s first register-based control program was established in 1997 in Darwin in the Northern Territory (1). In the first 2 years, there was a decline in the recurrence rate from 40% (prior to commencement) to 28% in the first year and 16% in the second year (20).

Tertiary prevention refers to interventions for individuals with RHD that aim to reduce symptoms and disability and prevent premature death (1). This includes hospitalisation and subsequent care, including valvular heart surgery where indicated. This is considered the least cost-effective approach from a public health perspective (18).

5) Establishing a register-based control program for Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

5.1 Context for establishing a register-based control program in New South Wales

A number of clinicians in NSW, particularly cardiologists, had been advocating for a register-based control program for ARF and RHD for a number of years. Given that follow up of patients with these conditions would require strong clinical input that is typically beyond the remit of public health agencies, it was not clear where a control program would best be placed within the NSW Ministry of Health structure. Nevertheless, Health Protection NSW had been having ongoing discussions with the Agency for Clinical Innovation – a NSW Health government organisation responsible for improving the “quality, effectiveness and efficiency” [18] of healthcare services regarding the establishment of a register.

There were also previous discussions as to whether a register-based control program was the best type of system for following up patients with these chronic conditions. Several stakeholders identified that patients with RHD may have other concurrent chronic conditions such as diabetes, hypertension or ischaemic heart disease. In children, ARF may occur in those who are known to be late with their immunisations, children with recurrent skin sores, chronic respiratory conditions and other health issues. Therefore, it was thought that a registry as a stand-alone system for following up complex patients with multiple co-morbidities may not provide the optimal systems solution.

However, further clout was added to the discussion when the Australian Health Minister’s Advisory Council (AHMAC) set out to identify national priorities for action to improve cardiac outcomes for Aboriginal and Torres Strait Islander people. This was in response to a report – the *2012 Aboriginal and Torres Strait Islander Health Performance Framework Report* – which showed that between 2006 and 2010, cardiovascular disease was the leading cause of death among Aboriginal and Torres Strait Islander people, with a mortality rate 1.7 times that of non-Indigenous Australians (21).

Cardiovascular disease was also the leading contributor to the gap in overall mortality rate (27%) and the leading cause of avoidable mortality (21).

Representatives from the Commonwealth and state and territory governments met in Sydney in March 2014 in a forum called the '*Better Cardiac Care for Aboriginal and Torres Strait Islander People*' to identify five priority areas for intervention to improve cardiac outcomes for Aboriginal and Torres Strait Islander people (22). One of these was to "strengthen the diagnosis, notification and follow-up of rheumatic heart disease". In addressing this priority area, one of the recommendations was that new cases are reported to a central register to facilitate tracking of patients and ensure ongoing care (22).

Given the momentum and political will garnered by the *Better Cardiac Care for Aboriginal and Torres Strait Islander People* forum and the likely need for notification of ARF and RHD in the state, it was decided that Health Protection NSW should take the lead in establishing a register-based control program for ARF and RHD in NSW.

5.2 Objectives of a register-based control program for Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

The objectives of a register-based control program for ARF and RHD in NSW, in keeping with the World Health Organization and the Rheumatic Heart Disease Australia (RHDA) guidelines, are to reduce the morbidity and mortality associated with RHD by:

- Identifying and registering new cases of ARF and RHD
- Improving the uptake of and adherence to secondary prophylaxis
- Increasing awareness of the diagnosis and management of ARF and RHD among healthcare providers, particularly those working with populations at high risk
- Improving clinical care and follow up in line with best practice
- Supporting health staff to provide education and support to patients, including education of the wider community
- Using data to monitor patient outcomes and improve program strategies.

5.3 Understanding the burden of disease of Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

In establishing a control program for ARF and RHD in NSW, it was important for us to understand the burden of disease of these conditions to justify its need for surveillance and to allocate resources appropriately. Burden of disease data also provides a valuable tool when communicating with stakeholders.

Given the scant evidence available on the incidence of ARF and the prevalence of RHD in NSW, we sought to draw estimates of these conditions in NSW through hospitalisation records. Hospitalisation statistics do not provide a measure of prevalence or incidence of a disease, but can provide valuable insights into the health of the population who use hospitals, through data on the number of, and reasons for, hospitalisation (11).

In NSW, the Admitted Patient Data Collection (APDC) records all inpatient separations (discharges, transfers and deaths) from all public, private, psychiatric and repatriation hospitals in NSW as well as public multi-purpose services, private day procedure centres and public nursing homes (23). It includes approximately 320 facilities. Information in this collection dates back to June 2000.

Data in the APDC are recorded by episodes of care (EOC). An episode of care ends when the patient is discharged home, transferred to another hospital or ward or has died (24). Therefore, one admission can create several episodes of care. Each EOC is coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) (25). Each EOC requires a principal diagnosis – that is, the main reason for the patient's episode of hospital care (11). In the APDC an additional 54 secondary diagnoses are possible. These secondary diagnoses may be other conditions that the patient was treated for in the currently admitted EOC or they may be pre-existing comorbidities.

NSW Health also has a Centre for Health Record Linkage (CHeReL) which allows hospital episodes of care to be linked to an individual patient. The CHeReL uses probabilistic matching of demographic details and assigns unique patient identifiers to an individual. In doing this, multiple episodes of care for a single hospital admission can be linked to an individual patient.

6) Organisation of this chapter

The methods and results in this chapter are divided into two parts to address two main objectives that we had in establishing the register-based control program in NSW:

- 1) To determine the rate of hospitalisation for ARF in NSW residents
- 2) To establish a surveillance and follow-up system for patients diagnosed with ARF and RHD in NSW

In detailing the methods for the establishment of a surveillance and follow-up system, I have followed the steps outlined in the United States Centre for Disease Control and Prevention (CDC) *Updated Guidelines for Evaluating Public Health Surveillance Systems (26)*. These guidelines are not only relevant for evaluating surveillance systems, they also apply to the establishment of a surveillance system. The steps outlined in this CDC document include engaging with stakeholders involved in the system, describing the resources used to operate the system, describing the case definitions to be used, describing the flow of information and data to be collected, establishing a legal authority for data collection and describing the system attributes.

Methods

Part 1: Hospitalisation rates for Acute Rheumatic Fever in New South Wales

1.1 Review of the New South Wales Admitted Patient Data Collection

We reviewed incident cases of ARF in the NSW APDC. An incident case was defined as the first known admission to hospital for ARF for the 10-year period from 2003 to 2012. Such cases had ARF as an ICD-10AM code I00 – I02 recorded as their principal diagnosis (Appendix 2). The year assigned to a case was based on the date of admission. All non-NSW residents were excluded.

This dataset included information on country of birth and Aboriginal and Torres Strait Islander status. Individuals whose Aboriginal or Torres Strait Islander status was classified as 'unknown' in the APDC was excluded from the analysis. New South Wales Health have taken steps to improve reporting of Aboriginal and Torres Strait Islander status in their by using an algorithm using record linkage to enhance reporting of Aboriginal status (23). Using the algorithm as the standard, the level of reporting of Aboriginal and Torres Strait Islander status in the Admitted Patient Data Collection was found to be 86% (23). The level of reporting was found to vary markedly between hospitals and local health districts.

1.2 Population Data

Population data were obtained from the 2011 Australian Bureau of Statistics census of population (27). To calculate average age-specific rates for the period 2003 to 2012, we averaged population numbers between 2003 and 2012 and this was used as the denominator population. Age-standardised rates by local health district were calculated using the direct method and we averaged local health district population numbers between 2006 and 2012 to obtain the denominator population.

1.3 Validating the results

To validate the results we obtained, we compared our data to available data on ARF in NSW in the published literature.

Part 2: Establishing a surveillance and follow-up system for patients with Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

2.1 Engaging stakeholders involved in the system

Stakeholders with an interest in the establishment of a system for ARF and RHD and their role(s) are described in Table 1.

Table 1: Key stakeholders and their involvement in a register-based control program for Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

Stakeholder	Involvement in care of patients with acute rheumatic fever and rheumatic heart disease
Clinicians including paediatricians, general practitioners, cardiologists, infectious disease specialists, cardiac surgeons	- Making the diagnosis of ARF and RHD - First source of information in the notification process - Clinical management and follow up according to best practice guidelines - Patient education
Aboriginal Medical Services	- Possible high case load - Making the diagnosis of ARF and RHD - Involvement in the notification process - Clinical management and follow up according to best practice guidelines - Patient education, family and community engagement
Public Health Units	- Point of contact for clinicians - Receipt of notifications - Verification of diagnosis before details are passed on to the registry

National Heart Foundation	- Provide best practice guidelines for the management of ARF and RHD - Advocacy in addressing healthcare gaps in vulnerable populations
Rheumatic Heart Disease Australia and other state register programs	- Advice and information on operational aspects of register-programs - Collaboration and information sharing between registry Coordinators
Data managers/administrative staff	- Management of data systems - Record keeping - Analysis and interpretation of data

We conducted one-on-one interviews with clinicians (including general practitioners, adult and paediatric cardiologists and infectious disease specialists) and other key stakeholders using non-standardized questionnaires, in order to:

- Gain an appreciation of their current patient load
- Understand processes currently in place for patients diagnosed with ARF and RHD, especially regarding the delivery of secondary prophylaxis
- Discuss possibilities for information flow
- Discuss potential barriers to uptake of the system
- Explore perceived effectiveness of a register-based program in NSW

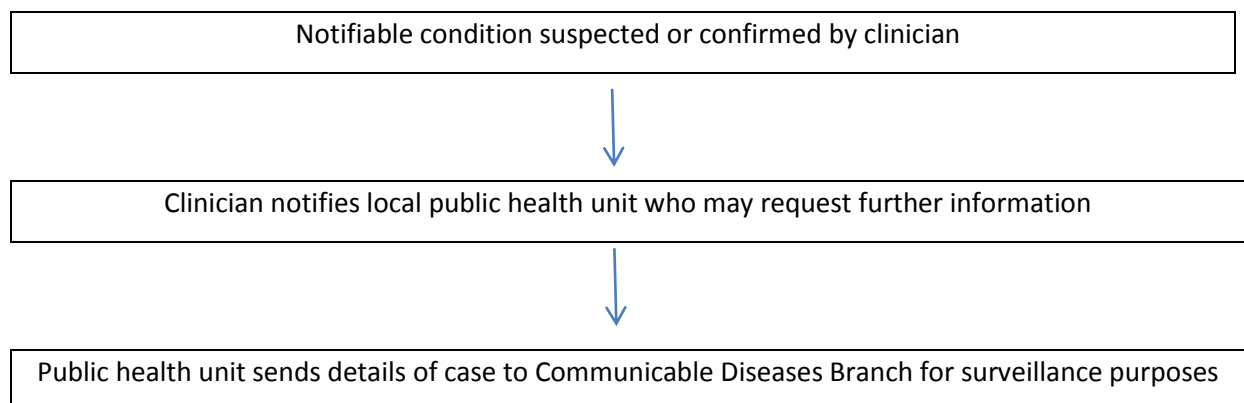
2.2 Case definitions

We consulted with RHD Coordinators in other jurisdictions where register-based control programs for ARF exist and considered case definitions currently in use. We investigated best practice guidelines for diagnosis of RHD and considered these for defining a case of RHD.

2.3 Flow of information into the system and data collection

We consulted with stakeholders and considered the system in which other notifiable conditions operate in NSW (Figure 3), to develop a model for the flow of information for a register-based program for ARF and RHD. The model considered the many players who would need to be involved in the notification and follow-up process - such as clinicians, public health practitioners and local health district staff - and how they should be involved. We consulted with RHD Australia and RHD Coordinators in other jurisdictions to identify the minimum set of data to be collected for the system.

Figure 3: Flow of information for routinely notified conditions at Communicable Diseases Branch, New South Wales Health



2.4 Resources required for operating the system

In considering the resources required to operate the system, we explored sources of funding, personnel requirements including the employment of any additional staff and infrastructure requirements.

2.5 Legal authority for data collection

We consulted with and sought advice from the NSW Health Legal Branch regarding the legal requirements for identifying individuals with ARF and/or RHD for invitation to the register and for disease surveillance purposes. We considered relevant sections of the *NSW Public Health Act 2010*, especially with respect to requirements for notification of these two conditions.

We assessed the suitability for ARF and RHD to be made notifiable conditions using criteria set by the Communicable Diseases Network of Australia (CDNA). There are 12 criteria which assess the public health priority of the condition and the feasibility of data collection, to be considered (unpublished report, CDNA). These criteria are: the necessity for public health response, utility and significance of notification for prevention programs, level of vaccine preventability, importance for Indigenous health, assessment of whether the condition is an emerging or re-emerging disease, the level of communicability and potential for outbreaks of the condition, disease severity and socioeconomic impact, preventability, level of public concern and/or political interest, whether a case is definable, data completeness is likely to be acceptable and whether alternative surveillance mechanism exist. A maximum score of 48 is possible and thresholds for action have been set at:

- < 15 points - national notification not recommended
- 15 to 25 points - national notification to be considered further
- 26+ points - national notification recommended

Informed consent is often required for patients to be on a disease register. We assessed consent models of established registers in the NT, WA and Queensland and discussed possible options with the NSW Health Legal Branch.

2.6 Attributes of the system

I undertook an assessment of the necessary attributes required for the system using the CDC's *Updated Guidelines for Evaluating Public Health Surveillance Systems* document. The attributes I assessed were usefulness – the ability of the “system to contribute to the prevention and control of adverse health events, including an improved understanding of the public health implications of that event”(26), simplicity – relates to the design and size of the system, sensitivity – refers to the ability for the system to capture all cases of disease, representativeness – refers to the ability for the system to “describe the occurrence of the condition over time and to characterise the distribution of disease in the population by place and person” (26), acceptability – a reflection of the willingness of surveillance staff to implement the system, and of the end users to accept and use the data generated through the system (26) and data quality – reflects on the clarity and ease-of-use of surveillance forms, the quality of training and supervision of people who complete the forms and the care taken in managing data systems (26).

Results

Part 1: Hospitalisation rates for Acute Rheumatic Fever in New South Wales

1.1 Description of data

From the APDC, we found 238 primary diagnoses of ARF between 2003 and 2012. Diagnoses fluctuated annually (between 10 and 35 per annum), with an average of approximately 24 cases per year over the 10 year period (Figure 4). The majority of hospitalisations (61 cases, 26%) occurred in the 10 to 14 year old age group with an age-specific rate of 13.6 per 100, 000 population over the 10 years (Figure 5). The age-specific rate was higher in males compared to females in this age group (14.8 per 100, 000 versus 12.4 per 100, 000 population). More than half of all hospitalisations (54%) occurred in individuals under 20 years of age, equally distributed between males (64, 50%) and females (65, 50%). Sixty-four of 238 (27%) ARF hospitalisations were in those aged over 40 years.

Figure 4: Number of hospitalisations in New South Wales with Acute Rheumatic Fever as a primary diagnosis code between 2003 and 2012

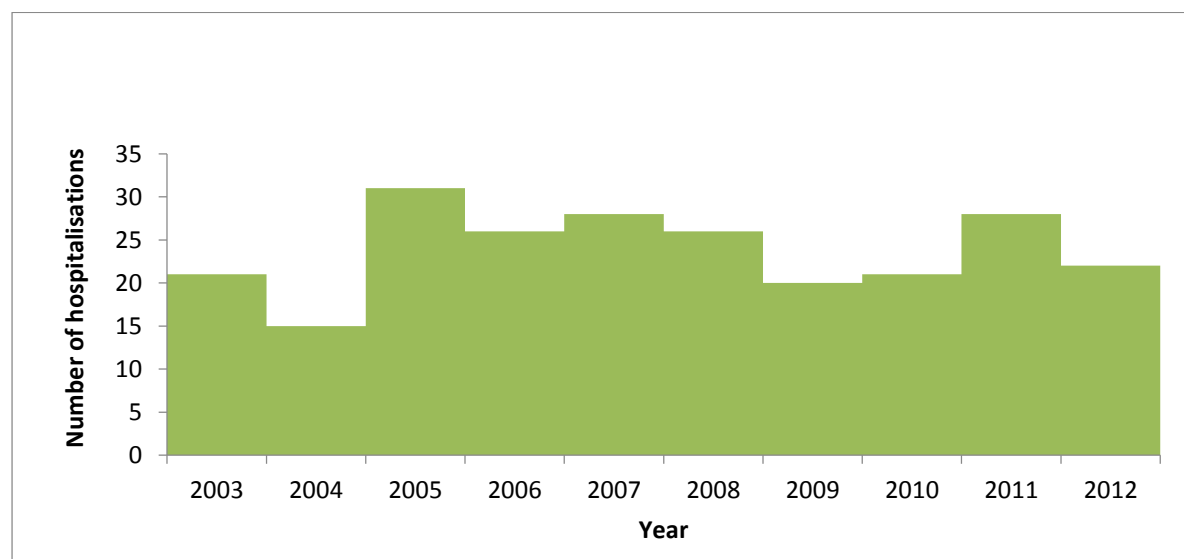
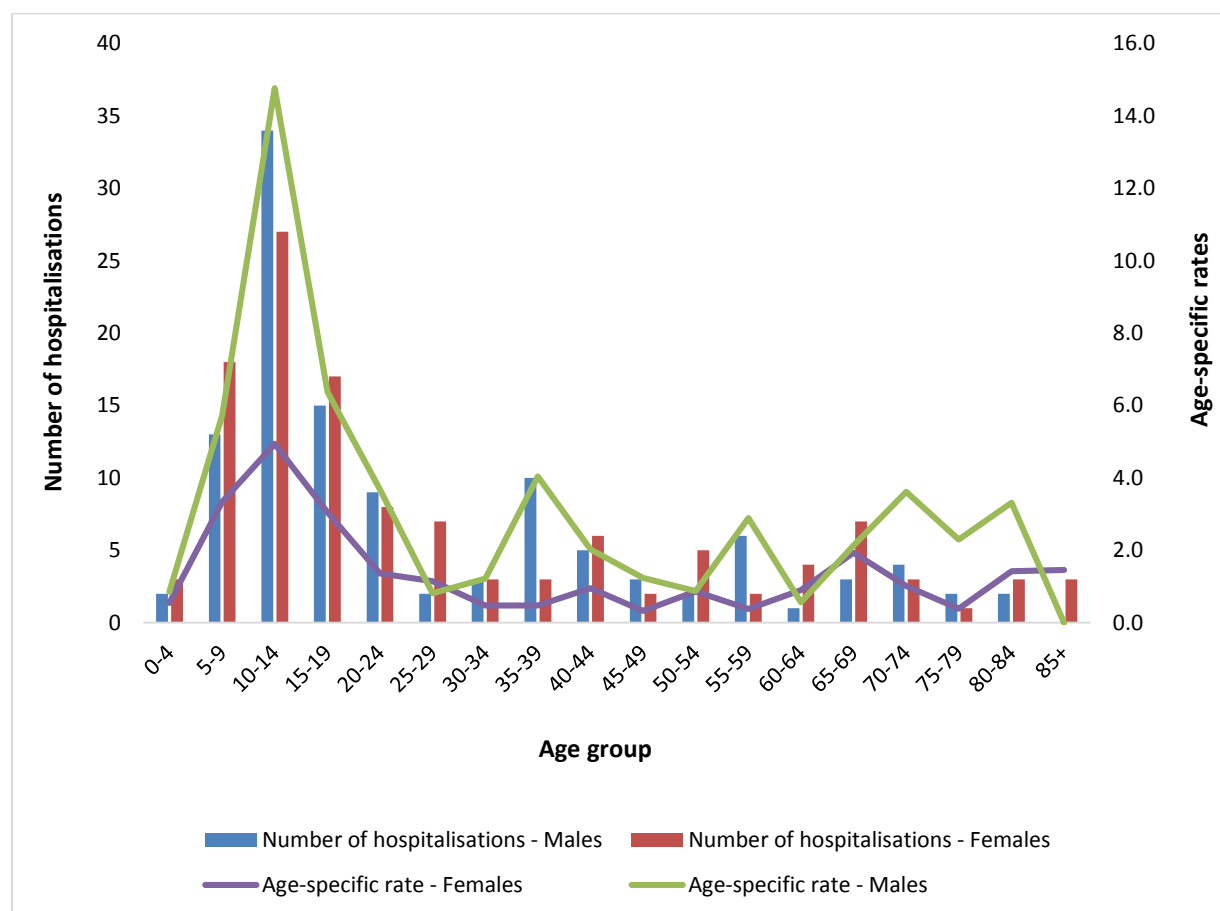


Figure 5: Number of hospitalisations and age- and sex-specific rates of primary diagnoses of Acute Rheumatic Fever in New South Wales between 2003 and 2012



The majority (178 out of 238, 75%) of ARF diagnoses occurred in patients reported as not being Aboriginal or Torres Strait Islander people (Figure 6). About a third (51 of 155) of ARF diagnoses were in Aboriginal and Torres Strait Islander people under 30 years of age. Almost three-quarters of ARF diagnoses were in individuals born in Australia, 10% (23 cases) in those born in New Zealand and 6% (14 cases) in Pacific Islanders (Figure 7). The Pacific-Island cases included four from Fiji Islands, five from Samoa, three from Tonga and one each from American Samoan and Tokelau. The seven south-east Asian cases included two from the Philippines, two from Vietnam and three from Pakistan.

Figure 6: Number of hospitalisations of primary diagnoses of Acute Rheumatic Fever in New South Wales between 2003 and 2012 by age-group and Aboriginal & Torres Strait Islander status

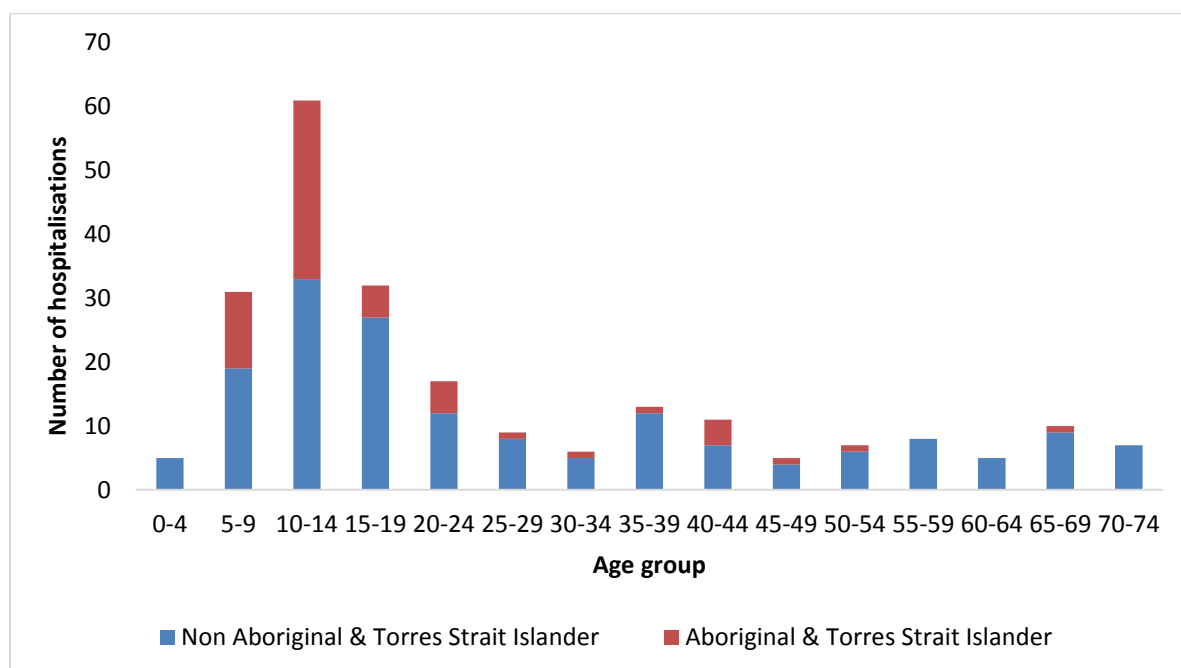
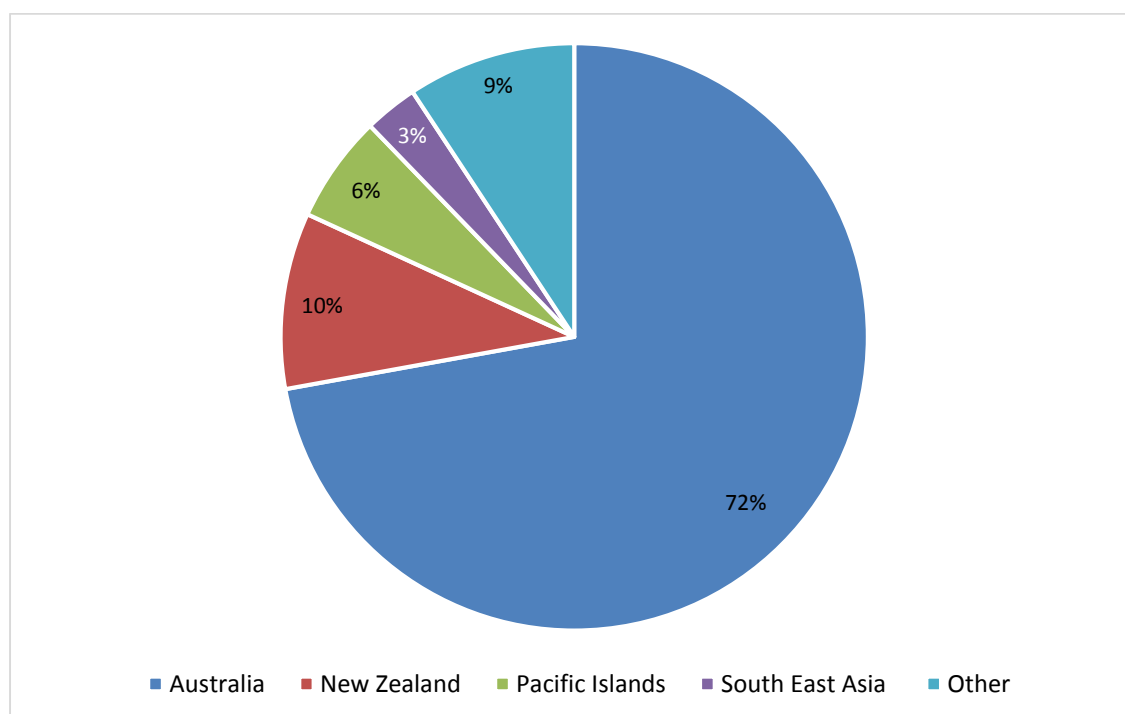
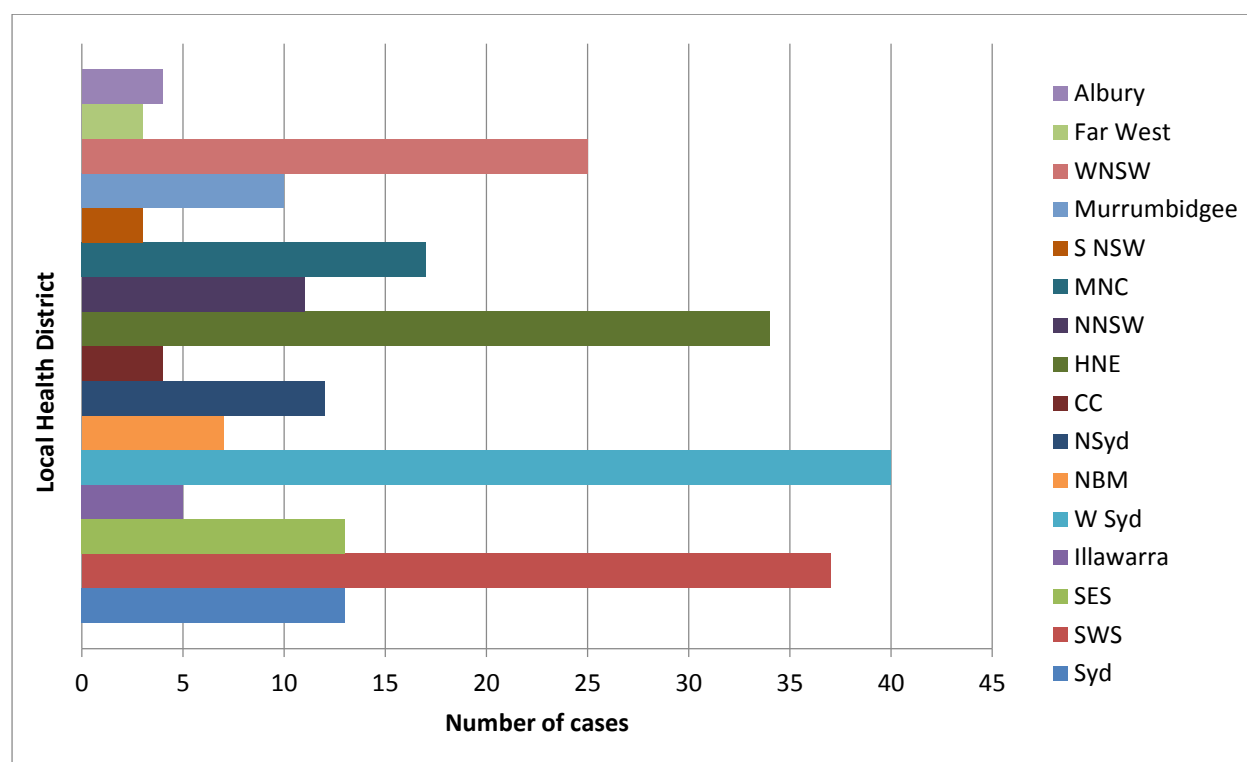


Figure 7: Proportion of primary diagnoses of Acute Rheumatic Fever in New South between 2003 and 2012 by country of birth



There was an uneven distribution of cases across the 15 local health districts of NSW (Figure 8). The highest burden of ARF disease was in Western Sydney with 40 cases over 10 years (17%), followed by Southwest Sydney with 37 cases (16%) and Hunter New England with 34 cases (14%).

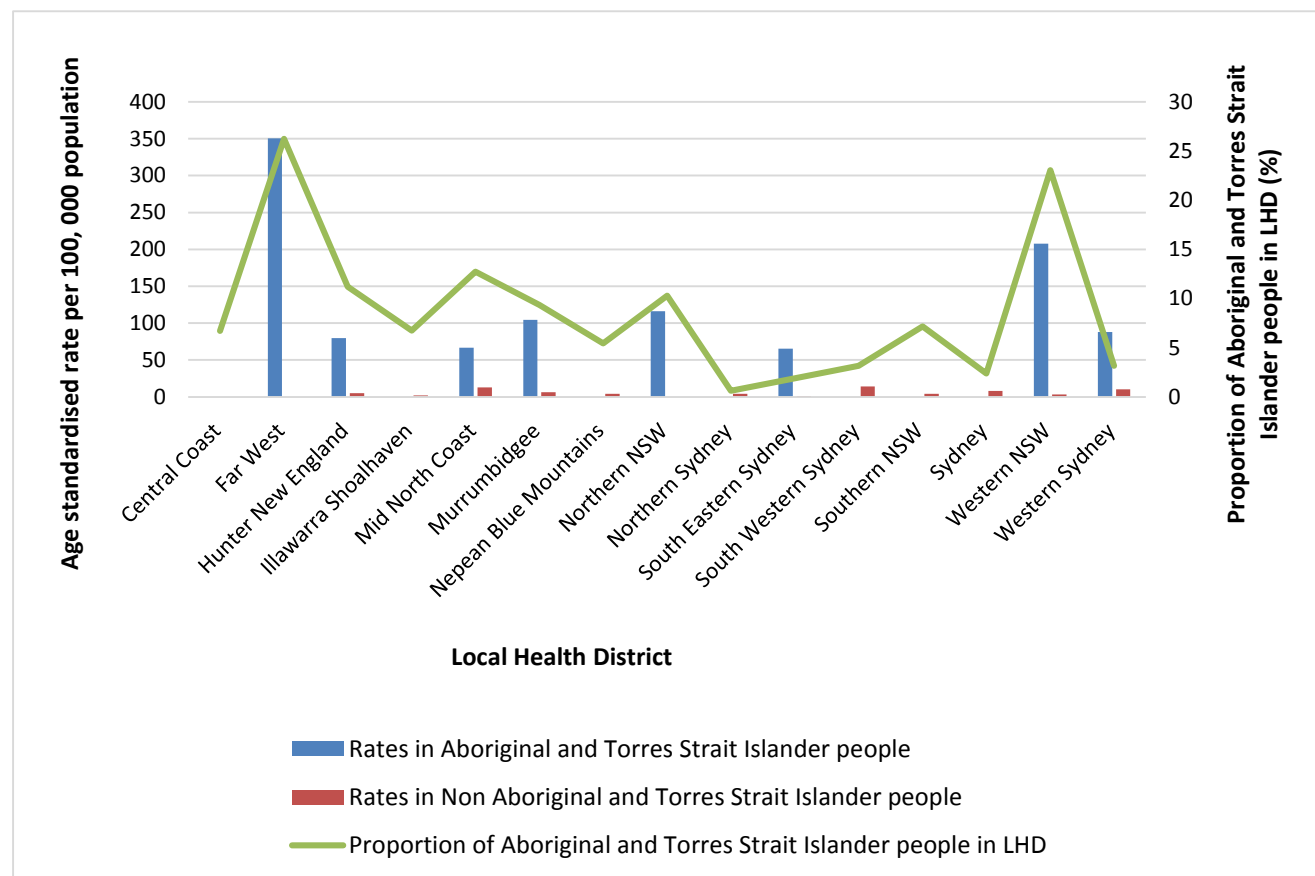
Figure 8: Number of hospitalisations with a primary diagnoses of Acute Rheumatic Fever in New South Wales between 2003 and 2012 by local health district *



* WNSW – Western NSW, SNSW – Southern NSW, MNC –Mid North Coast, NNSW – Northern NSW, HNE – Hunter New England, CC – Central Coast, N Syd – Northern Sydney, NBM – Nepean Blue Mountains, W Syd – Western Sydney, SES – Southeast Sydney, SWS – Southwest Sydney

Looking at the age-standardised hospitalisation rate in five to 14 year old children by LHD, we found the highest hospitalisation rates were in the Far West LHD at 350 per 100, 000 over 10 years, Western NSW LHD at 208 per 100, 000 over 10 years and Northern NSW LHD at 116 per 100, 000 over 10 years (Figure 9). The proportion of Aboriginal and Torres Strait Islander people in each of these LHDs (averaged between 2006 and 2012) were 26% in Far West, 23% in Western NSW and 10% in Northern NSW.

Figure 9: Age-standardised hospitalisation rates for primary diagnoses of Acute Rheumatic Fever in 5 - 14 year olds between 2003 and 2012, by New South Wales Local Health Districts



1.2 Validation of findings through published data

We found three studies in the literature with estimates of the incidence of ARF in NSW. The comparison of data from these studies to our results are described below.

Study 1 (14):

An APSU surveillance report in 2009 documented nine notifications of ARF in NSW between October 2007 and December 2008, with 88% or 100 paediatricians returning questionnaires. Comparing this figure to our data, we found 97 hospitalisations in individuals under 15 years of age over a 10 year period, roughly equating to 9.7 per year – a comparable number to that reported in the APSU report.

Study 2 (13):

A prospective study by Noonan and colleagues aimed to identify ARF in children up to 15 years of age between 1 October 2007 and 31 December 2010 by having ARF notifiable through the APSU. This study reported 18 notifications in NSW over this time. In our dataset, there were 27 hospitalisations with a primary diagnosis of ARF between January 2008 and December 2010. The study also assessed the level of case ascertainment by comparing APSU notifications with register notifications from the NT and Queensland. In doing this, they found that their study captured only 63% of locally notified cases in the NT and 62% of cases in Queensland. If we extrapolate this level of case ascertainment to our data, the APSU data represent 67% of cases found in our study.

Study 3 (15):

A retrospective review of medical records for children aged less than 15 years admitted to Children's Hospital Westmead in Sydney with ARF between 1 January 2000 and 30 December 2008 identified 26 children who met diagnostic criteria for ARF. Searching our results for children under 15 with a usual 'state of residence' from any state admitted to Children's Hospital Westmead over this same time period identified 22 cases. Again, we thought this to be a comparable number.

Part 2: Establishing a surveillance and follow-up system for patients diagnosed with Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

2.1 Results of stakeholder interviews

Interviews conducted with a general paediatrician, a paediatric infectious diseases specialist, a paediatric cardiologist, several adult cardiologists, an adult infectious diseases specialist and a general practitioner from an Aboriginal Medical Service found that all thought it was important to set up a register for ARF and RHD in NSW. While some had only seen between six to ten cases of ARF in their career, those who had seen more severe disease in young children were especially enthusiastic about this initiative.

The general practitioner thought that “having someone remind patients to come to the clinic” would be beneficial. One paediatric cardiologist said that “children often present late and sometimes with full-blown heart failure. Having a register to get cases early might help with this issue.” Adult cardiologists also emphasised the importance of having RHD made a notifiable condition so that these patients are better monitored, especially in the context of the patient requiring valvular surgery.

Representatives from the Aboriginal Health and Medical Research Council were keen that primary care practitioners were at the centre of patient follow-up and were involved in delivery of secondary prophylaxis. They recommended that the register system not take away the responsibilities of the primary care practitioner in following up individual patients, rather it should integrate with the primary health care system.

2.2 Case definitions

The case definitions for ARF used in the NT, Queensland, WA and SA are all based on the modified Jones criteria. Interviews conducted with RHD Coordinators in these jurisdictions found that while jurisdictions apply the same clinical and laboratory criteria to the case definition, jurisdictions do

vary in the required reporting of confirmed and probable cases. In NSW, we decided that both confirmed and probable cases should be notified to public health units. The case definition for RHD is based on the *World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease* (9). These guidelines are also recommended for use by RHD Australia.

Given that the prevalence of RHD is highest in adults aged 35 – 39 years of age and on consultation with numerous cardiologists, we decided that the age cut-off for notification of individuals with RHD should be set at 35 years of age. Individuals in this age group would still benefit from being followed up and receiving monthly prophylaxis to prevent progression of disease (1).

Case definitions for Acute Rheumatic Fever and Rheumatic Heart Disease in NSW

Acute Rheumatic Fever

A confirmed case[‡] requires

- Clinical definitive evidence **AND** Laboratory suggestive evidence.

A probable case requires

- Clinical definitive evidence **OR** Clinical suggestive evidence and laboratory suggestive evidence

Clinical definitive evidence – initial episode

The presence of two major manifestations **OR** one major and two minor manifestations.

Clinical definitive evidence – recurrent episode[€]

The presence of two major manifestations **OR** one major and one minor manifestations **OR** three minor manifestations.

Clinical suggestive evidence – initial or recurrent

A clinical presentation that falls short by either 1 Major or 1 Minor manifestation.

Laboratory suggestive evidence

Supporting evidence of preceding Group A streptococcal (GAS) infection includes the following:

- GAS bacteria isolated from a throat swab
- Elevated or rising streptococcal antibody (ASOT, anti-DNase B) titres.

[‡] Adapted from RHD Australia, National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. *Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease* (2nd edition). 2012.

[€] In a patient with known past ARF or RHD.

Streptococcal titres vary according to a number of factors, including age. The following titres are the upper limit of normal (ULN) for the given age groups:

Age group (years)	ASO titre (IU/mL)	Anti-DNase B titre (IU/mL)
1-4	170	366
5-14	276	499
15-24	238	473
25-34	177	390
≥35	127	265

	High risk groups ¹	All other groups
Major manifestations	• Carditis (including subclinical rheumatic valvulitis detected by echocardiogram) • Polyarthritits (classically, but not necessarily, migratory in nature) or aseptic mono-arthritis or polyarthralgia • Chorea (can be used as sole criterion for ARF, i.e. chorea does not require other manifestations or evidence of preceding GAS infection, if other causes of chorea excluded) • Erythema marginatum • Subcutaneous nodules	• Carditis (excluding subclinical rheumatic valvulitis detected by echocardiogram) • Polyarthritits (classically, but not necessarily, migratory in nature) • Chorea (can be used as sole criterion for ARF, i.e. chorea does not require other manifestations or evidence of preceding GAS infection, if other causes of chorea excluded) • Erythema marginatum • Subcutaneous nodules
Minor manifestations	• Fever (temperature ≥38°C, or a reliably reported fever during the current illness) • Monoarthralgia (not counted if arthritis or arthralgia already a major manifestation) • Elevated acute phase reactants (CRP ≥30 mg/L and / or ESR ≥30 mm/hr) • Prolonged PR interval on ECG (not counted if carditis already a major manifestation)	• Fever (temperature ≥38°C, or a reliably reported fever during the current illness) • Polyarthralgia or aseptic monoarthritis (not counted if polyarthritits already a major manifestation) • Elevated acute phase reactants (CRP ≥30 mg/L and / or ESR ≥30 mm/hr) • Prolonged PR interval on ECG (not counted if carditis already a major manifestation)

Epidemiological evidence: Not applicable

¹ In NSW, Aboriginal people and Torres Strait Islanders, Maoris, Pacific Islanders, and immigrants from countries with a high prevalence of RHD should be considered high risk. Low risk groups include all other populations.

Rheumatic Heart Disease

A confirmed case requires

- Clinical definitive evidence **AND** person to be less than 35 years of age

Clinical definitive evidence

An echocardiogram with valve changes consistent with RHD as defined by the 2012 World Heart Federation criteria:

Echocardiographic criteria for individuals aged ≤ 20 years

Definite RHD (Either A, B, C or D):

- A) Pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve
- B) Mitral stenosis mean gradient ≥ 4 mmHg
- C) Pathological aortic regurgitation and at least two morphological features of RHD of the aortic valve
- D) Borderline diseases of both the aortic valve and mitral valve

Echocardiographic criteria for individuals > 20 years

Definite RHD (either A, B, C or D):

- A) Pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve
- B) Mitral stenosis mean gradient ≥ 4 mmHg
- C) Pathological aortic regurgitation and at least two morphological features of RHD of the aortic valve, only in individuals aged < 35 years
- D) Pathological aortic regurgitation and at least two morphological features of RHD of the mitral valve

2.3 Flow of information in the system and roles and responsibilities of key players

Given the complexity of the ARF diagnosis and the necessity for clinical and public health involvement in its management, many different players needed to be engaged in the system. The proposed system for the notification and follow up of patients with ARF and RHD is outlined in Figure 10. Essentially, it involves a process where once a patient is suspected to have ARF or RHD under age 35, a notification form is filled in by the treating clinician, who then notifies their local PHU. The PHU acts as the first point of contact for notification and is eventually responsible for entering information onto an electronic register database. Given the complexity of the case definition and clinical nature of the response and follow up processes, the PHU will liaise with a dedicated LHD Coordinator. The involvement of an LHD Coordinator is the main difference with this system and the way other conditions are notified as per Figure 3. The LHD Coordinator will discuss

the case with the referring clinician and ascertain a case status according to the case definition. Once this is done and the patient gives their consent, the details will be forwarded on to the RHD register Coordinator, who will be located centrally at Health Protection NSW. The ongoing monitoring of clinical care and secondary prophylaxis will fall into the role of the LHD Coordinator, with the support of the RHD register Coordinator. The RHD register Coordinator will be responsible for overall management of the register, sending out reminders to patients about monthly injections and specialist follow up, data quality and reporting. The roles and responsibilities of the key players in the system are described in table 3.

Figure 10: Flow-chart for patient management and notification of Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

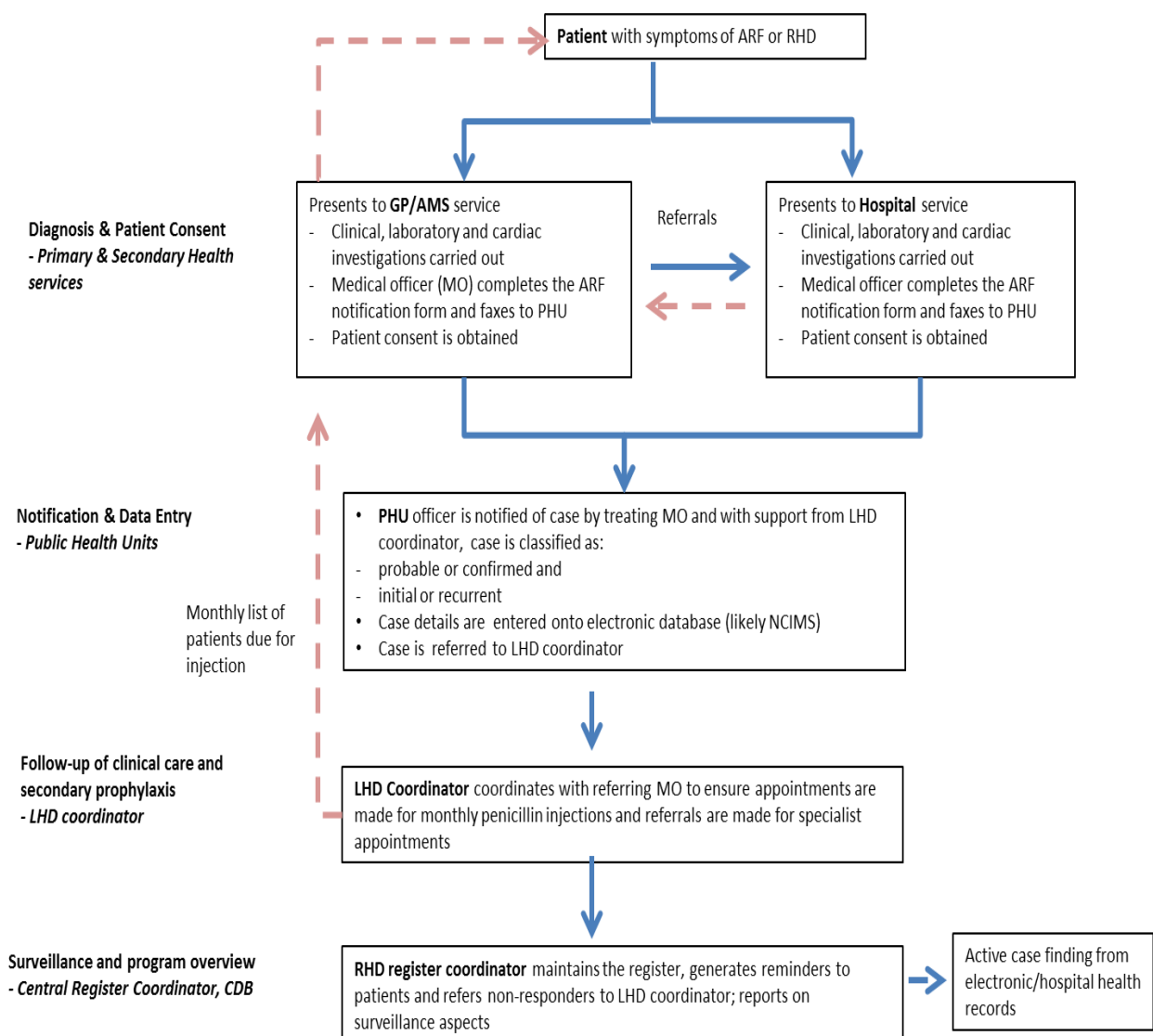


Table 3: Roles and responsibilities of key stakeholders in the register-based control program for Acute Rheumatic Fever and Rheumatic Heart Disease in New South Wales

Role	Responsibilities
Clinicians	- Investigate and diagnose Acute Rheumatic Fever / Rheumatic Heart Disease according to national guidelines - Consent patients for details to be passed on to the register - Notify cases to public health units - Manage cases clinically and/or refer for ongoing management as necessary
Public Health Unit staff	- Act as the first point of contact for notifications of ARF and RHD from primary and secondary care providers - Advise Local Health District Coordinator of suspected or confirmed cases of ARF/RHD - Ensure patient's consent is obtained before details are recorded on the register - Enter patient information on electronic register (likely NCIMS)
Local Health District focal point / Local Cardiac Clinical Nurse Consultant	- Liaise with primary care providers to facilitate monthly penicillin injections and specialist appointments. - Enter appointment data onto register - Coordinate discharge planning and follow-up with hospital staff when clients are in-patients - Follow up non responders - for an example by text message to encourage compliance - Alert RHD register Coordinator of patients moving between LHDs and of those wishing to leave the register

RHD register Coordinator at Health Protection NSW	• Generate monthly reminders of penicillin injections to patients • Receives responses from patients on compliance with injections and appointments and enters onto register; If no response, checks with primary practice to check patient attendance • Refers non-responders to Local Health District Coordinator • Deletes patients wishing to leave the register • Support public health units in case classification and serve as a 'helpdesk' for them • Actively identify individuals with known or suspected Acute Rheumatic Fever/Rheumatic Heart Disease by searching electronic and hospital patient health records (including administrative and clinical datasets); refer cases to public health units for follow up • Produce quarterly and annual surveillance reports • Perform regular audits on the register to ensure data quality • Liaise with Rheumatic Heart Disease Australia to provide educational and training material to NSW clinicians and public health staff • Evaluate the program and identify areas for targeted interventions including local strategies to improve adherence to secondary prophylaxis • Coordinate a Rheumatic Heart Disease steering committee that would act to inform and contribute to the ongoing development of the program
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2.4 Data collection

Data to be collected for entry on to the register, as currently done in other jurisdictional registers and as recommended by RHD Australia, are as follows:

- Personal Information – name, date of birth, gender, country of birth, Indigenous status, address, vaccination history, date and cause of death if applicable
- Service provider organisation

- ARF diagnosis and notification – onset date, laboratory test results, notification date, first/recurrent status, confirmation status
- Laboratory and clinical Details – examples are presence of carditis/chorea/erythema marginatum/arthritis, levels of Anti-streptolysin O (ASOT) titres, etc.
- ARF and RHD diagnosis – including presence and severity of valvular disease
- Health care practitioner review
- Antibiotic regimen – prophylaxis start date/expected end date
- Surgical procedures

2.5 Resources required to operate the system

Given that the register would lie within the operational framework of Health Protection NSW, existing systems would be used as much as possible for daily operation. This includes the use of database systems such as the existing NSW Notifiable Conditions Information Management Systems (NCIMS), human resource personnel in public health units and clinical notification systems and follow-up mechanisms already in place in each local health district.

The additional human resources needed were the RHD register Coordinator and the LHD Coordinator. In other states and territories, funding for the RHD register Coordinator position is provided by the Commonwealth as part of its *Closing the Gap* campaign. We found funding for this position from the NSW Health Centre for Aboriginal Health. Each LHD identified an individual from an existing position within the LHD to take on the role and responsibilities of the LHD Coordinator.

2.6 Legal authority for data collection

2.6.1 Mechanisms available to obtain legal authority for data collection

Upon consultation with the NSW Health Legal Branch, we found that there were a couple of mechanisms available to identify individuals with ARF and/or RHD for invitation to the register and for disease surveillance.

One mechanism agreed on at the *Better Cardiac Care for Aboriginal and Torres Strait Islander People* forum was to make both ARF and RHD notifiable in every state and territory. In assessing ARF and RHD against the CDNA criteria for national notification, both conditions scored 23.5 out of 48, indicating that they should both be considered for national notification (Appendix 3). This was supported by NSW Health and advocated for by leading local clinicians. The conditions would be made notifiable under the *NSW Public Health Act 2010* and would be added to Schedule 1 Category 1 (medical practitioners to notify) and to Schedule 2 (hospitals to notify). This would mean that both conditions would be notified when diagnosed by clinicians. Notification could also provide a mechanism to identify cases through regular audits of the Admitted Patient Data Collection. Notified individuals would then be approached and invited to join the register for ongoing clinical monitoring.

Another option is to make only ARF notifiable and to create a register for RHD under the *Public Health Act* Division 4, clause 97 and seek patient's consent to remain on the register for follow up. The Legal Branch at NSW Health advised that registers created under this section of the *Public Health Act* do not create a requirement to notify and only allow collection of de-identified data, unless patient consent or ethics approval is obtained. Requiring patient consent may limit the usefulness of the register in surveillance and may be particularly difficult with the population groups usually affected by RHD. Requiring ethics approval adds an administrative burden to Health Protection NSW to establish and maintain the register.

Weighing up both options, we decided that the most efficient mechanism for identifying patients for invitation to the register and for collecting information to inform a surveillance system was to make both ARF and RHD a medical practitioner and hospital notifiable condition. This would make it mandatory for clinicians to report cases to the register-based control program. The additional benefit of making these conditions hospital notifiable is that it provides an alternate mechanism and legal framework for hospital records to be searched regularly to actively identify cases for follow up.

2.6.2 Informed Consent

There were three possible approaches to obtaining patient consent for the register: opt-in, opt-out and non-consent (28). An opt-in approach assumes that an individual will not be part of the registry unless they have specifically consented to participation. An opt-out approach assumes that all individuals will be part of a registry, unless there is a specific refusal to participate. Finally, a non-consent model does not seek or require individual consent or refusal, but includes all relevant individuals in a registry. The NT, SA and WA register programs have opt-in registers whereas the Queensland program has an opt-out system.

We thought it most appropriate to use the opt-in model for consent as it provides an opportunity for patients, their families and communities to engage with the register system, especially given the length of time that patients will need to be followed up. It also allows for the system to gain access to patient's personal information which will be important in tracking patient movement over ten years.

2.7 Attributes of the system

The surveillance system attributes as they would apply to the proposed system for ARF and RHD are discussed below.

a) Usefulness

It is anticipated that a register-based control program for ARF and RHD would be useful because it would provide information that was not previously available in NSW. The system would also be useful if it helps to determine that which was previously thought to be an unimportant health event might actually be important.

Among others, the system would satisfy the conditions for:

- 1) detecting trends signalling changes in the occurrence of disease
- 2) providing estimates of the magnitude of morbidity and mortality related to ARF and RHD. By collecting information on individual patients, there would be an opportunity to collate this information and for the first time, gain an understanding of the burden of disease in NSW.

- 3) stimulating epidemiologic research leading to control or prevention programs
- 4) enabling and facilitating improved clinical management of ARF and RHD by health-care providers.

b) Simplicity

Unfortunately, owing to the complex nature of the disease entity itself, there becomes a need for multiple users and sources of information to be utilised. Firstly, the case definition requires the use of multiple clinical and laboratory information by a clinician. Then, the case definition needs to be verified by a public health unit officer who then reports it to the registry. An LHD Coordinator is also involved to liaise with general practitioners and hospitals. This involves multiple levels of reporting and information-sharing which may create administrative burden on users of the system and possible confusion by diagnosing clinicians accessing the system.

However, a similar system is being used in other states and is reportedly functioning reasonably well. It is expected that by having a register with a central coordinator who can collect, analyse and disseminate information, some of the complexity can be addressed and minimised. With time and experience of the processes in motion, the system should be fine-tuned to maximise efficiency and minimise complexity.

c) Sensitivity

The detection and notification of cases of ARF is a form of passive surveillance where the system relies on case identification from healthcare providers. Given that there is no single laboratory diagnostic test for ARF or RHD means that we were not able to have either disease made a laboratory-notifiable condition. Having the conditions made doctor- and hospital-notifiable only, means that the system relies on patients seeking healthcare when unwell, the clinician making the correct diagnosis and then notifying patients to the register through appropriate means. This mechanism does have the potential to underestimate the burden of disease because of inaccuracies in diagnosis and a lack of awareness of ARF and RHD among clinicians. In addition, experience from other doctor-notifiable conditions suggest that there is a failure of doctors to notify diagnosed cases (29). Factors reported to affect under-reporting of notifiable conditions by doctors are the accessibility and complexity of the notification form, lack of motivation because of poor feedback on reported cases, and a perception that it is useless to report notifiable conditions (29).

The sensitivity will also be affected by the fact that certain people will seek medical care over others and by people not giving their consent to be on the register.

We have attempted to improve sensitivity by having a form of active surveillance which involves routinely searching the Admitted Patient Data Collection for patients discharged with diagnoses of ARF or RHD (in individuals under 35 years of age).

Even if the system does not have high sensitivity, this does not mean that it is inadequate. The system can still be useful in monitoring trends as long as the sensitivity remains constant over time (26). Care must be taken when interpreting the sensitivity of the system in times when there is raised awareness of the disease, when a diagnostic test is newly introduced or if there are changes in the way surveillance is conducted.

d) Acceptability

Given that key stakeholders were consulted in the implementation of the program and the public health importance of the condition is well understood, it is anticipated that the system would be well accepted among those clinicians who have managed ARF and RHD patients and know of the importance of secondary prophylaxis. However, we are not certain of the acceptability of the system among general practitioners and other clinicians who may not have had much exposure or experience dealing with these conditions. It is therefore essential that we continually engage with users of the system and work to raise awareness of ARF and RHD among the medical community. We also have to be flexible in allowing for the system to adapt to the needs of its users and respond to their suggestions or comments. In addition, analysis of results from the register and surveillance information should be disseminated to users in a timely fashion to enable them to see the importance of their individual contribution to the system.

e) Representativeness

Given that representativeness is assessed by comparing the characteristics of reported events to actual events, it may be difficult to accurately measure this attribute due to the difficulty in ascertaining the number of actual events of ARF. In addition, certain groups of people, such as Aboriginal and Torres Strait Islander people, migrants and refugees from RHD-prevalent countries may be under-represented in surveillance data, due to differences in health-seeking behaviour, differences in access to health care and in engaging with the system.

Some judgment of the representativeness of surveillance data is possible based on knowledge of the characteristics of the population and by comparing multiple sources of data such as hospital separation records, echocardiography reports, correspondence of specialist reviews, primary healthcare clinic information and notifiable disease databases.

f) Data Quality

Using lessons learnt from other register programs and using established data reporting systems in NSW, we anticipate that forms used for data collection and reporting would be accepted and relatively easy to implement. The system requires input of data by surveillance officers in public health units - this is already a core component of their day-to-day work for other notifiable conditions. The input of data by users of the system would need to be evaluated by the RHD register Coordinator and improved upon where necessary.

Discussion

Acute Rheumatic Fever is a disease with its origins in childhood. However, if left untreated it can progress into a damaging condition later on in life, in the form of Rheumatic Heart Disease. Data from existing surveillance systems in Australia suggest that large inequalities exist in the occurrence of ARF and RHD when comparing Aboriginal and Torres Strait Islander people to other Australians. Additionally, ARF affects children and young adults and the medical consequences related to the subsequent development of RHD result in frequent hospitalisations and medical interventions such as cardiac surgery. Despite this, one of the most important reasons to keep this disease entity at the forefront of public health practitioner's minds is that almost all cases of RHD and associated death are *preventable*.

Our search of the NSW Admitted Patient Data Collection suggested that there may be approximately 24 diagnoses of ARF in NSW each year. ARF hospitalisations were highest in the five to 14 year old age group with an age-specific rate in males of 20.6 per 100, 000 population and in females of 20.8 per 100, 000 population (data not shown) over the 10 year period. Age-standardised rates of hospitalisation were higher in this age group in Aboriginal and Torres Strait Islander children from the Far West, Western NSW and Northern NSW districts. These are regions also known to have higher proportions of Aboriginal and Torres Strait Islander residents.

The rates of hospitalisation for ARF in NSW are not as high as incident rates reported in the five to 14 year old age group in the NT, where approximately 80 per 100, 000 cases per year were reported in males and 115 per 100, 000 cases per year were reported in females (12). The Queensland register also reported higher cases of ARF in the five to 14 year old age group with approximately 110 cases reported between 2009 and 2011 (12). Over the same time period, we found 25 cases in this age group in NSW. Our data might be more comparable to WA's register data. From their register, WA reported 21 new and recurrent cases of ARF between 1 July 2010 and 30 June 2011 (12). We found 21 cases of ARF in 2010 and 28 in 2011.

Individuals who identified as Aboriginal or Torres Strait Islander made up approximately half of hospitalisations in the 5 to 14 year old age group. This case load was highest in LHDs known to have large populations of Aboriginal and Torres Strait Islander people as well as migrants from areas of high RHD prevalence such as New Zealand, the Pacific Islands and South and Central Asia. According

to the 2011 Australian Bureau of Statistics population census, the three LHDs of Western Sydney, Southwest Sydney and Hunter New England had a combined population of 76, 932 or 37% of NSW's Aboriginal and Torres Strait Islander population (27) . NSW, overall, also has the largest number of Aboriginal or Torres Strait Islander people of any Australian state or territory, with approximately 30% of Australia's Indigenous population living here.

Over a quarter of ARF diagnoses were reported in individuals over the age of 40. This is contrary to what is commonly reported in the literature and what is known about the epidemiology of ARF in Australia (1, 2). We think that this most likely represents miscoding of the diagnosis during the hospital admission or a data entry error to the APDC. However, these assumptions were not further verified due to time and logistic constraints.

The findings of our study of hospitalised patients to determine the burden of ARF in NSW are subject to at least three limitations. First, this study is likely affected by ascertainment bias, because it only reports on ARF patients who sought care in hospital. Those with milder symptoms or less severe disease (i.e. where a clinician decided that hospitalisation was unnecessary) and those who do not seek health care, will not be represented in this dataset. Further, the clinical appearances of ARF can be non-specific and atypical in Aboriginal and Torres Strait Islander people (1, 30) meaning that many cases may go undetected. A study in the NT identified eight of 28 Aboriginal patients (29%) without prior recognised ARF or RHD with echocardiographic evidence of established RHD, indicating that previous episodes were missed (30). Another factor that will affect the identification and diagnosis of ARF from year to year is when sub-clinical presentations of ARF occur or if patients do not score highly enough on the modified Jones criteria for the diagnosis of ARF or if the clinician fails to make the diagnosis (1, 12). It is well-recognised that ARF is frequently under-diagnosed in the community due to patient and clinician factors (1).

Secondly, the accuracy of coding can be affected by inadequate documentation by treating clinicians or inaccurate coding of the diagnosis by the clinical coder (31). Demographic data is another area where hospitalisation data can be misrepresentative – in particular, with respect to the accurate identification of Aboriginal or Torres Strait Islander status (32). However, as previously mentioned, NSW Health have taken steps to improve reporting of Aboriginal and Torres Strait Islander status by using an algorithm using record linkage to enhance reporting of Aboriginal status (23).

Finally, medical records were not reviewed for concordance with ARF diagnostic criteria, potentially affecting the sensitivity and specificity of case ascertainment. We considered conducting a chart review of selected patient records. However, this would require ethics committee review, locating hospital medical records from various sites, extracting information from medical records and verifying recorded information against the standard diagnostic criteria. Given the additional time and resources this process would require, we did not further pursue this aspect. In view of these limitations, it is conceivable that ARF occurs at a much higher rate than is currently known.

The establishment of a register-based control program for ARF and RHD in NSW follows the example of other states and territories in Australia and many other countries around the world (1, 18). The WHO definition of a patient registry is “a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a pre-determined scientific, clinical or policy purpose” (33). Patient registries have been in place for several decades covering conditions such as cancers, birth defects and cardiovascular diseases. Previously, I discussed the uncertainty of whether a register program would be the most suitable integrated care system for following patients with multiple co-morbidities who may have complex social backgrounds. The challenges that we will encounter with this system remain to be seen. However, a European Commission on rare diseases suggested that patient registries may be particularly useful for a rare disease. The paucity of cases and the complexity of disease over a large geographical area means that data collection requires collaboration and continuous exchange (34). This is an important consideration with respect to a register system for ARF and RHD, given the length of time that individuals need to be followed up and the potential mobility of patients.

Secondary prophylaxis in an individual with ARF through the administration of a monthly penicillin injection and the support of a register-based program have proven to be the most cost effective means of preventing RHD at both the individual and population level (1, 4, 14). It is intuitive that such prevention programs would be more cost-effective than programs focused on primary or tertiary programs, and the evidence supports this. Secondary prevention programs have been estimated to cost less than half that of tertiary services (including cardiac surgery) and less than one-seventh that of primary prophylaxis (15). In New Zealand, the average hospital costs for treating RHD (which included the cost of surgery) accounted for 87% of total expenditures for ARF and RHD in 1985, whereas the ambulatory component of care accounted for only 13% of total expenditure (16). Management of chronic RHD alone can take as much as 71% of the total national allocation for treating ARF and RHD (17).

According to the Australian Institute of Health and Welfare Disease Expenditure Database, between 2008 and 2009, the estimated cost of ARF and RHD to the Australian public health system was \$74 million AUD (35). This equates to 1% of all cardiovascular disease related health expenditure (35). The vast majority (98.8%) of this money was spent on hospitalised patients (35). This cost, however, does not take into account non-admitted patient services, community health programs, patient transport services, health research, public health or other intangible expenditure (12). Nor does it take into account the costs to patients or society as a whole. As RHD tends to affect young adults, this productive segment of the population may be unable to contribute to national productivity. Other factors to consider are the socio-economic costs borne by parents of children affected with ARF, such as absenteeism from work and/or a loss of income. Much of this expenditure could be prevented with the development of cheaper secondary prevention programmes.

ARF and RHD in individuals under 35 years of age were made both medical practitioner-notifiable and hospital-notifiable conditions in NSW on October 2 2015. While ARF is a notifiable condition or is in the process of being made a notifiable condition in states where register-based programs exist, RHD has not been made notifiable in other states, to-date. However, WA are currently in the process of adding RHD to their list of notifiable conditions (personal communication, WA RHD Coordinator). Evidence from the NT suggests that about half of Aboriginal and Torres Strait Islander people on the NT register with RHD do not have a previous diagnosis of ARF (1). Individuals with RHD without a previous diagnosis of ARF would not be identified from ARF notification alone. It is a recommendation of the national coordinating body, RHD Australia, that RHD should be made a notifiable condition (1). This notion was further supported at the *Better Cardiac Care for Aboriginal People* forum in Sydney in March 2014.

Notification of a condition is a form of passive surveillance that relies on health care providers to report cases of disease. Its advantage is that it is a relatively straight-forward process and requires relatively few resources. The disadvantage is that it requires all elements of the surveillance system to function optimally to ensure that cases are not missed due to under-reporting. Patients must present to a healthcare service when unwell, clinicians must make the correct diagnosis and notify public health services in a timely manner. In our system, we also chose to pursue active surveillance mechanisms to enable more cases to be identified. This would require the Rheumatic Heart Disease Coordinator to regularly audit the APDC and ensure that all discharges from hospital coded as ARF or RHD (in under 35 year olds) also appear on the registry. Although this does necessitate an additional

administrative step, the net gain would be improved case ascertainment and a more complete register.

One of the ultimate goals in public health is to halt and reverse the development of modifiable risk factors for a disease at a population level - in other words, perform primordial prevention. For ARF and RHD, this means implementing “actions and measures that target environmental, social and behavioural conditions, cultural patterns of living... that are known to increase the risk of (Group A *Streptococcus* infection)” (35). While the available evidence does not support advocating for a specific environmental or social strategy, the National Heart Foundation and RHD Australia in their guidelines on the prevention, diagnosis and management of ARF and RHD state that “consistent data demonstrating an association between overcrowding and ARF risk across multiple countries would indicate that this particular factor is worthy of further study” (1). New South Wales Health have already made great strides towards addressing some health infrastructure issues in the form of the NSW Housing for Health Program. The Housing for Health program was set up in the late 1980s to improve living conditions in Aboriginal communities (36). The program aims to “assess, repair or replace health hardware so that houses are safe and the occupants have the ability to carry out healthy living practices.” An evaluation of the NSW Housing for Health Program was completed in 2010. The evaluation demonstrated that communities which received the Housing for Health interventions had a 40% reduction in hospital separations for infectious diseases compared to communities that did not receive the intervention (36). Applying these findings to ARF and RHD, in future, NSW Health can target initiatives such as this to areas of highest disease burden. This will help to address issues of household crowding and therefore household transmission of Group A *Streptococcus*.

In NSW, it has been agreed that there will be a voluntary register established for people diagnosed with ARF and RHD. The register will be used to monitor compliance with secondary prevention measures and will be managed by a Rheumatic Heart Disease Coordinator. By using this tool to directly measure the health status and behaviour of the NSW population, policy-makers will be able to better understand the true burden of these diseases, assess the need for future interventions and measure the effects of these interventions. In establishing a register for ARF and RHD in NSW, the State health department has committed to enhancing the care of patients living with these important public health conditions.

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Appendices

Appendix 1: Australian guidelines for the diagnosis of Acute Rheumatic Fever (ARF) – based on the modified Jones criteria *

	High risk groups #	All other groups
Definite initial episode of Acute Rheumatic Fever	2 major or 1 major and 2 minor manifestations plus evidence of a preceding Group A <i>Streptococcus</i> infection	
Definite recurrent episode of Acute Rheumatic Fever in a patient with known past Acute Rheumatic Fever or Rheumatic Heart Disease	2 major or 1 major and 1 minor or 3 minor manifestations plus evidence of a preceding Group A <i>Streptococcus</i> infection	
Probable Acute Rheumatic Fever (first episode or recurrence)	A clinical presentation that falls short by either one major or one minor manifestation, or the absence of streptococcal serology results, but one in which Acute Rheumatic Fever is considered the most likely diagnosis.	
Major manifestations	• Carditis (including subclinical rheumatic valvulitis detected by echocardiogram) • Polyarthrititis (classically, but not necessarily, migratory in nature) or aseptic mono-arthritis or polyarthralgia • Chorea (can be used as sole criterion for Acute Rheumatic Fever, i.e. chorea does not require other manifestations or evidence of preceding Group A <i>Streptococcus</i> infection, if other causes of chorea excluded) • Erythema marginatum • Subcutaneous nodules	• Carditis (excluding subclinical rheumatic valvulitis detected by echocardiogram) • Polyarthrititis (classically, but not necessarily, migratory in nature) • Chorea (can be used as sole criterion for ARF, i.e. chorea does not require other manifestations or evidence of preceding GAS infection, if other causes of chorea excluded) • Erythema marginatum • Subcutaneous nodules

* Adapted from RHD Australia, National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. *Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease* (2nd edition). 2012.

High risk groups are those living in communities with high rates of ARF (incidence > 30/100, 000 per year in 5 – 14 year olds) or RHD (all age-prevalence > 2/1000). Other high risk groups are Aboriginal and Torres Strait Islanders, Maori and Pacific Islanders and immigrants from developing countries

Minor manifestations	• Fever (temperature $\geq 38^{\circ}\text{C}$, or a reliably reported fever during the current illness) • Monoarthralgia (not counted if arthritis or arthralgia already a major manifestation) • Elevated acute phase reactants (C-reaction protein ≥ 30 mg/L and / or erythrocyte sedimentation rate ≥ 30 mm/hr) • Prolonged PR interval on electrocardiogram (not counted if carditis already a major manifestation)	• Fever (temperature $\geq 38^{\circ}\text{C}$, or a reliably reported fever during the current illness) • Polyarthralgia or aseptic monoarthritis (not counted if polyarthritis already a major manifestation) • Elevated acute phase reactants (C- reactive protein ≥ 30 mg/L and / or erythrocyte sedimentation rate ≥ 30 mm/hr) • Prolonged PR interval on electrocardiogram (not counted if carditis already a major manifestation)
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Appendix 2: ICD-10 AM codes searched in the NSW Health Admitted Patient Data Collection

I00-I02 Acute rheumatic fever

I00 Rheumatic fever without mention of heart involvement

I01 Rheumatic fever with heart involvement

- _ I01.0 Acute rheumatic pericarditis
- _ I01.1 Acute rheumatic endocarditis
- _ I01.2 Acute rheumatic myocarditis
- _ I01.8 Other acute rheumatic heart disease
- _ I01.9 Acute rheumatic heart disease, unspecified

I02 Rheumatic chorea

- _ I02.0 Rheumatic chorea with heart involvement
- _ I02.9 Rheumatic chorea without heart involvement

Appendix 3: Assessment of the need for national notification of Acute Rheumatic Fever and Rheumatic Heart Disease according to the revised Communicable Disease Network Australia criteria, 2014

Criterion	Score
Priority setting	
1. Necessity for public health response	2= case reporting important for detecting outbreaks that require investigating or contacts require routine intervention
2. Utility and significance of notification for prevention programs	3 = National prevention programs in place or WHO Western Pacific Regional Office (WPRO) targets for elimination or eradication
3. Vaccine preventability	0 = no vaccine available
4. Importance for Indigenous health	3 = High
5. Emerging or re-emerging disease	2= slowly re-emerging or increasing incidence/prevalence disease over the past 5 years
6. Communicability and potential for outbreaks	0= Not communicable or no outbreak potential
7. Severity and socioeconomic impacts	4= very high severity and socioeconomic impacts
8. Preventability	3= preventive measure with moderate efficacy/low side effects/acceptable uptake
9. Level of public concern and/or political interest	1= no to low public concern or political interest

Feasibility of collection	
10. A case is definable	2= A case is definable, but with complexities
11. Data completeness is likely to be acceptable	2= Data represent an proportion of community cases with a known undercount
12. Alternative surveillance mechanisms	2= Alternative surveillance mechanism in place, but not nationally co-ordinated, only sentinel sites or surveys, significant gaps or weaknesses e.g. rotavirus.

Chapter 3:

An outbreak of locally acquired hepatitis E virus infection in New South Wales

“Pork - no animal is more used for nourishment and none more indispensable in the kitchen; employed either fresh or salt, all is useful, even to its bristles and its blood; it is the superfluous riches of the farmer, and helps to pay the rent of the cottager”

- Alexis Soyer, 1810 – 1858

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Abbreviations

DPI	Department of Primary Industries
GP	General Practitioner
HEV	Hepatitis E virus
ICPMR	Institute of Clinical Pathology and Medical Research
NCEPH	National Centre for Epidemiology and Population Health
NSW	New South Wales
NSWFA	New South Wales Food Authority
PCR	Polymerase Chain Reaction
PHU	Public health unit
RNA	Ribonucleic acid
UK	United Kingdom
VIDRL	Victorian Infectious Diseases Reference Laboratory

Chapter Prelude

My role

I was very fortunate to have been involved in a fascinating and probing investigation into an outbreak of locally acquired hepatitis E virus (HEV) infection. When I first started at Health Protection New South Wales (NSW), one of my first tasks was to write up on three cases of locally acquired HEV infection that occurred at the end of 2013. As I got started on this, the story changed significantly when in May 2014, we were made aware of a work group who had dined at a local restaurant, several of whom became infected with HEV. In the months that followed, I was intimately involved in the outbreak investigation.

We formed an expert panel to guide the investigation. I was involved in organising teleconferences, writing minutes and distributing relevant information to those involved. I also did literature reviews on various aspects of HEV that helped provide contextual information. Topics that I researched included locally acquired HEV infection in high income countries, HEV infection in pigs and studies looking at the association between pork products and HEV infection in humans. This research informed the preparation of summary papers for meetings with the Department of Primary Industries (DPI) and Australia Pork Limited, and an updated NSW Health hepatitis E factsheet.

For the epidemiological investigation, I prepared a modified food history questionnaire that Public Health Units could use to interview cases that had dined at the implicated restaurant. I then analysed the food history results in Microsoft Excel and Epi info. I also drafted a protocol to conduct retrospective serological studies that aimed to test stored sera for HEV in two major laboratories in NSW.

To communicate these findings to the public health and medical communities, I drafted an alert for general practitioners that informed them of the outbreak and asked that they consider HEV infection in patients with signs and symptoms of hepatitis regardless of a history of overseas travel. Along with colleagues from the Communicable Diseases Branch and NSW Food Authority, I first presented

this outbreak at the OzFoodNet face-to-face meeting in August 2014. I also presented the findings at an NCEPH lunchtime seminar at ANU during our MAE course-block in February 2015. I had the opportunity to attend the International Conference on Emerging Infectious Diseases in Atlanta in August 2015 and presented the findings at this international meeting, where the paper was selected for a press summary. I also discussed these findings in an internal research forum at NSW Health – the Population Health forum, in October 2015.

I drafted the manuscript for this outbreak and submitted it to the *Medical Journal of Australia* where it has been invited for revision and re-submission. I received valuable input and guidance on the paper from fellow co-authors and the findings presented below are an expanded version of the submitted paper. The final submitted publication is attached at the end of this chapter.

Lessons learned

While I had previously been involved in outbreaks with my work in Medecins Sans Frontieres, I had not had the opportunity to work through the ten steps of an outbreak investigation as I had with this one.

The investigation taught me how important it is to have an open mind about possible exposures and sources of infection. The first locally acquired case of HEV infection was notified in October 2013 but the restaurant link was not made until May 2014 – seven months later. The importance of interviewing and re-interviewing cases and re-thinking a hypothesis was made clear.

The investigation taught me about the levels of evidence in an outbreak investigation and how epidemiological, laboratory and environmental facts have to be considered collectively to reach a conclusion. Perhaps, a piece of microbiological evidence that was lacking in the investigation was a link between the implicated food product and the source farm that the product originated from. If we could have recovered and matched the hepatitis E virus from pigs on the implicated farm to human cases, we would have added further weight to the evidence. However, as the aphorism goes, “absence of evidence is not evidence of absence”, and we did have other important epidemiological and laboratory evidence to support the investigation.

The findings also made me think that ‘we don’t know what we don’t know’. Locally-acquired cases of HEV linked to pork products had been reported in other high income countries and there was published evidence of HEV seroprevalence in Australian pig herds, however the two facts did not previously have the opportunity to be linked. It makes me wonder what else we might be missing regarding other infectious diseases. The importance of regularly scouring the literature, being aware of new research in other fields and collaborating with inter-disciplinary colleagues is a lesson that I will be taking from this experience.

The other important related concept I learnt was that of “one health”. The idea that human health and animal health could be so closely intertwined seems obvious in the context of zoonotic diseases

and although I have heard theoretical discussions related to overpopulation, increased production of food-producing animals and encroachment of natural habitats, this outbreak really drove those concepts home.

I also gained an appreciation for the importance of inter-agency collaboration and how outbreak investigation teams work. Working with pig veterinarians from DPI was an interesting learning experience and made me think about what drives different agencies to investigate acute public health problems and how each will act according to their own priorities. Working with the NSW Food Authority, public and private laboratories, public health units and members of the Communicable Diseases Branch was an invaluable experience. These were experts in the field and together brought a lot of experience and knowledge to the table. The investigative process can be resource-intensive and time-consuming but when all the pieces of the puzzle come together and the 'case is cracked', the collaborative effort is rewarding and importantly, fun!

Public health implications

This is the first reported outbreak of locally-acquired HEV infection in Australia and has important implications for clinical and public health practitioners as well as the food service industry and the general public of Australia.

Most general practitioners (GPs) would not have included HEV infection on their list of differential diagnoses when investigating a patient with acute hepatitis, especially without a history of overseas travel. However, as a result of the findings from this outbreak, it is important that all clinicians now consider the diagnosis of HEV in their patients with unexplained acute hepatitis, regardless of history of overseas travel. This has implications for public health and reference laboratories as well, as they will receive increased requests for HEV tests. Some laboratories may have to change usual practice so that they test all samples requested.

Public health departments around the country will have to be aware of these findings and be prepared to investigate their notified hepatitis E cases for local sources of infection. They should be aware that their current surveillance data likely represents an undercount of the true burden of HEV disease.

We have been able to show that HEV can be transmitted to humans via the foodborne route in offal sourced from domestic pigs. This gives impetus for food handlers and restaurateurs to cook pork products, and in particular pork liver, thoroughly. Messaging around the preparation and handling of pork products will need to reflect this.

This outbreak provides the basis for improved understanding and further research into HEV infection in Australia, especially in relation to its underlying prevalence and risk factors for acquisition.

Abstract

Background

Foodborne transmission of hepatitis E virus (HEV) has not previously been reported in Australia. In October 2013, NSW Health were notified of three locally-acquired HEV cases whose source of infection was unknown. In May 2014, two further cases, part of a larger dining group at a single restaurant X, were notified. Re-interviewing two of the 2013 cases found that both had dined at restaurant X, prior to infection.

Methods

In Australia, laboratory diagnoses of HEV infection (by IgG seroconversion, detection of HEV-specific IgM or nucleic acid) are notifiable to the respective public health authorities. We interviewed notified cases of HEV infection in New South Wales between January 2013 and December 2014 using a standard questionnaire about potential risk factors for HEV infection such as travel history, occupation and foods consumed during their incubation period. Further cases were identified by serological testing and interviewing co-diners of cases and by testing patients in whom viral hepatitis screening was requested between 1 September 2013 and 31 May 2014 at a major private and public reference laboratory, where hepatitis A, B, C, Epstein-Barr virus and cytomegalovirus infection had been excluded. In a retrospective cohort study of restaurant X diners, reported foods consumed by cases were compared with those reported by seronegative co-diners. HEV RNA detected in sera was genotyped and sequenced. We traced implicated foods back to the source.

Results

Of 55 HEV serologically-confirmed cases, 24 did not travel overseas in the incubation periods. Of these, 17 reported eating at restaurant X. Pork liver pâté was consumed by 15 restaurant cases with complete food histories, compared with four of seven uninfected co-diners ($p < 0.05$). The remaining seven locally-acquired cases all consumed a pork product. HEV RNA was detected in 17 cases; all

were genotype 3. Sequencing showed >99% homology amongst restaurant cases. Pork livers were traced back to a single Australian farm.

Conclusions

This is the first reported HEV outbreak in Australia. HEV should be considered in patients presenting with a compatible illness in the absence of overseas travel history. Food handlers and the public should ensure that pork liver products are thoroughly cooked before consumption.

Background

Hepatitis E virus (HEV) infection is usually a self-limiting disease with clinical features similar to that of other viral hepatitis. Common symptoms include jaundice, nausea and vomiting, anorexia, pale stools and dark urine (1). The incubation period is between 15 to 64 days (1). Hepatitis E virus infection is a major cause of epidemic and acute sporadic hepatitis in countries where the virus is endemic. In these regions of Asia, Africa and Central America, HEV accounts for more than half of all acute viral hepatitis (2). Inadequate sanitary infrastructure that allows the transmission of HEV via the faecal-oral route and contaminated water systems are thought to contribute to the high prevalence of disease (2). Of the four HEV genotypes, genotypes 1 and 2 predominate in these settings (3).

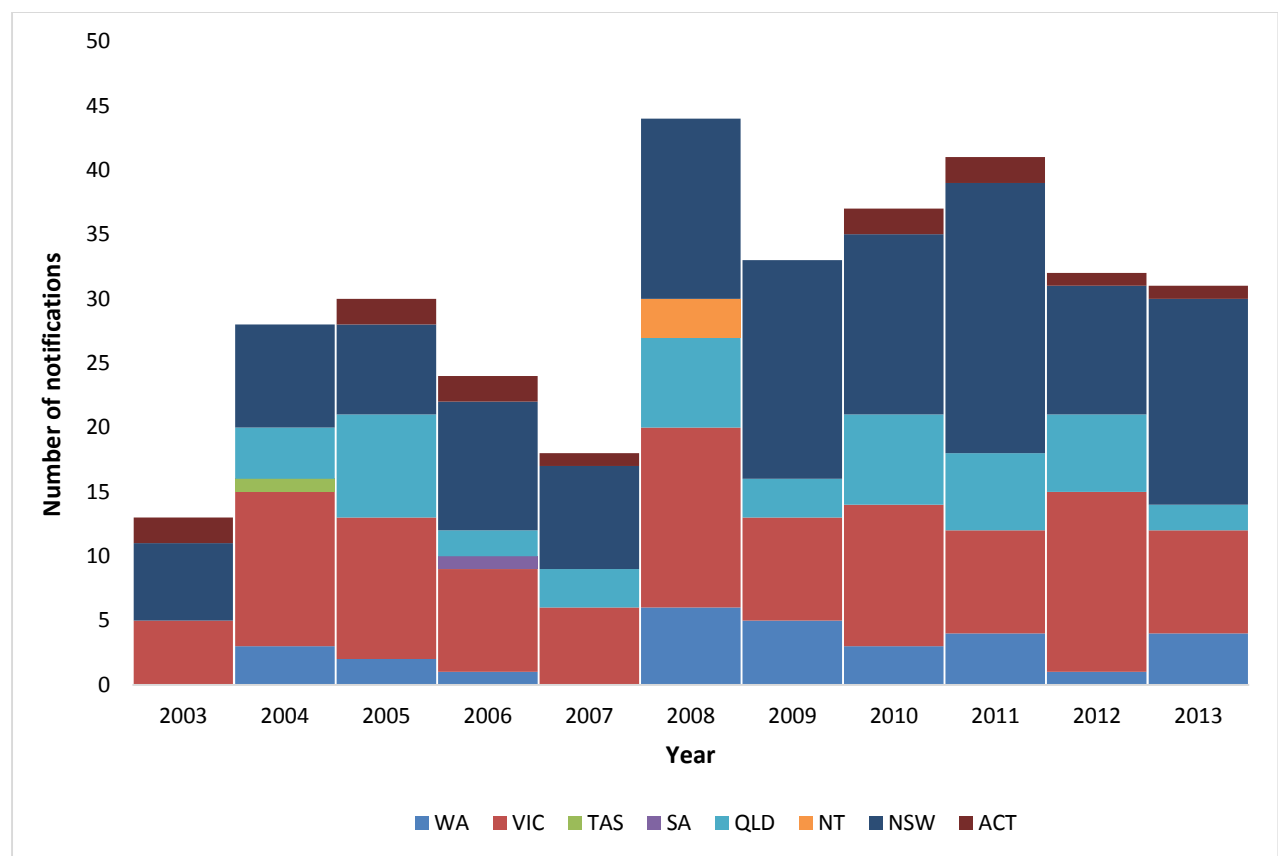
In more developed countries, HEV infections are sporadic and have been thought to occur predominantly in travellers returning from HEV-endemic areas. However, over the last two decades, there have been increasing reports of locally-acquired infections in parts of Europe, Japan, the United States and New Zealand (4). While there is no evidence for one main route of transmission or pre-disposing risk factor, several studies have demonstrated that zoonotic transmission via the foodborne route is likely. Implicated sources of infection have been undercooked meat products such as pork, deer and offal, and shellfish (3, 5-9). Genotypes 3 and 4 predominate in these settings and have been isolated from infected cases (3, 5-9).

Pigs in particular, may play a role in human HEV transmission (4). An increased risk of HEV infection with consumption of processed pork products was demonstrated in a recent case-control study in the United Kingdom (UK) (10). A focussed literature review of studies identifying the presence of HEV in pork or pork products is presented at the end of this chapter.

Human and swine HEV strains also show a high level of sequence relatedness - pigs are only infected with the genotype 3 HEV strain (6, 11, 12). Occupational exposure may also be important for pig veterinarians, pig farmers and abattoir workers, who are reported to have higher seroprevalence rates compared with healthy controls (13-15).

Outbreaks of HEV have not previously been reported in Australia. HEV infection is notifiable to the respective state and territory public health authorities according to each jurisdictions' *Public Health Act*. Common laboratory practice has been to test for HEV infection only in those with an overseas travel history in the incubation period. In Australia, each year between 15 – 45 infections in returned travellers from HEV-endemic regions are reported, with New South Wales (NSW) contributing 5 – 20 of these (Figure 1).

Figure 1: Hepatitis E virus notifications in Australia between 2003 and 2013, by state of residence



(Source data: National Notifiable Disease Surveillance System)

In October 2013, NSW Health was notified of two apparently unrelated cases of HEV infection over a two week period. Neither case reported overseas travel or other common exposures in the incubation period. HEV RNA from these two cases was genetically identical. A family member of one of the cases developed HEV infection four weeks later.

In May 2014, we received an HEV notification in a man who on interview, reported that a work colleague from another state also had HEV infection. Neither had travelled overseas during their incubation periods. The only common exposure was a meal shared with seven other colleagues at restaurant X. The index case reported that three other attendees at this meal were symptomatic. All co-diners were interviewed and tested for HEV infection. HEV was detected in three symptomatic co-diners. HEV RNA from the five cases was genotypically identical to each other and the two cases from 2013. In 2013, one of the cases had reported eating at restaurant X in their incubation period but the others did not. Of the others, only one was available for re-interview. This case remembered eating at restaurant X in their incubation period.

In this chapter, I describe an epidemiological study which investigated the source and extent of Australia's first reported outbreak of HEV infection.

Methods

1) Epidemiological investigation

1.1 Case definitions

We defined a case of HEV infection as a person who resided in NSW with laboratory-confirmed HEV, verified by IgG seroconversion or detection of HEV-specific IgM or HEV RNA with an onset date (or specimen collection date where unknown) between 1 January 2013 and 31 December 2014.

1.2 Case finding and data collected

We identified cases in three ways:

1.2.1 Routine notification

As part of routine surveillance, pathology laboratories are required by the NSW Public Health Act 2010 to notify public health units (PHUs) of HEV cases. Surveillance specialists from the PHUs interviewed cases using a standardised questionnaire. Information collected included symptoms of illness, occupation, travel history, water and food sources (including restaurants) in the incubation period. A food questionnaire with a list of food items commonly served at restaurant X was compiled. Where a case had eaten at restaurant X, the interviewer asked details of foods consumed.

1.2.2 Testing of co-diners from restaurant X

Co-diners of cases from restaurant X were interviewed prospectively between May and August 2014 using the same standardised questionnaire. They were tested for HEV using standard serological methods.

1.2.3 Retrospective serological surveys

We tested all sera stored at a large public laboratory with specimen collection dates between 1 September 2013 and 31 May 2014, where HEV testing had been requested but not carried out (due to the fact that laboratory protocols in NSW previously excluded testing where there was an absence of travel history (Survey 1; Appendix 1)).

We also tested sera stored at a major NSW private pathology laboratory with specimen dates between 1 January and 31 May 2014, where an alanine transaminase (ALT) level was >200 IU/L and hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus and cytomegalovirus infection had been excluded but HEV testing was not performed (survey 2).

2) Laboratory investigation

2.1 Serology

Anti-HEV IgM and IgG were detected using HEV IgM ELISA 3.0 and HEV ELISA kits respectively (MP Diagnostics, MP Biomedicals, Singapore) according to the manufacturer's instructions. Reactive sera were retested and reported as positive if repeat testing was reactive.

2.2 Viral detection and sequencing

Serum samples from confirmed cases were analysed at the Victorian Infectious Diseases Reference Laboratory (VIDRL). HEV RNA was extracted from serum using the QIAamp Viral RNA Mini Kit (QIAGEN, Melbourne, Australia) and initially tested using a commercial HEV RNA PCR assay (RealStar HEV RT-PCR, Altona Diagnostics, Germany). Samples containing HEV RNA were re-assayed by an in-house PCR assay using primers designed to amplify a portion of the open reading frame 2. The resulting PCR product was directly sequenced with internal primers. Sequences were aligned and compared with sequences in GenBank. GenBank is a comprehensive database that contains publicly available nucleotide sequences obtained through submissions from individual laboratories and batch submissions from large-scale sequencing projects (16).

3) Environmental investigation

3.1 Investigation and food testing linked to restaurant X

Food handling and safety procedures at restaurant X were reviewed on 15 May 2014. Preparation of pork liver pâté was observed in detail. The internal temperature of sliced pork livers was measured by inserting a thermometer into the thickest part of the liver after three and four minutes of cooking.

Three batches of chorizo sausage, three batches of cooked pork liver pâté, one sample of raw pork shoulder and raw pork jowl, one batch of cooked pork liver and eight raw pork liver samples from restaurant X were collected on 15 and 22 May 2014.

After extraction and purification using the MagMax™ Total RNA Isolation Kit (Life Technologies, California, USA), samples were tested for HEV by Advanced Analytical Australia using the hepatitis E@Ceeram Tools™ (Ceeram S.A.S, La Chapelle-Sur-Erdre, France), utilising real time PCR.

Pork products were traced back to their source by identifying the supplier from records held at the food premise. Through the supplier, we identified the farms from where the products originated.

3.2 Testing of pork liver sausages from hepatitis E virus cases not linked to restaurant X

One of the cases without a link to restaurant X reported eating pork liver sausages in their incubation period. This case had frozen uncooked sausages stored in a domestic freezer. Multiple samples were collected from several sausages and analysed for the presence of HEV at the Virology Laboratory, Elizabeth Macarthur Agriculture Institute, Menangle, NSW. Nucleic acid was purified

and tested by real time reverse transcription quantitative PCR (qRT-PCR) (17) using previously published primers and probe sequences (18).

4) Data analysis

Responses from case questionnaires were collated in a Microsoft Excel spreadsheet for analysis. Foods consumed by cases were compared with seronegative co-diners in a retrospective cohort study. Responses were analysed and relative risks and confidence intervals calculated using EpiInfo version 7. A two-tailed Fisher's exact test was used to test for significant differences between the two groups, with p-values less than 0.05 considered significant.

5) Ethics

These studies were conducted as part of a public health investigation under the NSW *Public Health Act* 2010. Therefore, review by a human research ethics committee was not required.

Results

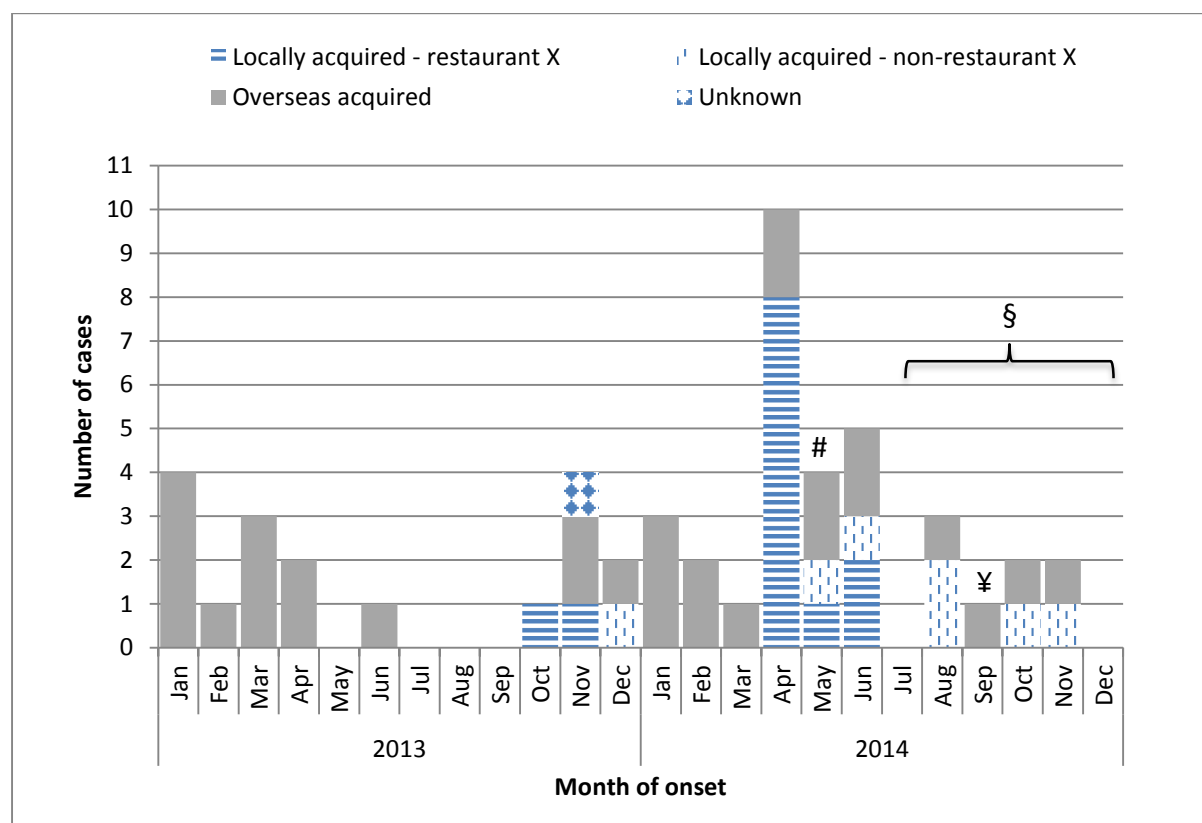
1) Epidemiological investigation

1.1 HEV cases notified to New South Wales Health

Between January 2013 and December 2014, laboratories notified 55 cases of HEV infection (Figure 2). The median age was 45 years (range 4 – 77 years), 36 (65%) were male and all but one (98%) lived in metropolitan Sydney. Twenty-four (44%) required hospitalisation, with a reported median length of stay (where known) of seven days (range 1 – 67 days). Three cases (identified as co-diners of notified cases) were asymptomatic, and symptoms were unknown for one case. Thirty seven cases had an alanine transferase (ALT) level recorded; elevated levels occurred in 33 cases with a median value of 1058 IU/L (range 26 – 4868 IU/L). None reported were pregnant.

Of the 55 cases, 30 (55%) reported a history of overseas travel in their incubation period, to South Asia (17), East Asia (6), South East Asia (2), Africa (2), Europe (2) and the Middle East (1). Apart from one case who could not be contacted, the remaining 24 (44%) did not report overseas travel in their incubation period.

Figure 2: Notifications of Hepatitis E virus infections in New South Wales with onset dates between January 2013 and December 2014, by likely source of acquisition *



* Excludes 3 asymptomatic cases and 1 case with unknown symptom history

May 2014: Restaurant X inspected and pork pate identified as possible source of infection; restaurant voluntarily removed pork pate from the menu. Alert issued to gastroenterologists and laboratories

¥ September 2014: Alert issued to general practitioners and public

§ July – December 2014: Increased HEV testing at main public laboratory

1.2 Restaurant X outbreak

Restaurant X mainly served dishes suitable for sharing in a group. The menu includes over 28 items of meat, seafood and vegetarian options.

Seventeen cases from nine separate groups with dining dates between October 2013 and May 2014 were linked to restaurant X. Of these, seven (41%) were identified through routine surveillance, eight by testing co-diners (47%) and two (12%) from the retrospective serosurveys. Two cases

refused further interview; food histories were collected from the remaining 15 cases and seven dining companions who tested HEV negative by serology.

The most commonly consumed food items are reported in Table 1. The highest attack rates were in those who consumed pork pâté and roast pork. All 15 cases with complete food histories reported consuming pork pâté compared with four of seven uninfected co-diners ($p < 0.05$).

Table 1: Characteristics and reported food consumption of diners at restaurant X over the period October 2013 to May 2014

Characteristic				Ill diners, n = 17			Well co-diners, n = 7	
Age group (years)								
≤ 39, no (%)				5 (29)			1 (14)	
40 – 59, no (%)				6 (35)			5 (71)	
60 +, no (%)				6 (35)				
Unknown							1 (71)	
All ages, median (range)				48 (29 – 75)			45 (29 – 47)	
Male sex, no (%)				12 (71)			4 (57)	
Food items consumed *								
	Number of people who ate			Number of people who did not eat			Relative risk (95% CI)	p-value
	Ill	Total	Attack rate (%)	Ill	Total	Attack rate (%)		
Brussel sprouts	5	8	63	8	12	67	1 (0.5 – 1.8)	1.00
Calamari	3	5	60	10	15	67	1 (0.5 – 2.0)	1.00
Eggplant	7	12	58	6	8	75	0.8 (0.5 – 1.5)	0.66
Pork chorizo	7	9	78	6	11	55	1.5 (0.8 – 2.7)	0.36
Pork pate	15	15	100	0	3	0	Undefined	0.02
Roast pork	9	13	69	4	7	57	1.2 (0.6 – 2.6)	0.64

* Complete food histories available for 15 of 17 ill diners and all 7 well co-diners

1.3 Locally acquired cases not linked to restaurant X

On interview, the seven locally-acquired cases not linked to restaurant X, reported consuming multiple pork products in their incubation periods. They included supermarket ham, prosciutto, pork liver, homemade pork liver sausage, pork chops and pork belly.

1.4 Retrospective serological surveys

Of 136 serosurvey samples, (31 in survey 1 and 105 in survey 2), nine (6.6%) were IgG positive, four (2.9%) were IgM positive and four (2.9%) were both IgM and IgG positive. Of the eight IgM positive cases, HEV RNA was detected in four with sequencing confirming genotype 3. Two of these four cases reported eating at restaurant X but no overseas travel, one reported travel to an HEV-endemic country and one was uncontactable.

2) Laboratory Investigation

HEV RNA was detected in 10 of the 17 restaurant X cases (five were PCR negative with mild or no symptoms, one was PCR negative but demonstrated seroconversion, and a sample was unavailable from one case). Sequencing of the ORF 2 region was successful for all ten samples and HEV was classified as genotype 3. There was 99% sequence homology in the targeted portion of open reading frame 2 between samples.

HEV RNA was also detected in six of the seven non-restaurant locally-acquired cases (one had insufficient specimen for testing) - five were genotype 3 and one had insufficient sample for genotyping. The viral sequence of these samples showed approximately 90% similarity to the samples from the restaurant-associated cases.

3) Environmental Investigation

3.1 Investigation of restaurant X

Restaurant X was found to be well managed with no breaches in food safety or handling identified. Staff were trained in hand washing and general food safety knowledge, including cross contamination and temperature control.

During the observed cooking process, the internal temperature of the pork livers reached 51°C at three minutes and between 82°C and 97°C at four minutes.

The pork liver used for pâté preparation was traced back to a single farm. The pork shoulder, jowl and chorizo products were all sourced from different suppliers to the pork livers. HEV was not detected in any of the food samples obtained from the restaurant.

3.2 Investigation of pork products of locally-acquired cases not linked to restaurant X

Pork products were purchased from four different butchers and three different supermarkets. Traceback of pork livers at two of these butchereries identified two different abattoirs supplied by multiple farms.

On testing, one pork liver sausage was found to have very low levels of HEV RNA. However, the levels were too low for viral sequencing.

4) Public health interventions

On 15 May 2014, restaurant X was informed of the possible link to a number of HEV cases. The importance of thorough cooking of pork products, including pork liver pâté, was stressed and the restaurant voluntarily removed this item from the menu. No further cases of HEV infection were subsequently linked to restaurant X.

NSW Health issued an alert to gastroenterologists in May 2014 and general practitioners in September 2014 requesting that they consider HEV infection in those with a compatible illness regardless of overseas travel (Appendix 2).

A joint media release with the New South Wales Food Authority (NSWFA) was issued in September 2014 urging the public to cook pork products thoroughly, and in particular to cook pork livers to 75°C at the thickest part for 2 minutes (19).

Discussion

This is the first Australian outbreak of locally-acquired HEV infection and to our knowledge, one of the largest linked to a restaurant internationally. Seventeen cases were linked to consuming pork liver pâté at restaurant X over a nine month period, and seven cases were linked to eating pork products bought from four butchers and three supermarkets from at least two different suppliers.

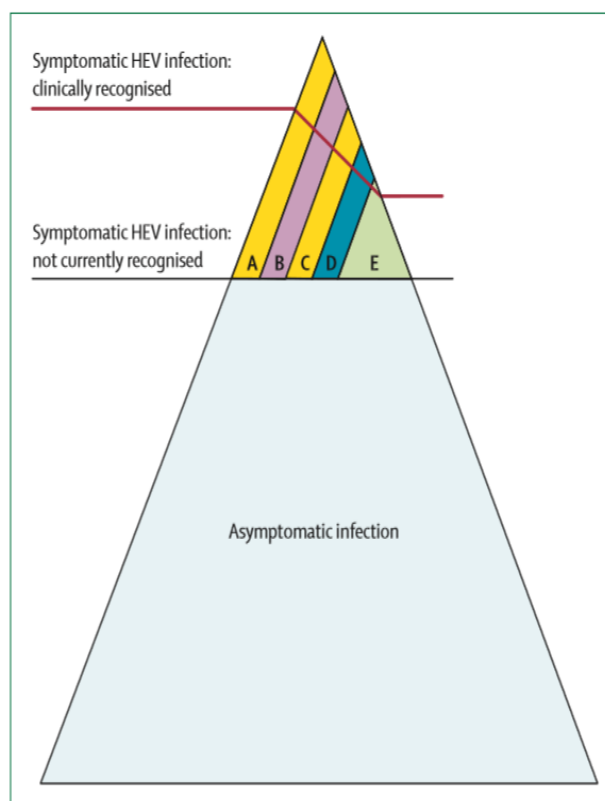
Twelve of 15 restaurant X cases (71%) and four of seven (57%) non-restaurant X cases were male, in keeping with the known epidemiology of genotypes 3 and 4 HEV infections (2). Compared with HEV genotype 1 and 2 infections in the developing world, in developed countries most locally acquired HEV infections are reported in middle-aged and elderly men (2) (20). There are however, no reported age or sex differences in exposure to HEV, suggesting that more men develop symptomatic hepatitis and that host factors must play a role in the development of more overt infection in this sub-population (2). No further explanation has been given to explain this pattern. Some authors suggest that clinically overt disease is more common in those who consume excessive amounts of alcohol (7, 21). This behaviour would put them at risk of hepatic steatosis or hepatic fibrosis which could impact on the host response to HEV infection. Although there may be biological reasons for the preponderance of genotype 3 infections in males, the proportion of males in our study may have been artificially raised due to the fact that five of nine male work colleagues in one dining group were infected.

Retrospective serological testing identified a further eight previously undiagnosed HEV cases (anti-HEV IgM). HEV RNA was detected in two of these who reported no overseas travel but did dine at restaurant X in their incubation period. A further six cases were notified after the restaurant outbreak, likely as a result of increased vigilance and testing by clinicians. Data from a large public health laboratory confirms this, with more than triple the number of HEV tests requested and carried out from July to December 2014 (after the laboratory began testing for HEV in people without a travel history) compared to the same period in 2013 (unpublished data).

To determine the extent of the outbreak, we found additional cases through a variety of methods – testing co-diners of cases, retrospectively testing stored sera and through enhanced awareness of

HEV infection among clinicians. These methods were useful in detecting locally-acquired HEV infections among co-diners of restaurant cases who were either asymptomatic or mildly symptomatic. This suggests that HEV infection is being under-recognised and under-diagnosed in Australia. A recent HEV serosurvey of blood donors conducted by the Australian Blood Service identified HEV infection in 14 of 194 (7%) blood donors without an overseas travel history (22). Asymptomatic infections have been estimated to exceed the number of symptomatic cases by two to four times in waterborne outbreaks and sporadic cases (Figure 3) (2). In parts of Europe, acute HEV infection is diagnosed in 5 – 15% of patients with acute hepatitis for whom Hepatitis A, B and C have been ruled out (20).

Figure 3: Symptomatic, unrecognised and asymptomatic infections with hepatitis E virus genotypes 3 and 4 #



Most infection with HEV3 and HEV4 is either asymptomatic or unrecognised. Current recognised clinical manifestations of HEV3 and HEV4 include: (A) acute icteric hepatitis (more common in elderly males and individuals who drink >22 units of alcohol per week) with a high mortality in patients with chronic liver disease. (B) Chronic infection (HEV3 only). It is usually asymptomatic, and anicteric, and seen in the immunosuppressed, including transplant recipients. (C) Drug-induced injury, often icteric. A few of such patients are misdiagnosed and have HEV3 infection. (D) Neurological injury, usually anicteric. HEV3 is neuropathogenic, but the incidence and scope of associated neurological injury are unknown. (E) Miscellaneous clinical syndromes (eg, HEV3 has been associated with glomerulonephritis).⁸⁵

Adapted from Kamar N, Bendall R, and Legrand-Abravanel F, *Hepatitis E*. The Lancet 2012. **379**: p. 2477–88.

Common source outbreaks of HEV infection in high-income countries are rare. However, our investigation concurs with previous French (6), British (10) and Japanese (11) studies that have linked HEV infection to consumption of under-cooked pork products. In these countries, locally-acquired HEV infections predominate, and in 2013 accounted for 99% of all cases in France (23) and almost 70% in the UK (24).

HEV is inactivated at 71°C (19). Review of pork liver pâté preparation at restaurant X found that it was adequately cooked at the time of inspection and testing of pork samples did not find HEV RNA. It is possible, however, that when the restaurant cases were exposed some weeks earlier, some of the pork livers could have been infected and may have been undercooked at the thickest part prior to being blended into the pâté. This may explain the relatively low number of cases at this popular restaurant.

Although we were able to isolate HEV RNA from the pork sausages of one of the non-restaurant X cases, we were not able to detect virus in the pork livers used to make pate at the restaurant. This is not an entirely unsurprising result. We tested approximately 20 liver samples from restaurant X. In comparison to other studies that have detected HEV in porcine products, this sample size is relatively small. Examples of sample sizes from other studies where HEV RNA has been detected are: eight positive samples from 200 livers tested in a German study (12), five positive from 112 livers in an Italian study (25) and six positive from 283 livers tested in a Canadian study (26). Virus detection is also dependent on the age of pigs that the sample is taken from. The highest rates of HEV seroprevalence is in piglets aged 5 to 12 weeks and in sows (27).

The majority of fresh pork products in Australia are locally produced. The presence of HEV in Australian pig herds was first noted in 1999 in a study that found HEV in commercial pigs in NSW and wild-pigs in the Northern Territory (28). Despite the link between HEV outbreaks and pork products overseas, this discovery of HEV in Australian pigs did not change public health policy nor clinical practice perhaps because HEV was not thought to be endemic to Australian pigs and due to an ignorance of the veterinary literature on this topic.

The findings of this outbreak lead to many possibilities for further research. Even though pork liver and pork sausage have been found to contain detectable levels of HEV, more research needs to be done on other pork products that are available for human consumption, such as various cuts of pork meat. Related to this and as an important control measure for the food service industry, the food and restaurant industry needs more information about the kill steps required to inactivate the virus using different cooking methods. The demographic features of HEV are also interesting. We still do not understand why elderly men are infected with HEV compared to younger men and women. In Australia, we are also yet to learn of the frequency of under-diagnosis and misdiagnosis of HEV infections. In other countries, HEV infection has commonly been misdiagnosed as drug-induced liver injury. A study in the UK showed that six of 47 patients (13%) who met standard criteria for drug-induced liver injury actually had locally-acquired HEV infection (29). A study in the US confirmed these findings with nine of 318 (3%) suspected drug-induced liver injury proving to have HEV 3 infection (30). It is also important that these studies are conducted in Australia. Much of what we know of locally-acquired HEV infections has come from research in European and northern hemisphere countries. These results may not necessarily be generalisable to the Australian population or to Australian pig herds.

A limitation in this investigation includes the delay in case-finding, particularly in testing co-diners of symptomatic cases from restaurant X. A lag in interviewing some cases and co-diners, coupled with the long incubation period of HEV, may have led to a recall bias in answering the questionnaires and food histories. The limited sample size made it difficult to infer statistically significant results. However, the results had biological plausibility and important associations could be deduced.

Our investigation of a cluster of locally acquired hepatitis E virus infection linked to a Sydney restaurant adds to our current understanding of the potential for HEV to be a food-borne illness in developed countries. Clinicians should request HEV testing in patients with acute hepatitis irrespective of travel history and where no aetiology has been determined. Laboratories should test for HEV where indicated to prevent under-recognition of infection. Health departments must be aware of the potential for undercount in hepatitis E surveillance data. Pork products, particularly pork livers, should be cooked until they reach 75°C at the thickest part for 2 minutes. Although much remains to be elucidated of this emerging infection in Australia, increased awareness and ongoing research will enable us to understand its true epidemiology.

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Literature Review

Aim of literature review and research question

In order to better understand the risk of HEV infection associated with pork and pork products, and to complement the outbreak investigation, I conducted a focussed literature review to answer the question:

What is the current evidence for the presence of Hepatitis E virus in pork or pork products in the developed world?

As this field is a constantly evolving area of public health research, I chose to look more specifically at studies published over the last five years - 2010 – 2014, inclusive. I also focussed on research conducted in the developed world setting as these would be most relevant to our outbreak in New South Wales.

Methods

In conducting the literature review, I searched the databases Medline OVID and Scopus for the period 1996 to 2014. Multiple broad and specific search terms were developed for population and outcome components of the question. I applied limits in each of the databases to publication years from 2010 to 2014, I only looked at human research and limited articles to those in the English language.

On the database Scopus, the search terms used were 'hepatitis e in pork liver'. This produced 33 hits. After applying the above limits, the resultant number of hits was 23.

The search terms used in Medline were (Hepat* and E) AND (Infect* or disease* or ill*) AND (pork or swine or pig) AND (Liver/ or Liver disease/). I used keyword and subject heading terms to broaden the scope. This search resulted in 116 hits. When the limits were applied, there were 17 references for consideration.

The abstracts of the 23 articles from Scopus and the 17 articles from Medline were reviewed for consideration of inclusion into the review. Exclusion criteria on abstract review were review articles, case reports, laboratory studies and studies that may have been relevant but were conducted in developing countries.

The final articles for inclusion in the study were four from Scopus and three from Medline (two articles were found to be duplicated in the searches and one of each was included for review).

The relevant articles were sourced from the Australian National University library's electronic journal interface. These journals included the International Journal of Food Microbiology, Emerging Infectious Diseases, Journal of Clinical Virology and the Journal of Infectious Diseases.

Figure 1: Flow chart of database searches, articles included and excluded and final articles for review.

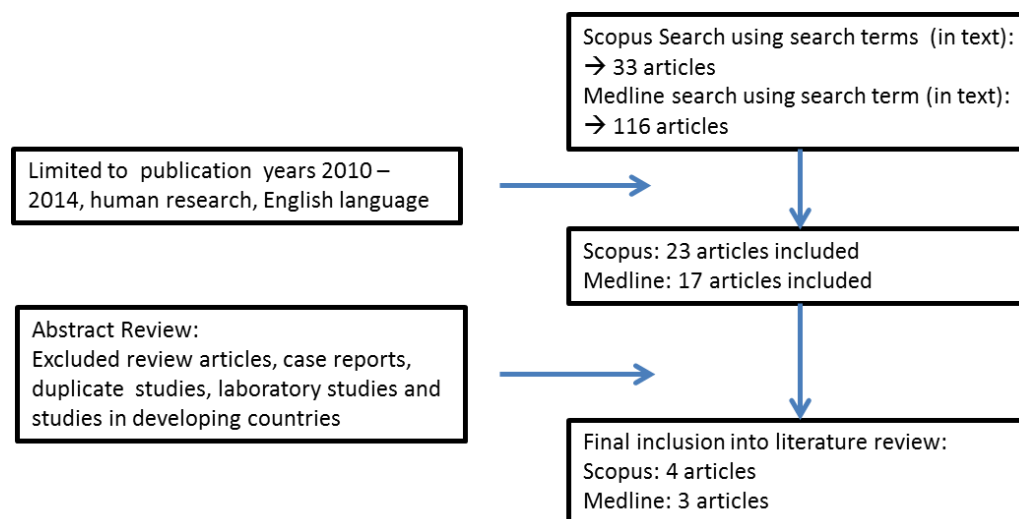


Table of studies published between 2010 and 2014 pertaining to the presence of Hepatitis E virus in pork and pork related products in the developed world

Authors	Reference Details	Country of study	Study Objectives	Relevant Methods	Key Results
Wilhelm B, Leblanc D, Houde A, et al.	International Journal of Food Microbiology 2014; 185: 33 - 40	Canada	To estimate HEV prevalence and load on Canadian retail pork chops and livers	- Retail pork chops and pork liver samples collected weekly from Ontario and Quebec between April 2011 – March 2012 - Nucleic acid extraction, RT-PCR (real time PCR) and viral load estimation was conducted on pork chops and liver	- 283 liver and 599 retail pork chops collected for analysis - HEV detected in 31 samples – 25 pork chops and 6 livers (3.5%); in retail liver prevalence was 8.8% - Mean load of HEV in liver ranged from 1 thousand – 4.7 million genome copies
Berto A, Grierson S, van der Honing RH, et al.	Emerging Infectious Diseases 2013; 19 (2): 264 – 266	France	To investigate the viability of HEV in pork liver sausages produced in France	- Presence of infectious HEV particles were tested by cell culture propagation in samples of HEV positive pork liver sausage from 4 independent manufacturers in 3 locations in Southern France	- HEV RNA was detected in the cell cultures of all 4 sausage samples up to 8 days post infection - 1 out of 4 of the samples had viable HEV that was infectious

Berto A, Martelli F, Grierson S, et al.	Emerging Infectious Diseases 2012; 18 (8): 1358 – 1360	United Kingdom	To investigate contamination by Hepatitis E virus in the pork production chain in the UK	- Between Dec 2009 to Oct 2010, samples from slaughtered pigs, human hands and the environment at critical points for contamination in a pig slaughterhouse, a processing plant and 3 points of retail sale, were collected - Samples were tested by RT-PCR	HEV RNA was detected at the: - slaughterhouse - 5/40 faecal samples, 1/40 livers, 1/4 swabs of workers hands - processing plant – 40 pig muscle samples were negative - points of sale – 6/63 sausages and 2/8 surface samples (knife & slicer swabs)
Di Bartolo I, Diez-Valcarce M, Vasickova P, et al.	Emerging Infectious Diseases 2012; 18 (8): 1282 – 1289	Czech Republic, Italy, Spain	To evaluate the prevalence of hepatitis E virus in the pork production chain in Czech Republic, Italy and Spain during 2010	- Samples were taken from pig faeces, pork liver, meat and sausages, workers hands and surfaces from slaughterhouses and 4 pig farms per country in Italy, Spain and the Czech Republic. - Samples were tested for presence of HEV by RT-PCR	-30/113 faecal, 5/112 liver and 3/112 meat samples were positive for HEV - 6/313 sausages found HEV - HEV was detected in 60% of working surfaces and 57 – 71% of hands and aprons

Wenzel JJ, Preiss J, Schemmerrer M, et al.	Journal of Clinical Virology 2011; 52: 50 - 54	Germany	To test for the presence of HEV RNA in raw, retail porcine livers	200 raw porcine liver samples from 81 butcher shops between April and August 2010 were tested for presence of HEV RNA by RT-PCR	8/200 purchased porcine livers had detectable HEV RNA
Colson P, Borentain P, Queraiux B, et al.	Journal of Infectious Diseases 2010; 202 (6): 825 – 834	France	To investigate the role of figatellu (pig liver sausage) in human HEV infection and to test for the presence of HEV RNA in figatellu	Presence of HEV RNA in 12 figatellu purchased in different stores in South- eastern France tested by RT- PCR	HEV RNA was detected in 7 of the 12 figatellu, with estimated 10^3 – 10^6 HEV RNA copies per slice of sausage
Leblanc D, Poitras E, Gagne MJ, et al.	International Journal of Food Microbiology 2010; 139: 206 – 209	Canada	To determine the viral load of HEV in liver, loin, bladder, lymph node, bile, tonsil, plasma and faeces of pigs at slaughter	Liver, loin, bladder, hepatic lymph node, bile, tonsil, blood and faeces samples were collected from 43 adult pigs, randomly selected from an experimental herd at slaughter over a period of 7 weeks. RNA extraction was performed on all samples and RT-PCR where HEV RNA was detected	- HEV RNA was detected in 14/43 pigs tested; presence in lymph nodes (11/43), bladder (10/43), liver (9/43), bile (8/43), faeces (6/43), tonsils (3/43), plasma (1/43) samples from infected animals; 0 positive in loin samples - Viral loads of 10^3 to 10^7 copies/gram were estimated in positive liver and bile samples.

Evaluation and synthesis of the literature

A focused review of the recent literature related to the presence of hepatitis E virus in pork products in developed countries resulted in the review of seven articles. Although sample sizes were not large, most studies made an attempt to calculate sample sizes required to achieve a significant result.

Although each research paper had slightly varying objectives, the theme around detection of HEV in pork or pork-related products was common.

Presence of HEV in pork products

Hepatitis E virus was detected from a range of porcine products. The presence of the virus in liver ranged from 8.8% - 20.9% in the Canadian studies (1, 2) and 2.5 – 4.5% in the United Kingdom, Czech Republic, Italy, Spain and Germany (3 – 5). Further, HEV was found in retail pork products such as pork liver sausages (figatellu) in France with seven out of 12 (58%) testing positive for HEV (6), six out of 63 (9.5%) sausages in the United Kingdom⁶ and six out of 313 (1.9%) in the Czech Republic, Italy and Spain (4).

Although the pork chops tested in the Canadian study by Wilhelm et al. (1), initially tested positive for presence of HEV, further analysis by quantitative PCR methods found that the virus was not able to be isolated. Interestingly, in the studies by Berto et al. in the United Kingdom (3) and Leblanc et al. in Canada (2), none of the 40 pig muscle samples or the 43 loin muscle samples, respectively, identified the presence of HEV. The relationship between uninfected pork muscle and non-detection of HEV in pork chops remains to be further investigated.

Further the study by Le Blanc et al. (2) detected HEV in hepatic lymph nodes (26%), bladder (23%) and tonsils (7%), suggesting that virus can be isolated from various porcine organs.

Infectivity and viral load of HEV in pork products

Three studies assessed the HEV viral load in pork products – the study by Wilhelm et al. found that the mean load of HEV in retail pork livers was between 1000 to 4, 700, 000 genome copies/gram (1), while the study by Leblanc et al. found between 1000 – 10, 000, 000 copies of the virus per gram liver and bile samples (2). While these two studies purely looked at quantifying viral load, the study by Colson et al. (6) was able to show some relation to human infection. These authors reported that an estimated 1000 – 1, 000, 000 HEV RNA copies per slice of figatellu was found (6).

The significance of the quantity of virus to infection was not further detailed in Colson's study. However Berto et al. in 2013 aimed to investigate the viability of HEV in the very sausages from the above outbreak. Testing of four samples of figatellu resulted in the detection of HEV RNA in all four (7). Further viral culture found that 1 of these 4 positive samples contained viable HEV that was seen on electron microscopy to replicate in-vitro.

Conclusions

The evidence for hepatitis E virus being an epi-zoonotic infection via the foodborne route is mounting. While epidemiological studies have been able to link pork products to human HEV infection, this review found that there is evidence for the presence of HEV in all stages of the pork production chain. HEV RNA is detected in raw and consumable pork products with viral loads significant enough to cause infection. Further research needs to be done to determine the infectious dose of HEV and to detect the presence of the virus in other pork products. More work also needs to be done locally, in Australia, to understand the risks of HEV infection with consumption of local pork products.

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Publication

Revised submission to the *Medical Journal of Australia*

Title: First outbreak of locally acquired hepatitis E virus infection in Australia

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Abstract

Objective: To determine the source and extent of a locally-acquired hepatitis E virus (HEV) outbreak.

Design, setting and participants: A cluster of notified cases HEV infection linked to a single restaurant X was identified in May 2014. Laboratory-confirmed HEV cases in New South Wales between January 2013 and December 2014 were interviewed about potential risk factors for HEV infection. Co-diners at restaurant X and patients with suspected but unexplained viral hepatitis were retrospectively tested. Foods consumed by cases were compared with seronegative co-diners in a retrospective cohort study. HEV RNA detected in sera from cases was sequenced and genotyped. Implicated foods were traced back to the source.

Main outcome measures: Potential sources of infection including overseas travel and foods consumed, origin of implicated food products.

Results: Of 55 serologically-confirmed cases, 24 did not travel overseas in their incubation periods. Of these, 17 reported eating at restaurant X, of whom 15 could be interviewed. All reported consuming pork liver pâté compared with four of seven uninfected co-diners ($p < 0.05$). The remaining seven locally-acquired cases all reported consuming a pork product in their incubation period. HEV RNA was detected in 16 of 24 locally-acquired cases; all were genotype 3. Sequencing showed >99% homology amongst restaurant X cases. HEV RNA was isolated from pork sausages consumed by one of the non-restaurant X, locally-acquired cases. Restaurant pork livers were traced back to a single Australian farm.

Conclusions: This is the first reported HEV outbreak in Australia. HEV should be considered in patients presenting with a compatible illness in the absence of an overseas travel history. Pork products should be thoroughly cooked before consumption.

Introduction

Hepatitis E virus (HEV) outbreaks have not previously been reported in Australia. HEV infection mostly occurs in developing countries where transmission occurs via the faecal-oral route and contaminated water, causing large outbreaks (1). HEV genotypes 1 and 2 predominate in these settings (2). Like other forms of acute viral hepatitis, symptoms of HEV include jaundice, malaise, anorexia, fever and abdominal pain (1). The incubation period is between 15 to 64 days (3).

Recently, HEV transmission has been reported in developed countries where infection has occurred via the foodborne route. Consumption of pork products, deer meat, wild boar and shellfish have been implicated, with HEV genotypes 3 and 4 being detected from infected cases (2, 4-8).

Pigs in particular, may play a role in human HEV transmission (9). An increased risk of HEV infection with consumption of processed pork products was demonstrated in a recent case-control study in the United Kingdom (UK) (10). Human and swine HEV strains also show a high level of sequence relatedness (5, 11, 12). Occupational exposure may be important with pig veterinarians, pig farmers and abattoir workers having higher seroprevalence rates compared with healthy controls (13-15).

In Australia, HEV infection is notifiable to state and territory public health authorities. Common laboratory practice has been to test for HEV infection only in those with a history of overseas travel. Annually, 30 – 40 infections in returned travellers from HEV-endemic regions are reported, with New South Wales (NSW) contributing 10 – 20 of these (16).

In October and November 2013, NSW Health was notified of two apparently unrelated cases of HEV infection over a two week period. The two cases were tested because of overseas travel, albeit outside the incubation period for HEV infection. HEV RNA isolated from these two cases was genetically identical. A family member of one of the cases developed HEV infection four weeks later.

In May 2014, we received a further HEV notification in a man who reported that a work colleague from another state also had HEV infection. Neither had travelled overseas during their incubation periods. The only common exposure was a meal shared with seven other colleagues at restaurant X, and the index case reported that three of the seven were symptomatic. All co-diners were interviewed and tested, and HEV RNA was detected in the three symptomatic co-diners. HEV RNA from the five cases was genotypically identical to each other and to two of the three cases from 2013. On routine interview of the three cases in 2013, one had reported eating at restaurant X in their incubation period while another had not. The third case reported eating at restaurant X in their incubation period when specifically asked about this exposure at re-interview in 2014.

Herein, we report our epidemiological study that investigated the source and extent of the apparent outbreak.

Methods

1. Epidemiological investigation

1.1 Case definition

We defined a case of HEV infection as a person who resided in NSW with laboratory-confirmed HEV, verified by IgG seroconversion or detection of HEV-specific IgM or HEV RNA with an onset date (or specimen collection date when unknown) between 1 January 2013 and 31 December 2014.

1.2 Case finding and data collected

We identified cases in three ways:

1.2.1 Routine notification

As part of routine surveillance, pathology laboratories are required by the NSW Public Health Act 2010 to notify public health units (PHUs) of HEV cases. Surveillance specialists interviewed cases using a standardised questionnaire. Information collected includes symptoms of illness, occupation, travel history, water and food sources (including restaurants) in the incubation period. Where a case had eaten at restaurant X, the interviewer asked details of foods consumed.

1.2.2 Testing of co-diners from restaurant X

Co-diners of cases from restaurant X were interviewed and tested for HEV.

1.2.3 Retrospective serological surveys

We tested all sera stored at a large public laboratory with specimen dates between 1 September 2013 and 31 May 2014, where HEV testing had been requested but not carried out because laboratory protocols excluded testing in the absence of relevant travel history (survey 1).

We also tested sera stored at a major NSW private pathology laboratory with specimen dates between 1 January and 31 May 2014, where the alanine transaminase (ALT) level was >200 IU/L and hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus and cytomegalovirus infection had been excluded but HEV testing was not performed (survey 2).

2. Laboratory investigation

2.1 Serology

Anti-HEV IgM and IgG were detected using HEV IgM ELISA 3.0 and HEV ELISA kits respectively (MP Diagnostics, MP Biomedicals, Singapore) according to the manufacturer's instructions. Reactive sera were retested and reported as positive if repeat reactive.

2.2 Viral detection and sequencing

Serum samples from confirmed cases were analysed at the Victorian Infectious Diseases Reference Laboratory (VIDRL). HEV RNA was extracted from serum using the QIAamp Viral RNA Mini Kit (QIAGEN, Melbourne, Australia) and initially tested using a commercial HEV RNA PCR assay (RealStar HEV RT-PCR, Altona Diagnostics, Germany). Samples containing HEV RNA were re-assayed by an in-house polymerase chain reaction (PCR) assay using primers designed to amplify a portion of the open reading frame (ORF) 2. The resulting PCR product was directly sequenced with internal primers. Sequences were aligned and compared with sequences in GenBank.

3. Environmental investigation

3.1 Investigation and food testing linked to restaurant X

Food handling and safety procedures at restaurant X were reviewed on 15 May 2014. Preparation of pork liver pâté was observed in detail. The internal temperature of sliced pork livers was measured by inserting a thermometer into the thickest part at three and four minutes of cooking.

Three lots of chorizo sausage, three batches of cooked pork liver pâté, one sample of raw pork shoulder and raw pork jowl, one batch of cooked pork liver and eight raw pork liver samples from restaurant X were collected on 15 and 22 May 2014.

After extraction and purification using the MagMax™ Total RNA Isolation Kit (Life Technologies, California, USA), samples were tested for HEV by Advanced Analytical Australia using the hepatitis E@ceeram Tools™ (Ceeram S.A.S, La Chapelle-Sur-Erdre, France), utilising real time PCR.

Pork products were traced back to their source by identifying the supplier from records held at the food premise. Through the supplier, we identified the farms from which the products originated.

3.2 Testing of pork liver sausages from HEV case not linked to restaurant X

One of the cases without a link to restaurant X reported eating pork liver sausages in the incubation period. This case had frozen uncooked sausages stored in a domestic freezer. Multiple samples were collected from several sausages and analysed for the presence of HEV at the Virology Laboratory, Elizabeth Macarthur Agriculture Institute. Nucleic acid was purified and tested by real time reverse transcription quantitative PCR (qRT-PCR) (17) using previously published primers and probe sequences (18).

4. Data analysis

Responses from case questionnaires were retrieved onto a Microsoft Excel spreadsheet for analysis. Responses from food histories were analysed and relative risks and confidence intervals calculated using EpiInfo version 7. A two-tailed Fisher's exact test was used to test for significant differences between groups with p-values <0.05 considered significant.

5. Ethics

These studies were conducted as part of a public health investigation under the NSW *Public Health Act* 2010 and human research ethics committee review was not required.

Results

1. Epidemiological investigation

1.1 Notified HEV cases

Between January 2013 and December 2014, laboratories notified 55 cases of HEV (Figure 1). The median age was 45 years (range 4 – 77), 36 (65%) were male and all but one (98%) lived in metropolitan Sydney. Twenty-four (44%) required hospitalisation with a reported median length of stay (where known) of seven days (range 1 – 67). Three cases (identified as co-diners of notified cases) were asymptomatic, and symptoms were unknown in one case. Thirty seven cases had ALT recorded; elevated levels occurred in 33 cases with a median value of 1058 IU/L (range 26 – 4868). None were pregnant.

Of 55 cases, 30 (55%) reported a history of overseas travel in their incubation period to South Asia (17), East Asia (6), South East Asia (2), Africa (2), Europe (2) and the Middle East (1). Apart from one case who could not be contacted, the remaining 24 (44%) did not report overseas travel.

1.2 Restaurant X outbreak

Restaurant X mainly served dishes suitable for sharing in a group. The menu includes over 28 items of meat, seafood and vegetarian options.

Seventeen cases from nine separate groups with dining dates between October 2013 and May 2014 were linked to restaurant X. Of these, seven were identified through routine surveillance, eight by testing co-diners and two from the retrospective serosurveys. Two cases refused further interview; food histories were collected from the remaining 15 cases and seven dining companions who tested HEV negative by serology.

The most commonly consumed food items are reported in Table 1. Highest attack rates were in those who consumed pork pâté and roast pork. All 15 cases with complete food histories reported consuming pork pâté compared with four of seven uninfected co-diners ($p < 0.05$).

1.3 Locally acquired cases not linked to restaurant X

On interview, these seven cases reported consuming multiple pork products in their incubation periods. They included supermarket ham, prosciutto, pork liver, homemade pork liver sausage, pork chops and pork belly.

1.4 Retrospective serological surveys

Of 136 serosurvey samples, (31 in survey 1 and 105 in survey 2), nine (6.6%) were IgG positive, four (2.9%) were IgM positive and four (2.9%) were both IgM and IgG positive. Of the eight IgM positive cases, HEV RNA was detected in four with sequencing confirming genotype 3. Two of these four cases reported eating at restaurant X but no overseas travel, one reported travel to an HEV-endemic country and one was uncontactable.

2. Laboratory Investigation

HEV RNA was detected in 10 of the 17 restaurant X cases (five were PCR negative with mild or no symptoms, one was PCR negative but demonstrated seroconversion and a sample was unavailable from one case). Sequencing of the ORF 2 region was successful for all ten samples and HEV was classified as genotype 3. There was at least 99% sequence homology in the targeted portion of ORF 2 between samples.

HEV RNA was also detected in six of the seven non-restaurant locally-acquired cases (one had insufficient specimen for testing) - five were genotype 3 and one had insufficient sample for genotyping. Viral sequence of these samples showed approximately 90% similarity to the samples from the restaurant-associated cases.

3. Environmental Investigation

3.1 Investigation of restaurant X

Restaurant X was found to be well managed with no breaches in food safety or handling identified. Staff were trained in hand washing and general food safety knowledge, including cross contamination and temperature control.

During the observed cooking process, the internal temperature of the pork livers reached 51°C at three minutes and between 82°C and 97°C at four minutes.

The liver used for pâté preparation was traced back to a single farm. The pork shoulder, jowl and chorizo products were all sourced from different suppliers to the pork livers. HEV was not detected in any of the food samples obtained from the restaurant.

3.2 Investigation of pork products of locally-acquired cases not linked to restaurant X

Pork products consumed by these seven cases were purchased from four different butchers and three different supermarkets. Traceback of pork livers at two of these butcheries identified two different abattoirs supplied by multiple farms. Further traceback was not done.

On testing, retained pork liver sausages from one case was found to have very low levels of HEV RNA. However, levels were too low for sequencing.

4. Public health interventions

NSW Health convened an expert panel involving public health, clinical, laboratory, agricultural and industry experts to assess the risks and guide the investigation.

On 15 May 2014, restaurant X was informed of the possible link to a number of HEV cases. The importance of thorough cooking of pork products, including pork liver pâté, was stressed and the restaurant voluntarily removed this item from the menu. No further cases of HEV infection were linked to restaurant X.

As part of case finding, NSW Health issued an alert to gastroenterologists and public and private pathology laboratories in May 2014. The information garnered was then used to inform general practitioners in an alert issued in September 2014 requesting that they consider HEV infection in those with a compatible illness regardless of overseas travel.

A joint media release with the New South Wales Food Authority (NSWFA) was issued in September 2014 urging the public to cook pork products thoroughly, and in particular to cook pork livers to 75°C at the thickest part for 2 minutes (19).

Discussion

This is the first reported Australian outbreak of locally-acquired HEV infection and to our knowledge, one of the largest linked to a restaurant internationally. Seventeen cases were linked to consuming pork liver pâté at restaurant X over a nine month period, and seven cases were linked to eating pork products bought from four butchers and three supermarkets from at least two different suppliers.

Retrospective serological testing identified a further eight previously undiagnosed HEV cases (anti-HEV IgM). HEV RNA was detected in two of these who reported no overseas travel but did dine at restaurant X in their incubation period. A further six cases were notified after the restaurant outbreak, likely as a result of increased vigilance and testing by clinicians. Data from a large public health laboratory confirms this, with more than triple the number of HEV tests requested and carried out from July to December 2014 (after the laboratory began testing for HEV in people without a travel history) compared to the same period in 2013 (unpublished data).

Active case finding amongst co-diners of restaurant cases detected some locally-acquired HEV infections who were either asymptomatic or mildly symptomatic, suggesting under-recognition and under-diagnosis of infection. A recent HEV serosurvey of blood donors conducted by the Australian Blood Service identified HEV infection in 14 of 194 (7%) blood donors without an overseas travel history (20). A case report in the Northern Territory (21) and a study in Victoria (22) describe one HEV case in each jurisdiction where overseas travel was not reported and no other risk factors were identified.

Common source outbreaks of HEV in high-income countries are rare. However, our investigation concurs with previous French (5), English (10) and Japanese (11) studies that have linked HEV infection to consumption of under-cooked pork products. In these countries, locally-acquired HEV infections predominate, and in 2013 accounted for 99% of all cases in France (23) and almost 70% in the UK (24).

HEV is inactivated at 71°C (19). Review of pork liver pâté preparation at restaurant X found that it was adequately cooked at the time of inspection and testing of available pork samples did not find HEV RNA. It is possible, however, that when the restaurant cases were infected some weeks earlier, some pork livers could have been contaminated with HEV and may have been undercooked at the thickest part prior to blending into pâté. This may explain the relatively low proportion of patrons infected with HEV at this popular restaurant. While we did not have access to leftover pâté samples served to restaurant X cases to test for HEV RNA, HEV RNA was detected in samples of retained pork liver sausages consumed by a non-restaurant X case.

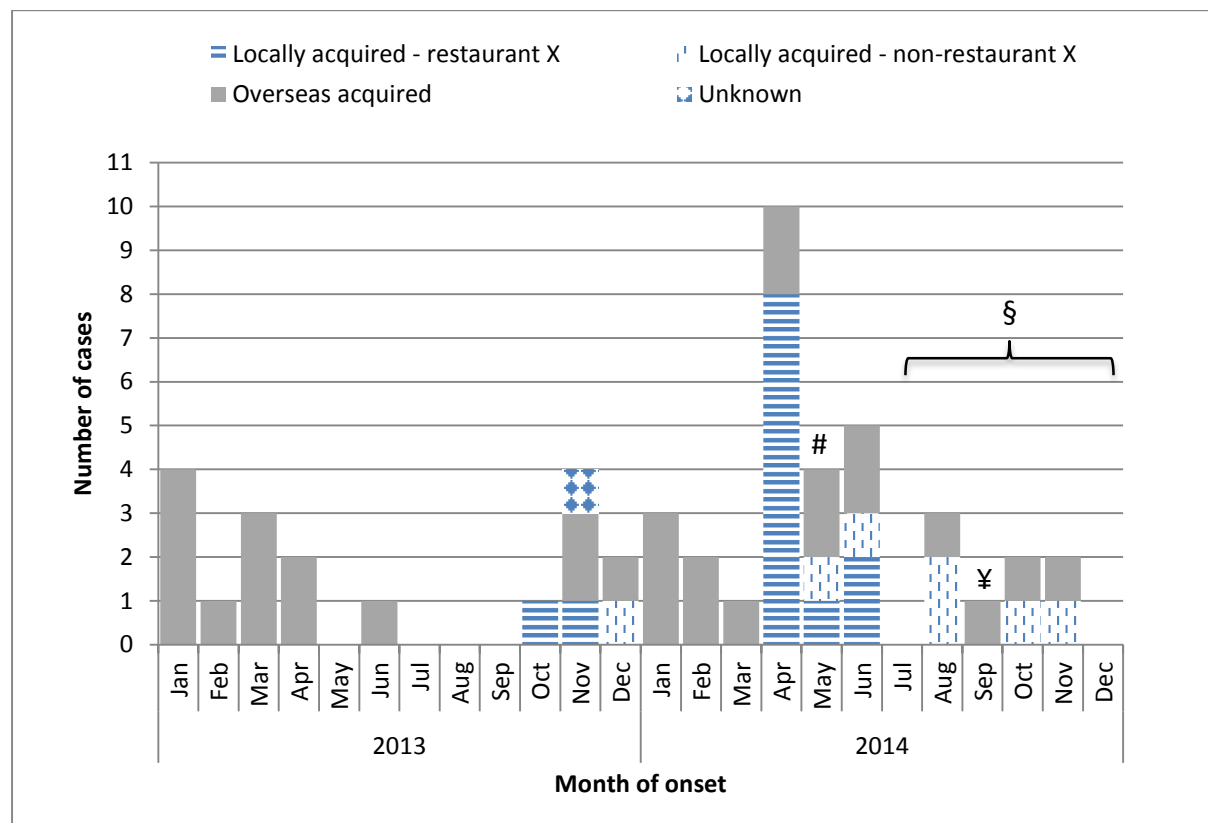
The majority of fresh pork products in Australia are locally produced. The presence of HEV in Australian pigs was first noted in 1999 in a study that reported seropositivity rates of 17% in wild-caught pigs and > 90% in commercial pigs by 16 weeks of age (25). To our knowledge, no further studies investigating the epidemiology of HEV in Australian pigs have been conducted. Despite the link between HEV outbreaks and pork products overseas, this discovery of HEV in Australian pigs did not translate into clinical practice perhaps because HEV was not thought to be endemic to Australian pigs and due to a lack of awareness of the veterinary literature in Australia.

A limitation in this investigation includes the delay in case-finding, particularly in testing co-diners of symptomatic cases from restaurant X. A lag in interviewing some cases and co-diners, coupled with the long incubation period of HEV, may have led to a recall bias in answering the questionnaires and food histories. The limited sample size made it difficult to infer statistically significant results. However, results had biological plausibility and important associations could be deduced.

This study adds to our current understanding of the potential for HEV to be a food-borne illness in developed countries. Clinicians should request HEV testing in patients with acute hepatitis irrespective of travel history, particularly where no aetiology has been determined. Laboratories should test for HEV where indicated to prevent under-recognition of infection. Health departments must be aware of the potential for undercount in hepatitis E surveillance data. Pork products, particularly pork livers, should be cooked until they reach 75°C at the thickest part for 2 minutes.

Increased awareness, ongoing research and collaboration between primary industries, animal and human health authorities should help in detecting and preventing this and future emerging infectious diseases in Australia. .

Figure 1: Notifications of HEV infections in NSW with onset dates between January 2013 and December 2014 by likely source of acquisition *



* excludes 3 asymptomatic cases and 1 case with unknown symptom history

May 2014: Restaurant X inspected and pork pate identified as possible source of infection; restaurant voluntarily removed pork pate from the menu. Alert issued to gastroenterologists and laboratories

¥ September 2014: Alert issued to general practitioners and public

§ July – December 2014: Increased HEV testing reported by main public laboratory

Table 1: Characteristics and reported food consumption of diners at restaurant X over the period October 2013 – May 2014

Characteristic				Cases, n = 17			Well co-diners, n = 7	
Age, median (range) years				48 (29 – 75)			45 (29 – 47)	
≤ 39, no (%)				5 (29)			1 (14)	
40 – 59, no (%)				6 (35)			5 (71)	
60 +, no (%)				6 (35)				
Unknown							1 (14)	
Male sex, no (%)				12 (71)			4 (57)	
Food items consumed *								
	Number of people who ate			Number of people who did not eat			RR (95% CI)	p-value
	Cases	Total	Attack Rate (%)	Cases	Total	Attack rate (%)		
Brussel sprouts	5	8	63	8	12	67	1 (0.5 – 1.8)	1.00
Calamari	3	5	60	10	15	67	1 (0.5 – 2.0)	1.00
Eggplant	7	12	58	6	8	75	0.8 (0.5 – 1.5)	0.66
Pork chorizo	7	9	78	6	11	55	1.5 (0.8 – 2.7)	0.36
Pork pate	15	19	79	0	3	0	Undefined	0.02
Roast pork	9	13	69	4	7	57	1.2 (0.6 – 2.6)	0.64

* complete food histories available for 15 of 17 cases and all seven well co-diners

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Conference oral presentation

International Conference on Emerging Infectious Diseases

Atlanta, Georgia

24 August 2015

First outbreak of locally acquired hepatitis E virus in Australia

Chatu Yapa

Furlong C, Rosewell A, Ward K, Adamson S, Bowden S, Kok J, Shadbolt C, Smedley L, McNeill T, Ferson M, Staff M, Sheppard V, McAnulty J

 Australian National University
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 NSW HEALTH

Furlong C, Rosewell A, Ward K, Adamson S, Bowden S, Kok J, Shadbolt C, Smedley L, McNeill T, Ferson M, Staff M, Sheppard V, McAnulty J



Genotype 1 and 2
• Indemic
• Waterborne

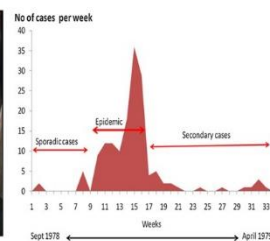
Genotype 3
• Sporadic
• Zoonotic

Genotype 4
• Sporadic
• Zoonotic

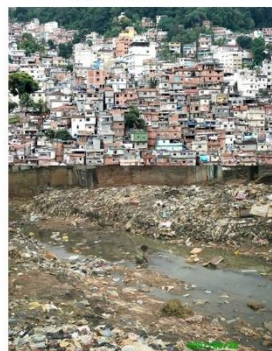
Genotype 5
• Sporadic
• Zoonotic

Source: Kamar et al., Hepatitis E, *Lancet*; 2012; 379 (9835): 2477–2488

- HEV first recognised in Kashmir in 1978



Genotypes 1 & 2



The diagram illustrates the water cycle and the flow of information between the environment and the brain. The water cycle is shown with a river, clouds, and arrows indicating evaporation, condensation, precipitation, and runoff. The flow of information is shown with arrows between the brain and the environment, labeled 'Senses' and 'Motor control'. The environment is depicted with a river, trees, and animals.

Source: Kamar et al., Hepatitis E, *Lancet*; 2012; 379 (9835): 2477–2488

- That famous yoghurt shake...

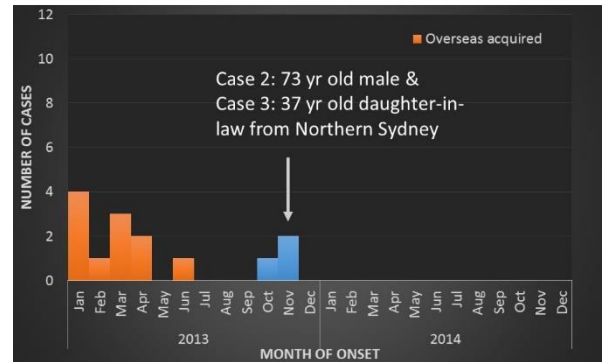


- Incubation period: 15 to 64 days

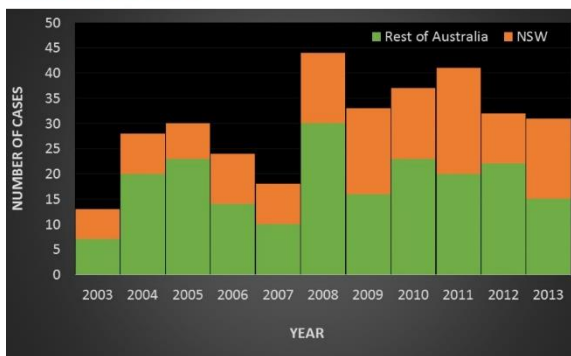
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Hepatitis E notifications in New South Wales, January 2013 – December 2014



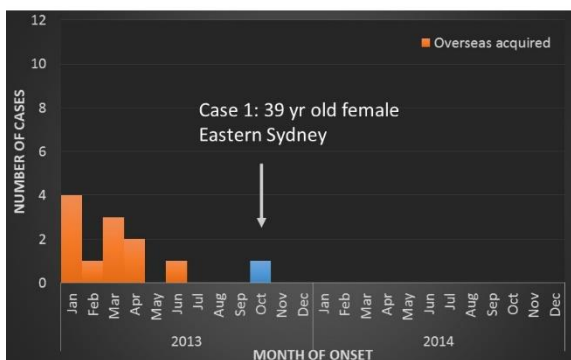
Hepatitis E notifications in Australia between 2003 and 2013



Investigations in 2013



Hepatitis E notifications in New South Wales, January 2013 – December 2014



More clues in May 2014...



- Man from Sydney & work colleague from Melbourne HEV positive
- Neither had history of overseas travel
- Only common exposure:
 - meal at restaurant X on 11 March 2014
- 9 attendees at dinner – all interviewed & tested
 - 3 more symptomatic & HEV positive

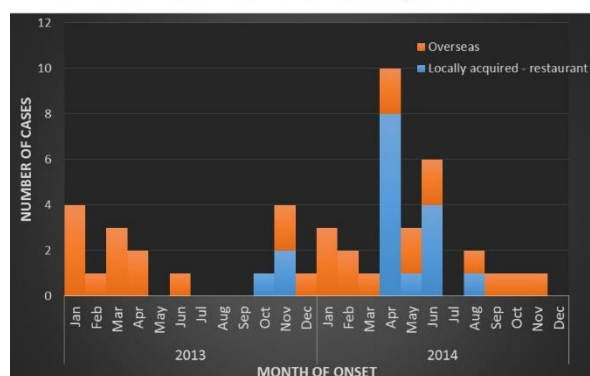
Back to 2013 -----

- Case 1
restal
- Case 2
questi
- Case 3

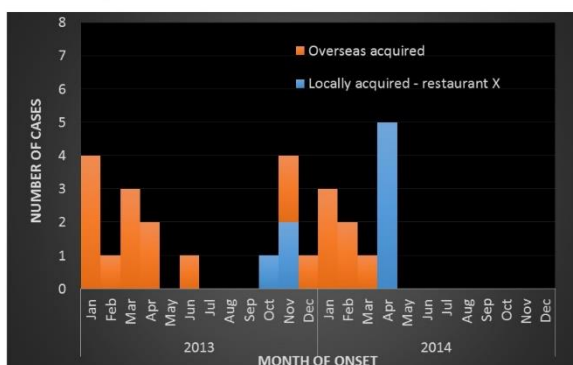


ating at
initial

18 cases linked to restaurant X with dining
dates between Oct 2013 & May 2014



Hepatitis E notifications in New South Wales, January 2013 – December 2014

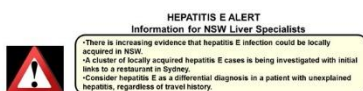


Description of HEV-infected diners

Characteristic	Ill, n = 18
Age, median (range) yrs	48 (29 – 75)
≤ 39 yrs	5
40 – 59 yrs	7
60+ yrs	6
Male sex, no (%)	13 (72%)
Hospitalised for infection	4 (24%)
Asymptomatic	3 (17%)

Further epidemiological investigations:

- Active case finding by:
 - Retrospective serological testing
 - Alerts to raise awareness of gastroenterologists, family doctors & laboratories
 - As cases emerged, interviewed and tested co-diners
- Retrospective clustered cohort study of diners



Description of HEV-infected diners & well co-diners

Characteristic	Ill, n = 18	Not Ill, n = 7
Age, median (range) yrs	48 (29 – 75)	45 (29 – 47)
≤ 39 yrs	5	1
40 – 59 yrs	7	5
60+ yrs	6	
Unknown		1
Male sex, no (%)	13 (72%)	4 (57%)
Hospitalised for infection	4 (24%)	N/A
Asymptomatic	3 (17%)	N/A

Restaurant X



Environmental & Microbiological Investigations

- Restaurant inspection satisfactory
- All pork samples tested from restaurant did not find HEV RNA
- Pig livers used for pate traced back to a single piggery in NSW
- 11/18 cases sequenced:
All genotype 3 with 95 – 99% sequence homology

What did they eat?

Foods consumed:	Ill, n = 15	Not ill, n = 7	RR (95% CI)	p-value
Brussels sprouts, no (%)	5 (33%)	3 (43%)	1 (0.54 – 1.84)	1.00
Calamari, no (%)	3 (20%)	2 (29%)	1 (0.51 – 1.95)	1.00
Eggplant, no (%)	7 (47%)	5 (71%)	0.8 (0.5 – 1.5)	0.66
Pork chorizo, no (%)	7 (47%)	2 (29%)	1.5 (0.8 – 2.7)	0.36
Pork pâté, no (%)	15 (100%)	4 (57%)	Undefined	0.02
Roast pork, no (%)	9 (60%)	4 (57%)	1.3 (0.6 – 2.6)	0.64



Veterinary Microbiology 68 (1999) 95–105

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microbiology**
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Serological evidence for swine hepatitis E virus infection in Australian pig herds

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Abstract

Hepatitis E virus (HEV) is an enterically transmitted human pathogen, with some similarities to caliciviruses. A variant of HEV was recently identified in pigs in the USA, inflicting almost 100% of animals in commercial herds. Phylogenetic analysis suggests that this is a true 'swine HEV' distinct from the human virus, but the swine virus may also infect man. Using an in-house ELISA based on a highly conserved, recombinant HEV protein, we have examined collections of sera from Australian pigs for evidence of HEV infection in local pig herds. Sera from one research herd (n = 32) were uniformly non-reactive, and this was used to establish an assay cut-off (= mean + 3 SD of reference pig serum reactivities). Screening of sera from other herds demonstrates that swine HEV is present in Australia.

Results: Food histories

Foods consumed:	Ill, n = 15	Not ill, n = 7	RR (95% CI)	p-value
Brussels sprouts, no (%)	5 (33%)	3 (43%)	1 (0.54 – 1.84)	1.00
Calamari, no (%)	3 (20%)	2 (29%)	1 (0.51 – 1.95)	1.00
Eggplant, no (%)	7 (47%)	5 (71%)	0.8 (0.5 – 1.5)	0.66
Pork chorizo, no (%)	7 (47%)	2 (29%)	1.5 (0.8 – 2.7)	0.36
Pork pâté, no (%)	15 (100%)	4 (57%)	Undefined	0.02
Roast pork, no (%)	9 (60%)	4 (57%)	1.3 (0.6 – 2.6)	0.64

Public health actions

- Communications with family doctors and laboratories
 - Consider HEV as cause of unexplained acute hepatitis regardless of travel history
- Media release



Media release

11 September 2014

Warning about Hepatitis E cases linked with pork liver
NSW Health is warning consumers of the public to thoroughly cook pork products, particularly pork liver, after three recent notifications of Hepatitis E in NSW in people who have not travelled to high-risk countries.
NSW Health is collaborating with the State Food Authority and the Department of Health to investigate the cases which were recorded over the past few days.
Dr Jeremy McIsaac, the Director of Public Health, said: "We have received reports from three individuals who have consumed pork liver, after consuming other pork liver in past few days, and have been diagnosed with Hepatitis E."
"Hepatitis E virus has previously been identified in Australian pig herds but until recently there has been no evidence that humans have acquired the virus from pork products in Australia."
"Hepatitis E is a highly contagious disease that is spread through the faeces of infected animals. It is not spread from person to person, and it is not spread from water, although infections have been linked to the consumption of pork products in other developed countries. The virus has been seen in Australia before."
The cases were seen in notifications of Hepatitis E to NSW. In 2013 there were 25 notifications and in 2012 there were 12 notifications. All 2014 cases thought to have been acquired overseas.

Summary

- First outbreak of locally acquired HEV infection in Australia
- Undiagnosed cases found as a result of active case finding
- Pork pate sourced from pigs at a local farm implicated in infection

Conclusions:

- HEV should be considered as a differential diagnosis in a patient with unexplained acute hepatitis, regardless of travel history
- Australian pigs are a potential source of HEV infection
- Pork products, especially liver, should be thoroughly cooked

Acknowledgements:

Outbreak investigation team
Dr Jeremy McAnulty
CIDMLS, RPAH and DHM laboratories
Public Health Units
National Centre for Epidemiology & Population Health

Summary for lay person

Press Release for 2015 International Conference on Emerging Infectious Diseases Conference, Atlanta, Georgia, August 2015

PAPER CONTROL NUMBER: 620

POPULAR TITLE: First outbreak of hepatitis E virus in Australia

TECHNICAL TITLE: First outbreak of locally acquired hepatitis E virus infection in Australia

PRESENTATION SUMMARY:

Epidemiologists identified the first outbreak of hepatitis E virus (HEV) in Australia in May 2014. The outbreak occurred amongst diners at a single restaurant in Sydney with undercooked pork liver pate being the most commonly consumed food item among infected diners.

As a result of this outbreak, the public and restaurateurs have been urged to cook pork livers thoroughly before consumption. Australian doctors have been asked to consider testing for HEV in patients presenting with a compatible illness.

This work was led by the Enterics team at the Communicable Disease Branch (CDB) of Health Protection New South Wales (NSW), located in Sydney, Australia. Other collaborators included the NSW Food Authority, public health reference laboratories and public health units. Funding, where needed, was provided by the CDB. The findings will be presented at the International Conference on Emerging Infectious Diseases in Atlanta, Georgia on 26 August 2015.

Infection with HEV usually occurs in developing countries where large outbreaks occur due to contaminated water systems and poor sanitation. In the developed world, the risk of acquiring HEV from contaminated food products is increasingly evident, but has never been reported in Australia.

The epidemiological investigation was conducted over the period October 2013 to September 2014. Investigators found cases through multiple ways - routine notification by laboratories, testing and interviewing co-diners of cases, testing patients with suspected viral hepatitis and by alerting medical practitioners to the outbreak. In total, 17 HEV cases were linked to the restaurant with dining dates between October 2013 and May 2014.

Information was collected on foods consumed at the restaurant from both cases and their dining companions for comparison. Pork liver pâté was the only food consumed by all 15 restaurant cases with complete food histories.

Blood samples from confirmed cases were sent to the Australian reference laboratory to check whether HEV could be detected. Viral material could be picked up in 11 of the 17 cases. Further testing showed that there was more than 99% similarity in the viral genetic material between cases.

An official restaurant inspection found it to be well managed with no major breaches in food safety and handling. After the restaurant assessment and subsequent removal of the pork liver pate from the menu, no further cases of HEV infection were linked to the restaurant.

Appendices

Appendix 1: Study proposal for retrospective testing of stored sera for Hepatitis E Virus

For dissemination to: Institute of Clinical Pathology and Medical Research (ICPMR)

Background on Hepatitis E:

Infection with the hepatitis E virus (HEV) is a major cause of epidemic and acute sporadic hepatitis in countries where it is considered hyper-endemic - more than 50% of hepatitis cases in regions of Asia, Africa and Central America are due to HEV. It is thought that the high prevalence in these countries is due to weak public health systems and poor sanitary conditions which aid in the transmission of the virus via the faecal-oral route and contaminated water systems.

In more developed countries, hepatitis E infections are thought to occur infrequently and are predominantly in individuals who have acquired the infection during travel to an endemic area. However, more recently, there have been increasing reports of autochthonous infections in parts of Europe, Japan and the United States. While there is no evidence for one main transmission route or risk factor, several reports have demonstrated evidence for foodborne zoonotic transmission. Sources implicated have been undercooked meat products such as pork, deer and offal, as well as shellfish. Contact with animals (such as pigs and domestic cats/dogs) and parenteral transmission via HEV-contaminated blood transfusions have also been reported as other routes of transmission.

Seroprevalence studies, mostly conducted on blood donors in developed countries report variable rates of HEV prevalence. It ranges from 3% in Japan, 16.6% - 40% in different parts of France, 16% in southwest England and 21% in the USA.

Clinical Presentation and Diagnosis:

The clinical presentation of hepatitis E in humans is indistinguishable from hepatitis A. It is a self-limiting illness and commonly reported symptoms are fever, anorexia, abdominal pain, nausea and vomiting accompanied by jaundice and hepatomegaly.

The diagnosis of acute infection is based on the presence of anti HEV IgM antibodies that can be detected during the acute, symptomatic phase of the illness and can last for 4 or 5 months. IgG antibodies appear soon after the rise of IgM and they steadily increase from the acute to the convalescent phase, and may be present for up to 4.5 years after acute infection. Definitive laboratory evidence requires detection of the virus by nucleic acid testing, IgG seroconversion or a fourfold or greater rise in titre to hepatitis E virus.

In Europe, acute HEV infection is diagnosed in 5 – 15% of patients with acute hepatitis for whom Hepatitis A, B and C have been ruled out. Requests for HEV testing in patients without a travel history continue to be infrequent and consequently the actual number of hepatitis E cases may be underestimated.

Current Situation in NSW

HEV infection has not been considered a risk in NSW. Each year, there are between 10 to 20 cases notified of which almost all report overseas travel in their incubation period.

However, since November 2013 to date, there have been 8 notified cases of HEV in NSW which have all been locally acquired. Seven of the eight cases did not have a history of overseas travel in their incubation period, and the remaining one was overseas for only 2 days during the risk period.

Aims of this proposed study

To identify any possible 'missed cases' in New South Wales, we propose to conduct a study of sera which have been stored at ICPMR.

Sera will be tested for Hepatitis E IgG and IgM at ICPMR if the following criteria are met:

- Request for Hepatitis E regardless of travel history
- Request for hepatitis screen and Hepatitis A, B and C negative
- ALT level indicative of acute hepatitis
- Tested between 1 September 2013 and 30th May 2014
- Resident of New South Wales

Requirements from ICPMR

A line listed of de-identified sera based on the above criteria, with the following information:

- Specimen number
- Collection date 01/09/13 - 30/05/14
- Referring laboratory/hospital (+ referring laboratory specimen ID if available to monitor for duplication with PaLMS, DHM)
- Date of birth
- Requesting doctor
- Residential post code (in NSW)
- ALT level – if available
- HAV IgM, HbsAg, Anti-HCV – if available

Where information on an ALT level, Hepatitis A/B/C results are unknown, CDB will attempt to access these results from the referring laboratory. Further testing - If any selected sera are found to be HEV IgM positive, they should be held and considered for referred to VIDRL for HEV PCR.

Ethical considerations

Hepatitis E is a notifiable condition in NSW, hence any patients testing positive for HEV should be notified to NSW Health.

If a case is identified through the serostudy by being IgM and/or PCR positive, the referring doctor of the case will be contacted by Health Protection NSW or the local PHU, informed of the diagnosis and requested to inform their patient. The case will then be followed up as per usual protocols.

Financial implications:

An HEV IgM and IgG test costs \$73 per sample at ICPMR. A sample size calculation to determine the number of samples that should be tested to estimate the population prevalence with good precision was done. This showed that 240 samples should be tested (using a HEV seroprevalence rate of 6% in Australia as per the confidential results of the Australian Red Cross serosurvey of blood donors).

If this number of samples was tested, the total cost would be \$17,520. However, it is anticipated, that by using the criteria for testing above, the likely number of samples tested will be much less than 240, reducing the cost.

Impact of study

This study will add to our understanding of the epidemiology of HEV in New South Wales – a condition which has not been considered of major public health significance in Australia.

It will also help inform a current investigation of a possible food-borne outbreak of HEV at a restaurant in Sydney.

Appendix 2: Hepatitis E alert to New South Wales Liver specialists

Information for NSW Liver Specialists



1. There has been a cluster of locally acquired hepatitis E cases linked to a restaurant in Sydney.
2. An investigation is currently underway to identify the source of the outbreak – the most likely possibility is that it is foodborne.
3. Consider hepatitis E as a differential diagnosis in a patient with unexplained hepatitis, regardless of travel history.

Key points:

- Since November 2013, there have been 7 confirmed cases of hepatitis E (HEV) notified in NSW and 1 in Victoria all linked to eating in a single Sydney restaurant.
- 7/8 cases had an illness with liver enzyme derangement, several with classical viral hepatitis presentation.
- Food histories from the cases so far (6/6) reveal that all have eaten at least one pork product at this restaurant.
- Future actions are focused on active human case finding and investigation of HEV in Australian pigs.

Background:

- Hepatitis E infection is uncommon in the developed world and is usually associated with a history of travel to an endemic area.
- Locally acquired cases have been reported in parts of Europe, Japan and the USA and have been linked to shellfish and undercooked meat products such as pork, deer and offal. Seroprevalence studies suggest HEV prevalence is relatively high in these countries – 20-40% in France, 20% in USA.
- In NSW, there are 10-20 cases of HEV notified per year of which almost all report overseas travel in their incubation period. The infection has not been considered a risk in NSW.
- Clinically, HEV presents similarly to hepatitis A with symptoms of nausea, vomiting, abdominal pain, fever, dark urine and jaundice.

Investigations:

1. Consider testing for HEV in individuals who have unexplained jaundice and liver enzyme derangement with or without a history of travel to an HEV endemic country.
2. The presence of HEV IgM or IgG is suggestive of infection and levels are detectable at the onset of symptoms.
3. Definitive laboratory evidence requires detection of the virus by nucleic acid testing, IgG seroconversion or a fourfold or greater rise in titre to hepatitis E virus

Further information:

- To notify suspected cases or for further information please phone your local Public Health Unit at any time on 1300 066 055 and ask to speak with a member of the Infectious Diseases team.
- NSW Health Hepatitis E website:
http://www.health.nsw.gov.au/Infectious/factsheets/Pages/Hepatitis_E.aspx

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Chapter 4:

Outcomes of a Medecins sans Frontieres Ebola Transit Unit in Liberia

“About a year ago, we were invaded by an enemy we did not know and were not prepared to confront. The deadly Ebola Virus Disease caused the deaths of many of our fellow citizens and robbed many more of their livelihoods. It overwhelmed our recovering health care system and threatened to reverse our economic recovery gains”

Ellen Johnson Sirleaf, President of Liberia

State of the Nation address, April 2015

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Abbreviations

AusMAT	Australian Medical Assistance Teams
CDC	Centre for Disease Control and Prevention
EMC	Ebola Management Centre
ETU	Ebola Transit Unit
EVD	Ebola virus disease
MoH	Ministry of Health
MSF	Medecins sans Frontieres
NCCTRC	National Critical Care Centre and Trauma Response Centre
NSW	New South Wales
PVP	Positive value predictive
WHO	World Health Organization

Chapter Prelude

My role

In our outbreak investigation course in February 2014, one of our lecturers asked the class what our dream outbreak investigation would be. My answer was 'an Ebola outbreak in Uganda' - this was the most exotic outbreak I could think of to investigate. When the West African Ebola epidemic made the news just a month later, little did I know that I should have been careful what I wished for!

I was fortunate enough to have been able to respond to the current Ebola virus disease (EVD) epidemic when in November 2014, I worked with Medecins sans Frontieres (MSF) to open an Ebola transit centre in Monrovia, Liberia. My role was as a clinician and medical team leader at the centre. As the only doctor at the centre, I was responsible for the decision to admit or discharge suspect EVD patients based on their history of symptoms or contact. Together with other international team members, we made sure that all MSF infection control protocols were strictly adhered to and that staff were safe in their working environments.

I was also responsible for the health of national and international staff on the project – about 200 people. This was perhaps the most daunting task. A fever for a national or international staff member meant immediate isolation and testing for EVD, a period of monitoring for all other team members who had contact with that staff member, and for international staff, it meant a call to the MSF Ebola Taskforce in Geneva for consideration of medical evacuation. Unfortunately this mechanism was not available for national staff colleagues. This situation arose three times – twice with national staff and once with an international staff colleague.

I conducted media interviews during my time in Liberia – a radio interview with RadioNZ and interviews with British and Italian newspapers. On return to Australia, as part of MSF's mandate to conduct

'temoignage' or 'bear witness', I spoke at various MSF events and did interviews with SBS TV news, ABC TV news and Radio 2SER.

I was invited to be an external speaker and trainer for a workshop conducted by the National Critical Care and Trauma Response Centre (NCCTRC) in Darwin. The NCCTRC are responsible for coordinating the Australian government's response to international medical emergencies and for training its medical assistance teams (AusMAT). The workshop was held over four days for two groups of AusMAT team members from around the country with the theme, 'Infectious Diseases in Emergencies'. There was a heavy focus on EVD with theory and practical simulated exercises.

In New South Wales (NSW), I spoke of my experience in Liberia at meetings held by the Royal Australasian College of Medical Administrators (RACMA), the Royal College of Public Health Medicine and at a Health Protection NSW quarterly meeting. I also gave a two hour lecture on EVD to Masters in International Public Health students at the University of New South Wales.

Lessons learned

Before I left for Liberia, I was involved on the sidelines of Ebola preparedness planning at NSW Health. This was an interesting learning experience. It was incredible to see all the planning that happened at a district level and then at a state level in the event that there would be an imported case of EVD to NSW. In a way, it seemed that the effort taken was disproportionate to the actual threat of such an event occurring. However, I learned that public health preparedness, public accountability and politics meant that the system needed to consider every possibility and be prepared for each circumstance.

As part of field readiness for my mission to Liberia, I attended a mandatory MSF Ebola training course in Brussels, Belgium. This was excellent and I learned a lot about the disease itself from some of the world's experts. I learnt how to don and doff personal protective equipment, how to implement infection control procedures in Ebola management centres and about MSF's strategy regarding Ebola outbreak response and control.

Another important lesson I learned both on the field and from watching public health practitioners at work was the role that open and transparent risk communication plays in allaying public fear. As an example, when the first case of EVD was exported to the United States (US), the message that the Director of the US Centre for Disease Control and Prevention (CDC) told the public was, "While it is not impossible that there could be additional cases associated with this patient in the coming weeks, I have no doubt that we will contain this" (1). However, in the next week, a nurse who cared for this patient also became infected with EVD. The messaging that occurred as a result of this event appeared to have the Director on the back foot, "We have to rethink the way we address Ebola infection control". This example highlights to me that when dealing with infectious diseases where a lot remains unknown, it is important to convey this uncertainty to the public and be transparent in communications. As the saying goes, "when nothing is sure, everything is possible". However, this transparency has to be balanced with ensuring the public have confidence in the system to protect their health.

Along these lines, I learned more about the huge role that the media have in influencing public opinion. When the outbreak was at its peak in August and September 2014, we saw cataclysmic images on television of West Africans dying outside hospital doors, saw ‘hollywood-esque’ images of foreign medical teams dressing up in personal protective equipment heard stories of local governments passing impossible quarantine laws while infectious disease experts speculated on possibilities of the virus being transmitted via the airborne route. The net effect of these types of messaging and imagery was the creation of hysteria and panic among the public. People protested outside the White House with posters asking the American government to “*turn back the planes*”, Australian politicians talked about selfish humanitarian workers bringing back disease into the country and sadly, some of my MSF colleagues were banned from seeing family members upon return from the field. I have learned in my work with MSF over the years that what the media portray to be truth can be very different to what actually happens on the ground. As it is impossible for everyone to personally witness world events as they happen, we rely on different media channels to communicate accurate messages to the public. As public health practitioners, we cannot guarantee how our words will be taken by the media, but I have learned that we must speak scientifically, empathically and most importantly truthfully about the topic in question so that media receive accurate and up-to-date information to inform the public. Failing to do this can create confusion and misconceptions of the truth, which can have detrimental consequences.

Public health implications

This emergency was assessed by the World Health Organization (WHO) to be a 'public health emergency of international concern'. As such, everyone who worked towards controlling this epidemic acted in the best interests of the international community. Responding to an outbreak at its source is the essence of outbreak control and management.

I was in Liberia at a time when the reported incidence of EVD across the country was reducing to 60 to 70 cases per week compared to about 150 just a month before. As important as it was to still isolate infected cases in Ebola management centres, this stage in the epidemic required strategies focussed on working with communities that were difficult to engage but still had high case numbers. There was also a need to facilitate the re-opening of healthcare facilities for care of diseases other than EVD as it was becoming clear that many more people were dying from non-Ebola related disease such as malaria, complications of pregnancy and chronic diseases, than from EVD. The Ebola transit unit that we established aimed to tackle these two issues. The implications of our work meant that we were able to provide an alternate place for EVD testing and confirmation and therefore limit virus transmission within a resistant community in Monrovia that had been a 'hotspot' throughout the epidemic. We also worked with one of the biggest public hospitals in Monrovia and helped them re-open. The model of care that we established is one that can be used to prevent EVD entering other general healthcare facilities in Liberia and other EVD-affected countries.

Upon return to Australia, by being able to share experiences and lessons learnt with the medical and public health communities here, I was able to contribute to Australia's preparedness plans and international response in the event that this happened.

Abstract

Background

The Ebola virus disease (EVD) epidemic of 2014-15 resulted in the loss of lives, the closure of hospitals and raised general fear and distrust among affected communities in Guinea, Liberia and Sierra Leone. The peak of the epidemic in Liberia was in early September 2014 but there was a sharp decline in cases by mid-October (2). In response to this evolving phase of the epidemic, Medecins sans Frontieres (MSF) developed a new model of care in the form of an Ebola transit unit (ETU) in Monrovia, Liberia. The purpose of the ETU was to screen presenting patients in an area of Monrovia with active transmission and admit and test these patients if a 'suspect' or 'probable' case definition for EVD was met. This report aims to describe the characteristics of patients who presented to the ETU in its first month of opening and compare the symptomatology and exposure history of patients who were admitted to the ETU to those who were not admitted.

Methods

We pre-screened patients presenting to the unit at either the entrance to the ETU or at Redemption Hospital. If certain criteria were met, we interviewed patients further at the ETU triage area and collected demographic information, dates of illness, symptom and contact history and source of referral. Patients who met a modified Liberian Ministry of Health suspect or probable case definition for EVD were admitted to the ETU and tested for EVD and malaria. Medically unstable patients were transferred directly to an Ebola management centre (Elwa 3) for EVD testing and further clinical management. Simple descriptive analyses was performed to describe those patients who were admitted to the ETU and tested positive for EVD, those who were admitted to the ETU but tested negative for EVD and those who were discharged from triage. The results of admitted patients was combined and compared to patients who were not admitted to the ETU.

Results

Between 20 November and 20 December 2014, 70 patients met the pre-screening criteria and were assessed at the ETU. Of these, 38 (54%) met the suspect or probable case definition and were tested for EVD and malaria at the ETU and a further 13 (19%) were tested at Elwa 3. Of the 38 patients tested at the ETU, 16 were positive for EVD (42%) and eight were positive for malaria (21%). Five of the 13 patients (38%) tested for EVD at Elwa 3 were positive. The median age of EVD-confirmed patients was 35 years, 57% were female and only 52% had a measured temperature greater than 37.5°C at pre-screening. Six of seven patients (86%) referred from the Redemption Hospital pre-screening area tested positive for EVD and there were no reported cases of EVD entering the hospital during this time. Nineteen patients did not meet either of the case definitions and were discharged from triage. Symptoms that were more commonly reported by admitted patients compared to non-admitted patients were weakness (91% versus 37%, $p < 0.05$), headache (57% versus 21%, $p < 0.05$) and joint pain (43% versus 0, $p < 0.05$). Compared to non-admitted patients, admitted patients most commonly reported contact with a sick person in the 21 days prior to becoming unwell (17 out of 35, $p < 0.05$).

Conclusion

We recommend that a history of fever in addition to a measured temperature $> 37.5^{\circ}\text{C}$ should be considered for inclusion in the probable and suspect case definition for EVD. Robust screening at entrances to general healthcare facilities associated with an adjacent isolation unit is an effective mechanism for identifying cases of EVD and is a strategy that should be considered for use at other major hospitals in EVD-affected countries.

Background

The Ebola virus was first discovered in the Yambuku region of former Zaire (now the Democratic Republic of Congo) in 1976 (3). It caused an outbreak in this remote village characterised by rapid person-to-person spread, nosocomial transmission and transmission via the use of contaminated needles and syringes in hospitals and clinics (3). Ebola virus disease (EVD) has since resulted in 24 outbreaks between 1976 and the most recent outbreak in 2014, infecting 2400 people with a case-fatality ratio ranging from 55 to 90% (4). The current EVD outbreak in West Africa affecting the countries of Guinea, Sierra Leone and Liberia is unprecedented in size and geographical spread. As of 11 October 2015, there were 28 490 infected cases across the region and 11 312 deaths (5).

The symptoms of EVD, like other viral haemorrhagic fevers are non-specific in the first few days of infection with fever, malaise and general body aches (6). By day three to five, gastrointestinal symptoms begin, with reports of epigastric pain, nausea, vomiting and diarrhoea (6). This is when patients typically present to a healthcare facility. Other possible symptoms at this time and up to 10 days are profound weakness, headache, conjunctival injection, chest pain, abdominal pain, arthralgia, myalgia, hiccups and delirium (3, 6). The natural progression of the disease is to cause a distributive shock resulting in a reduced state of consciousness or coma. Gastrointestinal haemorrhage and secondary infections are late complications and typically occur after 10 days (6). Recovery, if it occurs, is expected between day seven and 12 of infection (6).

Isolation of the sick from the rest of the population has been the cornerstone of EVD outbreak control since the virus was discovered (6). The construction of Ebola management centres (EMCs) for isolation of cases has been a necessary strategy in preventing further transmission of the virus and has been particularly effective in controlling small outbreaks in remote settings (6, 7).

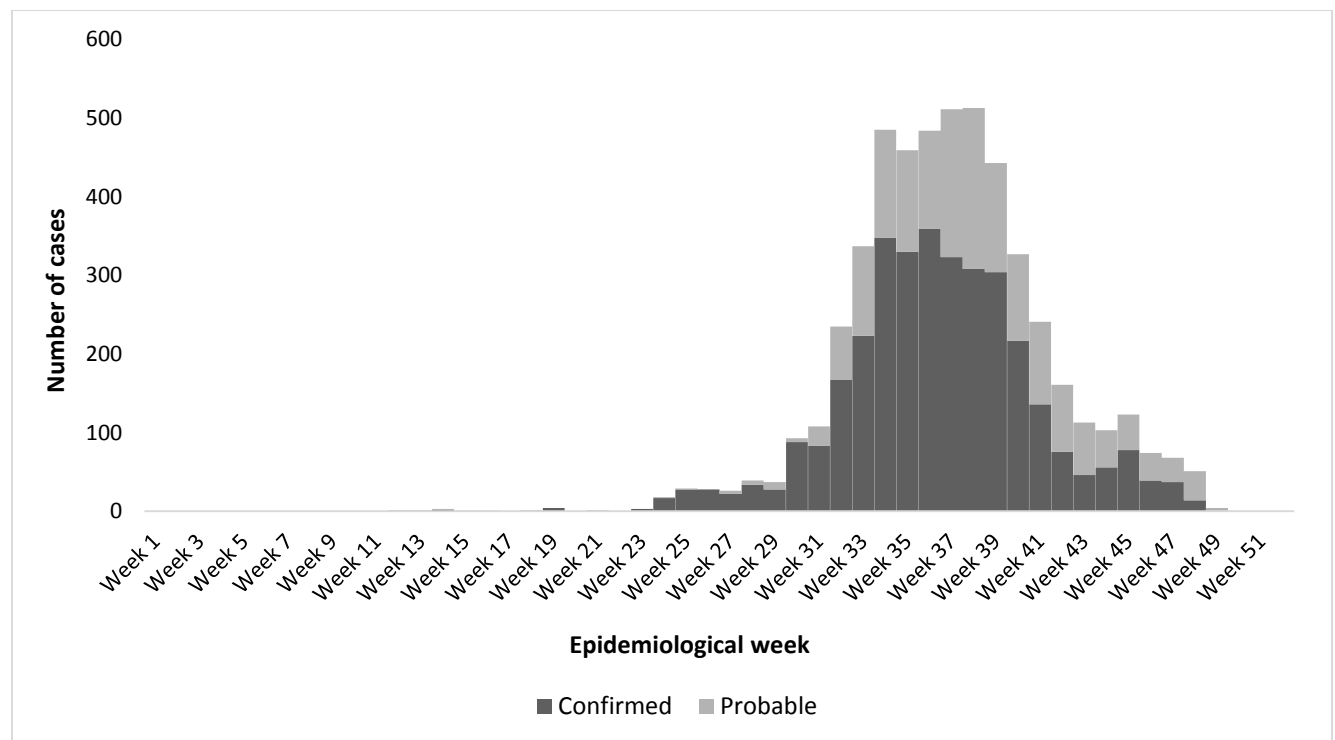
The first case of EVD in the current epidemic was reported in Guinea in early January 2014. By late March 2014, neighbouring Liberia reported its first case. The epidemic was declared a public health

emergency of international concern (PHEIC) by the World Health Organization (WHO) in August 2014 when more than 1700 people were infected and 930 people had died from EVD (8). Although organisations such as Medecins sans Frontieres (MSF) criticised the WHO for its slow response and for declaring the PHEIC too late (9), this declaration was a necessary step in mobilising the international community to act in limiting the spread of EVD. The desired effect of increased assistance to the countries affected was achieved and more facilities for isolating infected patients were constructed.

In the first week of September 2014, Liberia was at the peak of the epidemic with 359 confirmed cases reported in week 36 (Figure 1) (2) . However, the situation turned for the better over the next five weeks and in late October 2014, the case incidence in Liberia declined sharply to 46 cases per week by week 43 (2). Albeit past the peak of the epidemic and despite the reducing incidence, international aid still went into building isolation centres and increasing bed capacity in the country's capital and urban centres. In November 2014, there were 672 beds available throughout the country for approximately 15 reported cases (10). However, it was determined that only 23% of probable and confirmed EVD cases at this time were actually hospitalised and isolated (10), suggesting that while bed capacity was sufficient, people were not presenting to EMCs when unwell or that EMCs weren't accessible to communities at risk.

In addition, there remained great challenges in identifying active chains of transmission, engaging with and raising awareness of EVD among affected communities and in re-opening general healthcare facilities (HCFs) for non-EVD related illnesses. This phase of the outbreak called for those involved in the response to be flexible and adaptive in their strategy for case finding and isolation (11).

Figure 1: Total probable and confirmed cases of Ebola virus disease in Liberia between January 2014 and December 2014



In response to this evolving situation, MSF developed an alternative model of care in Monrovia, in the form of an Ebola transit unit (ETU). The primary purpose of the ETU was to screen presenting patients and determine whether they met the case definition for a ‘suspect’ or ‘probable’ case of EVD. If an individual met either of the two definitions, they were admitted to the ETU, tested for EVD and given a standard regime of medications including regular analgesia, regular anti-emetics, a course of antibiotics and daily multivitamins. Food, water and drinks were provided three times daily and upon request. Patients found to be positive for EVD were referred to an Ebola management centre (EMC).

Health promotion occurred both in the ETU and in the community. In the ETU, health promoters worked in the triage area to assist in history taking, to further explain the function of the ETU and expected process and addressed patient concerns. Health promoters in the community worked in neighbourhoods around the ETU to promote the purpose of the unit, spread health messages about the disease and provide advice on infection control methods. They also helped community leaders engage with members of their community.

Another objective in constructing the ETU was to work with a major hospital in Liberia and attempt to re-open this facility. In consultation with the Liberian Ministry of Health (MoH), we constructed the ETU in New Kru Town, Monrovia. New Kru Town is home to a large urban slum community with an approximate population of 90 000. It was an area in Monrovia that was severely affected by the EVD epidemic. Between August and September 2014 (at the peak of the epidemic), more than half of all patients admitted to the largest EMC in Monrovia - Elwa 3 - came from this community (unpublished data, MSF).

New Kru Town is also home to Redemption Hospital. Redemption Hospital is a 200 bed in- and out-patient paediatric, adult and emergency hospital and one of the few free public hospitals in Monrovia (12). It provides services to the population of the greater Monrovia region and Montserrado county. Redemption Hospital reported the first case of EVD in Monrovia in April 2014 and at the height of the epidemic, regular hospital services were shut down so that the hospital could be used as an Ebola holding centre (12). After the death of 12 of their staff members, the hospital shut down completely in September 2014.

In this report, I aim to describe the characteristics of patients who presented to the MSF Monrovia Ebola transit unit in its first month of opening (20 November 2014 to 20 December 2014). Specifically, I will examine differences in symptoms and exposure history between those who met the case definition and were admitted to the ETU and those who did not meet the case definition.

Methods

1) Case definitions

We used standard case definitions established by the Liberian Ministry of Health at the onset of the epidemic, but modified these to include a reported *history* of fever as well as a measured temperature greater than 37.5°C. The case definitions and where they were used at the ETU are described in Table 1.

Table 1: Operational case definitions used at the Medecins sans Frontieres Monrovia Ebola Transit Unit and sites where they were used

Case definition	Criteria	Sites where case definitions were used
Pre-screening	1. History of fever or measured temperature > 37.5°C with: at least 3 symptoms of vomiting, diarrhoea, pain, anorexia and weakness OR any bleeding symptoms. 2. Contact with a suspect or confirmed Ebola virus disease suspect case (contact with an unwell household member, an unexpected death in the family, attending a funeral or visiting sick person) 3. High index of suspicion for Ebola virus disease based on medical assessment – for example, general lethargy, drowsiness, haemorrhagic signs or if there were inconsistencies between reported symptoms and physical manifestations.	- At entrance to Ebola transit unit - At entrance to Redemption Hospital
Suspect	Either 1. History of fever or measured temperature ≥ 37.5°C with any 3 symptoms of headache, weakness, vomiting, diarrhoea, anorexia, muscle, pain, joint pain, abdominal pain, chest pain, headache, cough,	- At the Ebola transit unit triage area

	sore throat, difficulty swallowing, difficulty breathing, jaundice, conjunctivitis, photophobia, hiccups, skin rash OR 2. History of fever or measured temperature $\geq 37.5^{\circ}\text{C}$ with unexplained bleeding	
Probable	History of fever or measured temperature $\geq 37.5^{\circ}\text{C}$ AND contact. Contact includes any of the following activities in the previous 21 days: cared for or washed the clothes of a person who was sick or has since died, slept with someone who has since died, touched or washed the body of someone who died, attended the funeral of an Ebola virus disease confirmed case, had contact with someone who was admitted to the suspect area of an Ebola management centre and was subsequently discharged following a negative laboratory result	- At the Ebola transit unit triage area

The role of the pre-screening case-definition was to ensure that people did not unnecessarily enter the ETU and risk themselves being exposed to EVD. Hence, these definitions were more sensitive than the suspect or probable case definitions and were used at the entrance to the ETU and at Redemption Hospital.

Cases who appeared medically unstable - defined subjectively by an inability to walk unaided, displayed signs of confusion or disorientation or who showed visible signs of haemorrhage were transferred immediately to an Ebola management centre (EMC) via ambulance. The EMC that we worked most closely with was another MSF facility called Elwa 3.

2) Patient flow at the Ebola transit unit

Patients entered the ETU via a main gate directly to the triage area where interviews were conducted (Appendix 2). Those meeting the suspect or probable case definitions were escorted to an isolation room by a nurse and hygienist where they remained for the duration of their admission. Patients who did not meet the case definitions exited the triage area back through the main gate with a letter confirming that they were seen by a health professional at the ETU and did not meet criteria for EVD testing at that point in time.

Only one patient was interviewed at a time. If multiple patients presented at the same time, the most acute was seen first and others seated in a waiting area in chairs spaced two metres apart.

3) Data collection

A doctor, nurse and health promoter conducted interviews with presenting patients in the triage area and collected information on demographics, dates of illness and symptom and contact history. Information was also collected on the referral source of the patient. This information was recorded on standardised MoH case questionnaires (Appendix 3). A data entry officer then entered the data onto a Microsoft Excel database.

4) Laboratory investigations

Upon admission to the ETU, we collected a blood sample from each patient for EVD and malaria testing. Blood samples were sent to the United States (US) Navy medical research laboratory which was located 10 minutes away from the ETU, by road transport (Appendix 1). The US navy laboratory uses real-time polymerase chain reaction (rt-PCR) to target two Ebola virus genes. The exact targets used were not disclosed to us. The cut-off value for a positive EVD result was set at 40 PCR cycles. A value above this number is deemed to be EVD test-negative. The malaria test was also conducted at the US navy laboratory using an antigen-based rapid diagnostic test (SD Bioline Malaria Ag P.f/Pan) which detects *Plasmodium falciparum* and other *Plasmodium* species in human whole blood (13).

Results were available within six to eight hours. A repeat blood test was taken 72 hours after symptom onset if a patient was EVD-negative on initial testing to ensure that the window period for detection of viral antigen had passed before repeat laboratory testing. This repeat test was not necessary if symptom onset was greater than 72 hours.

5) Statistical analysis

I performed simple descriptive analysis to compare three groups of patients: 1. those who presented to the ETU and were confirmed to be positive for EVD (EVD-positive), 2. those who were admitted to the ETU but tested negative for EVD (EVD-negative), 3. those who presented to the ETU but did not meet the suspect or probable case definitions (Discharged from triage).

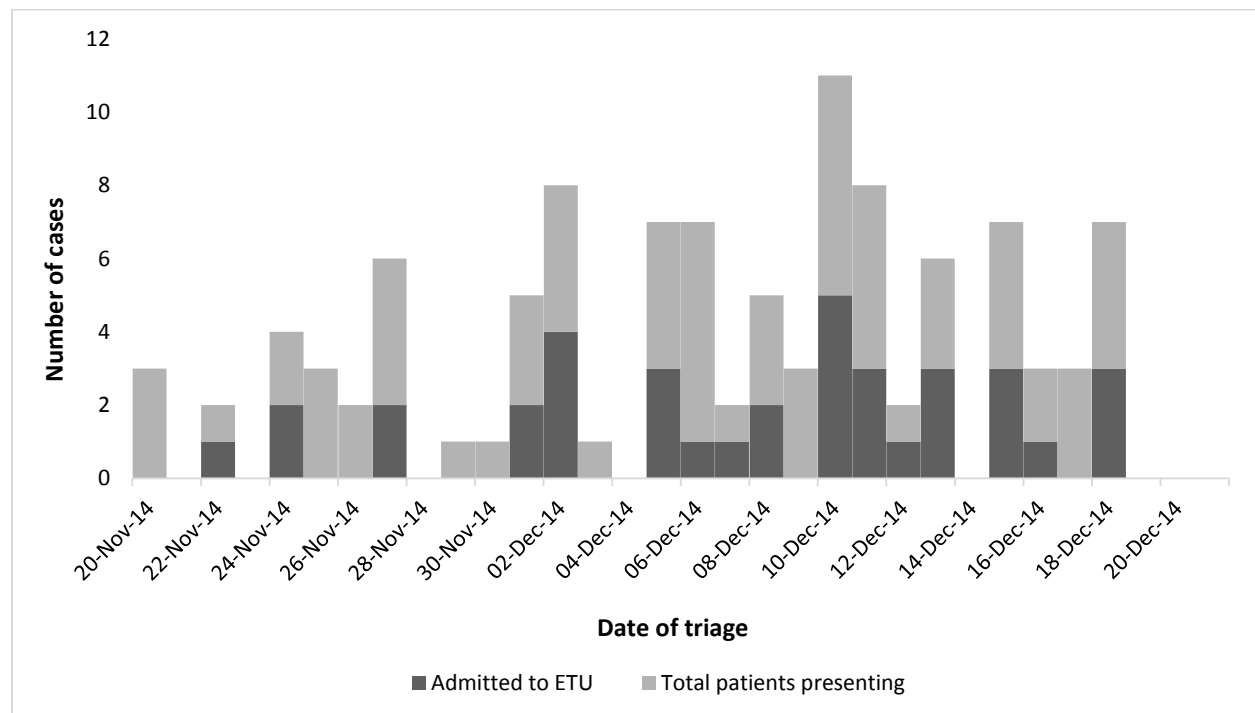
I then combined the results of all those who were admitted to the ETU for meeting the suspect or probable case definitions (EVD-positive and EVD-negative) and compared them to those who were not admitted for not meeting the suspect or probable case definitions (Discharged from triage). I analysed responses using Stata version 13.1 and used chi-square tests to compare differences in symptom and exposure history between groups. P-values less than 0.05 were considered significant.

Results

1) Patients presenting to the Ebola transit unit

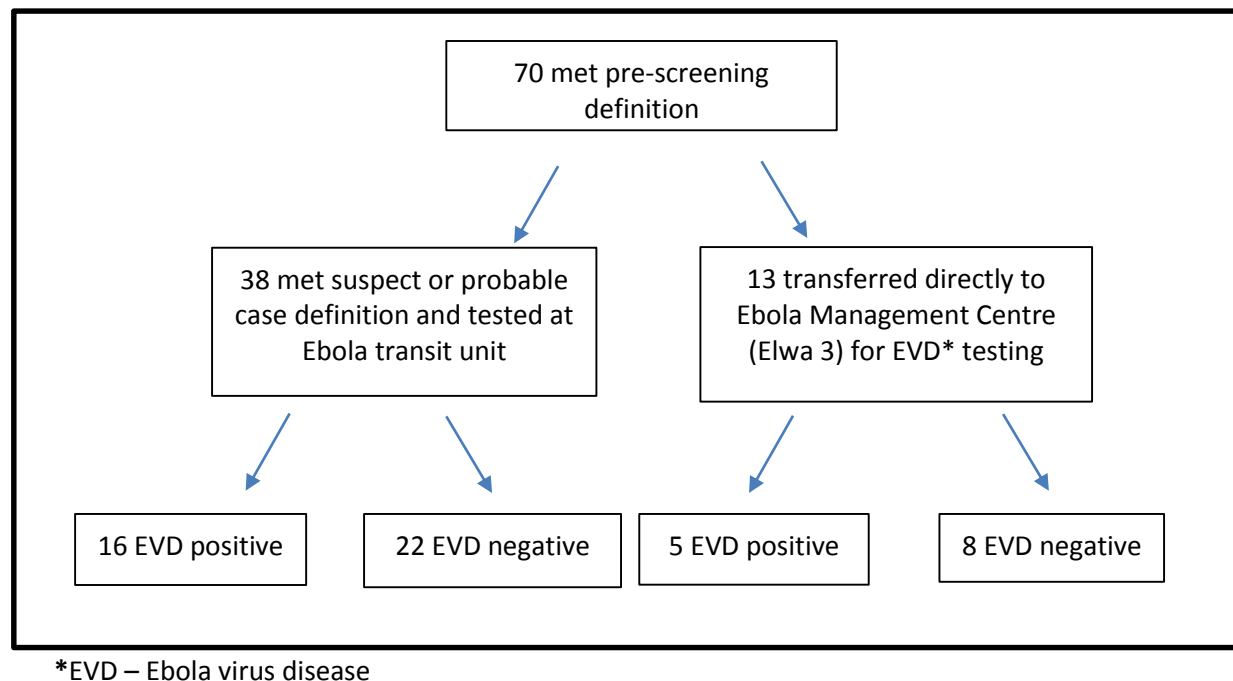
The transit unit opened on 20 November 2014. Between 20 November and 20 December, 70 people met the pre-screening definition and were assessed at the ETU (Figure 2). Of these, 38 (54%) met the suspect or probable case definition and were admitted for EVD testing at the ETU. In addition, 13 of the 70 assessed (19%) were clinically unstable and referred directly to ELWA 3 for EVD testing (Figure 3). Sixteen of the 38 (42%) admitted at the ETU and five of the 13 (38%) transferred to ELWA 3 were confirmed to be EVD-positive - a total of 21 EVD confirmed patients. The 22 patients who had a negative EVD result were discharged to a general healthcare facility for ongoing treatment or home if they were well.

Figure 2: Patients who presented to the Medecins sans Frontieres Ebola transit unit, Monrovia, Liberia between 20 November and 20 December 2014



The majority of patients admitted to the ETU (27/38, 71%) reported a symptom onset greater than 72 hours and therefore were able to be referred to an EMC if positive or discharged home if negative, on the day of admission. Thirteen patients (19%) were admitted to the ETU for one night, three patients (4%) for two nights and five (7%) for three days.

Figure 3: Patients assessed at the Medecins sans Frontieres Ebola transit unit, Monrovia, Liberia between 20 November and 20 December 2014



2) Characteristics of patients presenting to the Ebola transit unit

The range in ages of all patients who presented to the ETU was between 8 months and 68 years (Table 2). The median age was similar regardless of whether or not they met the case definition, ranging from 31 to 35 years. A higher proportion of EVD-confirmed patients were in the younger (0 to 15 years) and older (46+ years) age groups. More EVD-confirmed cases were women (57%) while those who sought general healthcare and did not meet the case definitions were more often men (68%). However, these results were not statistically significant (Table 3).

The majority (44/54, 81%) of patients who presented usually lived in New Kru town itself or within a 10 kilometre radius of the ETU (Clara town, Caldwell, Logan Town) (Table 2). Nine patients (17%) came from the Greater Monrovia region or out of Montserrado county (Table 2). There were no statistically significant differences in admission to the ETU and usual place of residence (Table 2).

Table 2: Summary of patient characteristics admitted to the Ebola transit unit who tested EVD-positive, admitted to the Ebola transit unit who tested EVD-negative and patients discharged from triage at the Medecins sans Frontieres Monrovia Ebola transit unit, 20 November - 20 December 2014

Characteristic	EVD-Positive, n = 21	EVD Negative, n = 14	Discharged from Triage, n = 19
Patient demographics			
Median Age (range), years	35 (4 – 64)	34.5 (3 – 62)	31 (8 months – 68)
0 – 15 years, no. (%)	9 (43)	2 (14)	5 (26)
16 – 29 years, no. (%)	0	4 (29)	4 (21)
30 – 45 years, no. (%)	6 (29)	6 (43)	7 (37)
46 + years, no. (%)	6 (29)	2 (14)	3 (16)
Sex, no. of female (%)	12 (57)	6 (43)	6 (32)
Usual residence			
New Kru Town, no. (%)	9 (43)	6 (43)	10 (53)
Clara Town, no. (%)	6 (29)	0	3 (16)
Caldwell, no. (%)	3 (14)	1 (7)	1 (5)
Logan Town, no. (%)	1 (5)	1 (7)	1 (5)
St. Paul River, no. (%)	1 (5)	0	0
Greater Monrovia, no. (%)	0	5 (36)	3 (16)
Out of Montserrado county, no. (%)	1 (5)	1 (7)	1 (5)

Referral source:			
Redemption pre-screening, no. (%)	6 (29)	0	1 (5)
MSF Community health promoters, no. (%)	7 (33)	6 (43)	0
Other NGO [#] health promoters, no. (%)	3 (14)	0	3 (16)
Community leaders, no. (%)	1 (5)	2 (14)	6 (32)
Self-referred, no. (%)	4 (19)	6 (43)	9 (47)
ILLNESS INFORMATION:			
Median time from symptom onset to presentation, days (range; mode)	5 (1 – 21; 4)	3.5 (1 – 30; 3)	3 (1 – 31; 2)
Symptoms:			
Fever (reported & measured), no. (%)	21 (100)	12 (86)	12 (63)
- Measured temp $\geq 37.5^{\circ}\text{C}$, no. (%)	11 (52)	2 (14)	8 (42)
Weakness / fatigue, no. (%)	20 (95)	12 (86)	7 (37)
Anorexia, no. (%)	15 (71)	12 (86)	10 (53)
Headache, no. (%)	12 (57)	8 (57)	4 (21)
Joint pain, no. (%)	11 (52)	4 (29)	0
Vomiting, no. (%)	10 (48)	4 (29)	7 (37)
Diarrhoea, no. (%)	7 (33)	8 (57)	4 (21)
Muscle pain, no. (%)	7 (33)	3 (21)	2 (10)
Exposure history*			
Visited a health facility, no.	7	2	6
Contact with sick person, no.	14	3	1
Contact with confirmed Ebola case, no.	10	2	1
Attended funeral, no.	1	0	0
Travelled outside usual residence, no.	1	2	1
Consulted traditional healer, no.	0	0	1
Ate bush meat, no.	0	0	0

NGO – non-governmental organisation; *exposures are not mutually exclusive

2.1 Referral Source

While the majority of patients who were discharged from triage brought themselves to the ETU (9/19, 47%), most EVD-confirmed cases were referred either from the Redemption Hospital pre-screening area (29%) or from MSF community health promoters (33%) (Table 2). Community leaders referred nine patients, most (67%) of whom did not meet the case definition for admission (Table 2).

2.3 Illness information

Patients who had EVD generally took longer to present to the ETU with most presenting four days after symptom onset with a wide range between 1 to 21 days (Table 2). Those who were confirmed not to have EVD commonly presented within three days, while those who were discharged from triage usually presented within two days. The median time from symptom onset to presentation between those who were admitted and those not admitted was statistically significant (Table 3).

Table 3: Comparison of presenting patients to the MSF Ebola transit unit who met the case definition to those who did not, 20 November to 20 December 2014

Characteristic	Admitted, n = 35	Not admitted, n = 19	p-value*
Patient demographics			
Median Age (range), years	34 (3 – 64)	31 (8 months – 68)	
0 – 15 years, no. (%)	11 (31)	5 (26)	0.8
16 – 29 years, no. (%)	4 (11)	4 (21)	
30 – 45 years, no. (%)	12 (34)	7 (37)	
46 + years, no. (%)	8 (23)	3 (16)	
Sex, no. of female (%)	18 (51)	6 (32)	0.2
Usual residence:			
New Kru Town, no. (%)	15 (43)	10 (53)	0.7
Clara Town, no. (%)	6 (17)	3 (16)	

Caldwell, no. (%)	4 (11)	1 (5)	
Logan Town, no. (%)	2 (6)	1 (5)	
St. Paul River, no. (%)	1 (3)	0	
Greater Monrovia, no. (%)	5 (14)	3 (16)	
Out of Montserrado county, no. (%)	2 (6)	1 (5)	
Illness information:			
Median time from symptom onset to presentation, days (range; mode)	4 (1 – 31; 3)	3 (1 – 31; 2)	< 0.05 #
Fever (reported & measured), no. (%)	33 (94)	12 (63)	
-Measured temp $\geq 37.5^{\circ}\text{C}$, no. (%)	13 (37)	8 (42)	1.0
Weakness / fatigue, no. (%)	32 (91)	7 (37)	< 0.05
Anorexia, no. (%)	27 (77)	10 (53)	0.1
Headache, no. (%)	20 (57)	4 (21)	< 0.05
Joint pain, no. (%)	15 (43)	0	< 0.05
Vomiting, no. (%)	14 (40)	7 (37)	0.5
Diarrhoea, no. (%)	15 (43)	4 (21)	0.1
Muscle pain, no. (%)	10 (29)	2 (10)	0.1
Exposure history *			
Visited a health facility, no.	9	6	0.4
Contact with sick person, no.	17	1	< 0.02
- Contact with <i>confirmed Ebola</i> case, no.	12	1	0.05
Attended funeral, no.	1	0	0.7
Travelled outside usual residence, no.	3	1	0.6
Consulted traditional healer, no.	0	1	0.4
Ate bush meat, no.	0	0	--

*exposures are not mutually exclusive; # calculated using a Student's t-test

The most commonly reported symptoms of EVD-confirmed patients were fever (100%), weakness (95%), anorexia (71%), headache (57%), joint pain (52%), vomiting (48%), diarrhoea (33%) and muscle pain (33%) (Table 2). Only 11 out of 21 (52%) confirmed cases had a temperature greater than 37.5°C on screening (Table 2). There was a statistically significant difference between admitted and non-admitted patients with respect to reporting of weakness (91% versus 37%, $p < 0.05$), headache (57% versus 21%, $p < 0.05$) and joint pain (43% versus 0, $p < 0.05$) (Table 3).

2.4 Exposure history

The most commonly reported exposure by EVD-confirmed cases was contact with a sick person – reported by at least 14 of 21 (67%) cases, ten of these contacts were with another EVD-confirmed case (Table 3). This was the most statistically significant reported exposure by those admitted ($p < 0.02$, Table 3). Six people who were not admitted to the ETU reported visiting a health facility. Sixteen of 21 (76%) confirmed cases reported one or more exposures (data not shown).

2.5 Laboratory data

Of the 38 patients admitted to the ETU, eight (21%) were positive for malaria (Table 4); two patients were co-infected with malaria and EVD. Further characterisation showed that five of the eight malaria infections (63%) were *Plasmodium falciparum* and three (37%) were mixed *Plasmodium falciparum*/*Plasmodium ovale* infections.

**Table 4: Ebola virus disease and Malaria test results of admitted patients to Medecins sans Frontieres
Monrovia Ebola transit unit, 20 November - 20 December 2014**

		Ebola		TOTAL
		Positive	Negative	
Malaria	Positive	2	6	8
	Negative	14	16	30
TOTAL		16	22	38

Discussion

We assessed 70 people from the neighbouring communities of New Kru Town, Monrovia in our first month of opening between 20 November and 20 December 2014. Of these, 51 were tested and 21 (41%) were found to be positive for EVD. The median age of EVD-confirmed patients was 35 years, 57% were female and only 52% had a measured temperature greater than 37.5°C at pre-screening. Six of seven patients (86%) referred from the Redemption Hospital pre-screening area tested positive for EVD and there were no reported cases of EVD entering the hospital during this time. Nineteen patients did not meet either of the case definitions and were discharged from triage.

The most frequently reported symptoms of patients confirmed to have EVD were fever, weakness, anorexia, headache and joint pain. This clinical picture is in keeping with other published studies (6, 7, 14). Less than half of patients reported enteral symptoms of vomiting (48%) and diarrhoea (33%). There is variable reporting of these symptoms in the literature (6, 15). Data collected at a time of higher disease prevalence from all three countries and from various settings – i.e. remote clinics to district level Ebola management centres to Ebola management centres in capital cities – have documented that two-thirds of patients report symptoms of vomiting and diarrhoea (15). This difference may reflect the proximity of patients' usual residence to the ETU which allowed easier access to the centre when experiencing vague symptoms (e.g. weakness, anorexia, headache), before progression to the advanced, 'wet' symptoms of vomiting and diarrhoea. Earlier presentation has additional benefits to patient's household members and community as it reduces transmission of virus through person to person contact with highly infectious bodily fluids.

To my knowledge, there are no published studies assessing reported symptoms of patients not admitted to an Ebola management centre. Our purpose in assessing this group was to understand reasons for general health-seeking behaviour by the community. There was a significant difference in the reporting of weakness, headache and joint pain by admitted patients compared to non-admitted patients. These symptoms in themselves are not likely to aid in the differential diagnosis of EVD given their relative non-specificity. The combination of symptoms is also not helpful as the very nature of the case definition

requires that any three symptoms necessitate an admission to the ETU. Anorexia, weakness, vomiting and diarrhoea were the most commonly reported symptoms in the non-admitted group and in my clinical judgement the majority of patients likely had viral gastroenteritis, malaria or acute on chronic illness related to chronic infections such as HIV and tuberculosis. Unfortunately, no further medical assistance was able to be provided to these patients at our centre. For some admitted patients who went on to test negative for EVD, it was clear that their clinical syndrome was caused by medical conditions other than EVD. In my opinion, some of these included bleeding due to a gynaecological disorder, fever and abdominal pain due to a urinary tract infection or fever and cough due to chronic tuberculosis. It was a difficult decision to admit such patients to a facility where they could be potentially exposed to patients with Ebola virus disease, resulting in cross-contamination. However, given the risk associated with even a single misclassified case returning to the community, it was important that these patients were screened and tested to exclude a concurrent EVD infection.

The predictive value positive (PVP) of our triage process was 41%. This is much lower than the PVP of 76% at the peak of the epidemic in August and September 2014 (unpublished data, MSF). This reduced PVP likely reflects a reduction in the prevalence of disease at the time the ETU opened, as MSF triage protocols remained consistent throughout the epidemic. It is also a reflection of the poor specificity of the case definition. EVD in its early stages of illness look much like any other viral or parasitic illness. Malaria in particular, can mimic the early symptoms of EVD. Malaria is endemic to Liberia and in 2013, comprised approximately 35% of outpatient department attendance and 33% of inpatient deaths in the country (16). In our cohort of admitted patients, six of 22 (27%) confirmed to be EVD-negative tested positive for malaria, during Liberia's 'off-peak' season for malaria. In a study conducted by the UK Medical Research Council looking at the excess morbidity caused by malaria during this EVD epidemic, the authors reported that if malaria care ceased, untreated cases of malaria would have increased by 140% (credible interval 135–147%) in Liberia in 2014 (17). Across Guinea, Sierra Leone and Liberia, an additional 3.5 million (95% credible interval 2.6 million to 4.9 million) untreated cases and 10,900 additional deaths would be attributable to malaria (17).

Over December 2014, the ETU was the referral source of more than half of all EVD-confirmed cases to ELWA 3 – the largest EMC in Monrovia (unpublished data, MSF). New Kru Town has been an area of

active transmission in Monrovia ever since the first case of EVD was reported here. Before the transit unit opened in New Kru Town, the closest EVD testing facility was more than 10 kilometres away. We felt that by having a facility that was easily accessible, clearly visible, and with a holistic approach to patient care with health promotion and psychological support, community anxiety in seeking healthcare when unwell, was alleviated. The referral data support this notion. There was an increase in presentations over December likely owing to increased health promotion activities and community awareness of the centre. The majority of patients (six of nine) referred by community leaders did not meet the case definition, but by allowing such cases to be screened and discharged with a letter confirming their health status, patients and their community could be reassured in knowing that the individual could live among them. Community involvement and response was crucial in turning the tide of Ebola. Ebola survivors and community volunteers have and will continue to play an important role in reducing stigma, identifying future cases and in educating their communities about the spread of disease and protective measures.

While the number of referrals from the Redemption Hospital pre-screening area was the lowest of any referral source, the proportion of EVD-confirmed cases was highest (86%). This likely reflects a referral case definition that was too specific as the overall positivity rate at the ETU was much lower (42%). The use of the definition of fever could have been one of the factors that accounted for this discrepancy. At RH pre-screening, due to the high volume of patients entering the outpatient department, a measured fever greater than 37.5°C alone was used, while at the ETU pre-screening area, a reported *history* of fever described as the body feeling hot and cold, shivers or sweats, was also accepted in the case definition. Our findings suggest that just over half of EVD-confirmed cases presented with a fever greater than 37.5°C. Given the possibility for fluctuations in temperature in the early stages of the illness, clearly a measured temperature alone will not reliably detect cases of EVD in the screening process. We recommend that a history of fever in addition to measured temperature be used in all Ebola and general healthcare facilities.

Being affiliated with a large public hospital such as Redemption Hospital was pertinent. As this hospital serves the population of Monrovia and the greater county of Montserrado, an opportunity exists to screen a large number of people from a wide geographical area. Having a pre-screening area within the

hospital and the ability to refer suspect cases to the adjacent ETU allowed the hospital to prevent EVD transmission within the hospital. In the first month, there were no reported cases of EVD within Redemption Hospital and the last case of EVD in Liberia was picked up at the pre-screening area in Redemption Hospital (personal communication, MSF). Not only was nosocomial transmission prevented with this system, healthcare workers were also protected from possible infection. Another benefit of the association with Redemption Hospital was that patients who were screened at the ETU who did not meet the criteria for admission and those who were discharged after a negative EVD test but who still felt unwell, could be referred to the outpatient department at the hospital for further medical care and treatment.

One of the major limitations in this study was its small sample size which limited sufficient power to achieve statistical significance. There may also have been an information bias in that we were not able to collect complete information for eight of the 22 (36%) admitted but discharged EVD-negative patients. This may affect the demographic and symptomatology results. Further, nursing and health promotion staff rotated through the triage area. The level of skill and interview technique of these staff members will have had an impact on the history elicited, and therefore the assessment of whether or not a patient met the case definition. Patients may also have under-reported symptoms that they knew were consistent with EVD or not been forthcoming in their reporting of known exposures, in order to avoid the stigma of being admitted to a unit designated for EVD patients. We attempted to mitigate the effects of these factors by having regular staff training on history-taking and by attempting to have the medical doctor always present at triage, to allow for consistency in admission to the ETU. We also supplemented our information base by obtaining collateral history from family members and friends who brought patients to the centre. Counsellors were used at triage to alleviate patient fear and anxiety and to explain to patients, the purpose and function of the ETU. Family members were also offered psychological support.

The description of patients who presented to the MSF Monrovia ETU in its first month of opening provided valuable information that allowed us to inform ongoing strategies – both in the community and at Redemption Hospital. In the community, we were able to target health promotion activities in neighbourhoods where the most number of EVD-confirmed patients resided. We were able to provide

this information to partners such as the Liberian Ministry of Health for their surveillance and contact-tracing activities. The awareness of a measured temperature greater than 37.5°C being an unreliable criteria of the case definition allowed us to implement more robust screening strategies at the entrance to Redemption Hospital. The knowledge of differences in reported symptoms and exposure histories between admitted and non-admitted patients informed our history-taking process and gave us an indication of non-EVD related illness in the community.

The Ebola epidemic is currently in an early phase of recovery with no confirmed cases reported across the three countries as of 11 November 2015 (18). Both Liberia and Sierra Leone have interrupted all remaining chains of Ebola virus transmission and have been declared 'Ebola-free' by WHO. One of the unintended consequences of the Ebola epidemic was the secondary effects on other health issues, adding to the complexity and severity of the crisis. In all three Ebola-affected countries, essential health care services have been and continue to be severely disrupted (17). Re-establishing the health care systems in the three countries will be a great challenge. Our experience of an Ebola transit unit in Monrovia at a time of lower disease prevalence may help in guiding interventions that could be implemented in this region at this time.

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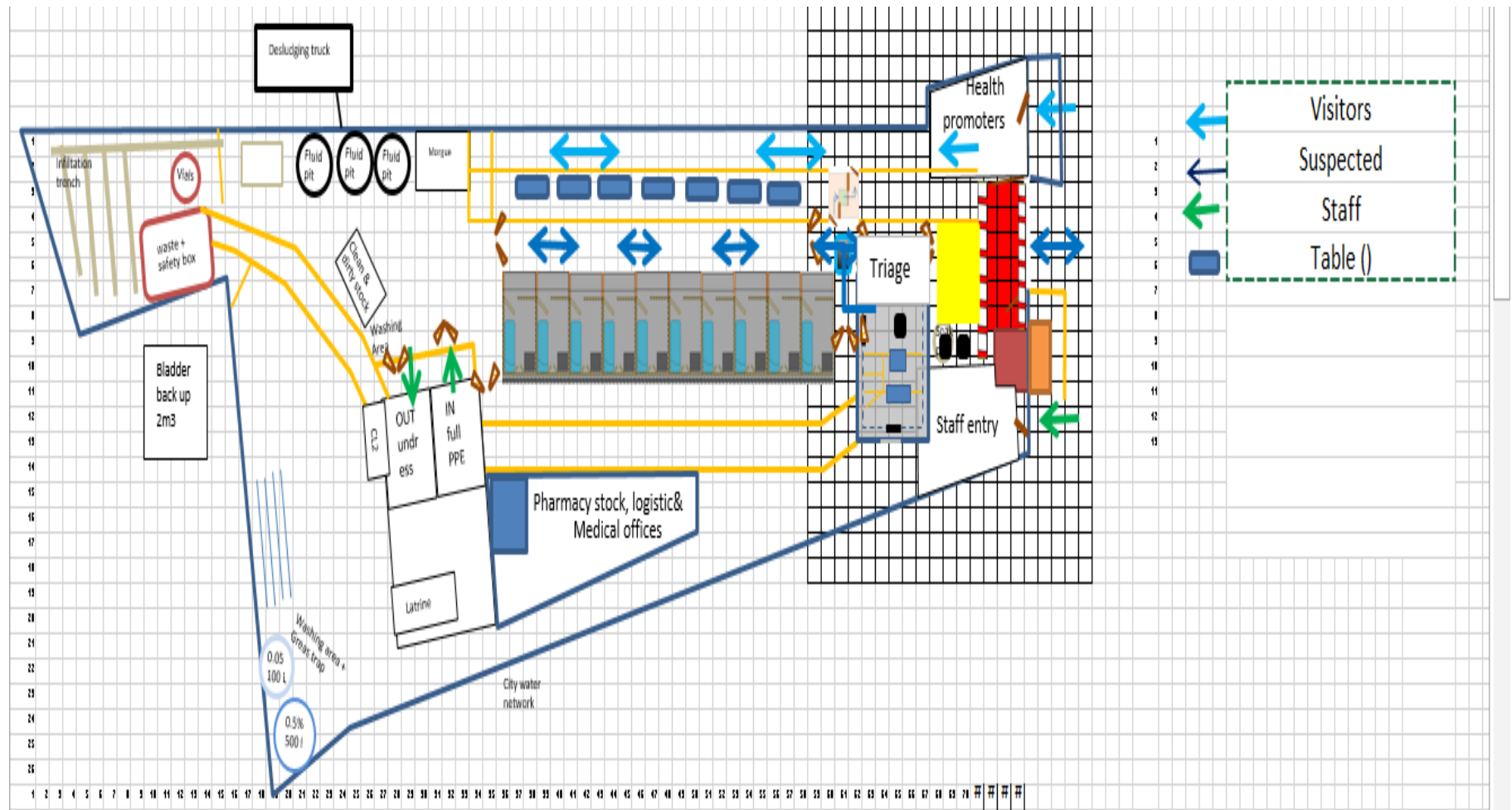
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Appendices

Appendix 1: Mobile testing unit for Ebola virus disease using real-time polymerase chain reaction, United States Navy Medical Research Laboratory, Monrovia, Liberia, December 2014



Appendix 2: Layout of Medecins sans Frontieres Ebola transit unit, Monrovia, Liberia, November 2014



Appendix 3: Liberian Ministry of Health Ebola virus disease case questionnaire

LIBERIA VIRAL HEMORRHAGIC FEVER CASE INVESTIGATION FORM		Outbreak Case ID: <u>LIB-Mont</u>		
Date of Case Report: ____/____/____ (D. M. Yr)		Health Facility Case ID: <u>ETU-ELWA3</u>		
Section 1. Patient Information				
Patient's Surname: _____ Other Names: _____ Age: _____ ☐ Years ☐ Month Gender: ☐ Male ☐ Female Phone Number of Patient/Family Member: _____ Owner of Phone: _____				
Status of Patient at Time of This Case Report: ☐ Alive ☐ Dead If dead, Date of Death: ____/____/____ (D,M,Yr)				
Permanent Residence: Head of Household: _____ Village/Town: _____ Country of Residence: _____ County: _____ District: _____				
Occupation: ☐ Farmer ☐ Butcher ☐ Hunter/trader of game meat ☐ Miner ☐ Religious leader ☐ Housewife ☐ Pupil/student ☐ Child ☐ Businessman/Woman; type of business: _____ ☐ Transporter: type of transport: _____ ☐ Healthcare worker; position: _____ healthcare facility: _____ ☐ Traditional/spiritual healer ☐ Other: please specify occupation: _____				
Location Where Patient Became Ill: Village/Town: _____ County: _____ District: _____ GPS Coordinates at House: latitude: _____ longitude: _____ If different from permanent residence, Dates residing at this location: ____/____/____ (D.M.Yr)				
Section 2. Clinical Signs and Symptoms				
Date of Initial Symptom Onset: ____/____/____ (D.M.Yr)				
Please tick an answer for ALL symptoms indicating if they occurred during this illness between symptom onset and case detection:				
<table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> Fever ☐ Yes ☐ No ☐ Unk If yes, Temp: _____ °C Source: Axillary Oral Rectal Vomiting/Nausea ☐ Yes ☐ No ☐ Unk Diarrhea ☐ Yes ☐ No ☐ Unk Intense Fatigue/general Weakness ☐ Yes ☐ No ☐ Unk Anorexia/loss of appetite ☐ Yes ☐ No ☐ Unk Abdominal Pain ☐ Yes ☐ No ☐ Unk Chest pain ☐ Yes ☐ No ☐ Unk Muscle Pain ☐ Yes ☐ No ☐ Unk Joint Pain ☐ Yes ☐ No ☐ Unk Headache ☐ Yes ☐ No ☐ Unk Cough ☐ Yes ☐ No ☐ Unk Difficulty Breathing ☐ Yes ☐ No ☐ Unk Difficulty Swallowing ☐ Yes ☐ No ☐ Unk Sore throat ☐ Yes ☐ No ☐ Unk Jaundice (yellow eyes/gums/skin) ☐ Yes ☐ No ☐ Unk Conjunctivitis (red eyes) ☐ Yes ☐ No ☐ Unk Skin rash ☐ Yes ☐ No ☐ Unk Hiccups ☐ Yes ☐ No ☐ Unk Pain behind eyes/sensitive to light ☐ Yes ☐ No ☐ Unk Coma/Unconscious ☐ Yes ☐ No ☐ Unk Confused or disoriented ☐ Yes ☐ No ☐ Unk </td> <td style="width: 50%; vertical-align: top;"> Unexplained bleeding from any site ☐ Yes ☐ No ☐ Unk if yes: Bleeding of the gums ☐ Yes ☐ No ☐ Unk Bleeding from injection site ☐ Yes ☐ No ☐ Unk Nose bleed/epistaxis ☐ Yes ☐ No ☐ Unk Bloody or black stools (melena) ☐ Yes ☐ No ☐ Unk Fresh/red blood in vomit (hematemesis) ☐ Yes ☐ No ☐ Unk Digested blood/coffee grounds in vomit ☐ Yes ☐ No ☐ Unk Coughing in blood (hemoptysis) ☐ Yes ☐ No ☐ Unk Bleeding from vagina ☐ Yes ☐ No ☐ Unk other than menstruation Bruising of the skin ☐ Yes ☐ No ☐ Unk (petechiae/ecchymosis) ☐ Yes ☐ No ☐ Unk Blood in Urine (hematuria) ☐ Yes ☐ No ☐ Unk Other hemorrhagic symptoms ☐ Yes ☐ No ☐ Unk if yes, please specify: _____ Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk if yes, please specify: _____ </td> </tr> </table>			Fever ☐ Yes ☐ No ☐ Unk If yes, Temp: _____ °C Source: Axillary Oral Rectal Vomiting/Nausea ☐ Yes ☐ No ☐ Unk Diarrhea ☐ Yes ☐ No ☐ Unk Intense Fatigue/general Weakness ☐ Yes ☐ No ☐ Unk Anorexia/loss of appetite ☐ Yes ☐ No ☐ Unk Abdominal Pain ☐ Yes ☐ No ☐ Unk Chest pain ☐ Yes ☐ No ☐ Unk Muscle Pain ☐ Yes ☐ No ☐ Unk Joint Pain ☐ Yes ☐ No ☐ Unk Headache ☐ Yes ☐ No ☐ Unk Cough ☐ Yes ☐ No ☐ Unk Difficulty Breathing ☐ Yes ☐ No ☐ Unk Difficulty Swallowing ☐ Yes ☐ No ☐ Unk Sore throat ☐ Yes ☐ No ☐ Unk Jaundice (yellow eyes/gums/skin) ☐ Yes ☐ No ☐ Unk Conjunctivitis (red eyes) ☐ Yes ☐ No ☐ Unk Skin rash ☐ Yes ☐ No ☐ Unk Hiccups ☐ Yes ☐ No ☐ Unk Pain behind eyes/sensitive to light ☐ Yes ☐ No ☐ Unk Coma/Unconscious ☐ Yes ☐ No ☐ Unk Confused or disoriented ☐ Yes ☐ No ☐ Unk	Unexplained bleeding from any site ☐ Yes ☐ No ☐ Unk if yes: Bleeding of the gums ☐ Yes ☐ No ☐ Unk Bleeding from injection site ☐ Yes ☐ No ☐ Unk Nose bleed/epistaxis ☐ Yes ☐ No ☐ Unk Bloody or black stools (melena) ☐ Yes ☐ No ☐ Unk Fresh/red blood in vomit (hematemesis) ☐ Yes ☐ No ☐ Unk Digested blood/coffee grounds in vomit ☐ Yes ☐ No ☐ Unk Coughing in blood (hemoptysis) ☐ Yes ☐ No ☐ Unk Bleeding from vagina ☐ Yes ☐ No ☐ Unk other than menstruation Bruising of the skin ☐ Yes ☐ No ☐ Unk (petechiae/ecchymosis) ☐ Yes ☐ No ☐ Unk Blood in Urine (hematuria) ☐ Yes ☐ No ☐ Unk Other hemorrhagic symptoms ☐ Yes ☐ No ☐ Unk if yes, please specify: _____ Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk if yes, please specify: _____
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Section 3. Hospitalization Information				
At the time of this case report, is the patient hospitalized or currently being admitted to the hospital? ☐ Yes ☐ No If yes, Date of Hospital Admission: ____/____/____ (D.M.Yr) Health Facility Name: _____ Village/Town: _____ County: _____ District: _____ Is the patient in isolation or currently being placed there? ☐ Yes ☐ No if yes, date of isolation: ____/____/____ (D.M.Yr)				
Was the patient hospitalized or did he/she visit a health clinic previously for this illness? ☐ Yes ☐ No ☐ Unk if yes, please complete a line of information for each previous hospitalization:				
Date of Hospitalization	Health Facility Name	Village	County	Was the patient isolated?
____/____/____ (D.M.Yr)				☐ Yes ☐ No
____/____/____ (D.M.Yr)				☐ Yes ☐ No

Case
Name:

Outbreak
Case ID:

Yellow
LIB-MONT

Section 4. Epidemiological Risk Factors and Exposures

IN THE PAST ONE(1) MONTH PRIOR TO SYMPTOM ONSET:

1. Did the patient have contact with a known or suspect case, or with any sick person before becoming ill? ☐ Yes ☐ No ☐ Unk
If yes, please complete one line of information for each sick source case:

Name of Source Case	Relation to Patient	Dates of Exposure (D, M, Yr)	Village	County	Was the person dead or alive?	Contact Types**
		___/___/___ - ___/___/___			☐ Alive ☐ Dead, date of death: ___/___/___ (D, M, Yr)	
		___/___/___ - ___/___/___			☐ Alive ☐ Dead, date of death: ___/___/___ (D, M, Yr)	
		___/___/___ - ___/___/___			☐ Alive ☐ Dead, date of death: ___/___/___ (D, M, Yr)	

**Contact Types:
(list all that apply)

- 1 - Touched the body fluids of the case (blood, vomit, saliva, urine, feces)
2 - Had direct physical contact with the body of the case (alive or dead)
3 - Touched or shared the linens, clothes, or dishes/eating utensils of the case
4 - Slept, ate, or spent time in the same household or room as the case

2. Did the patient attend a funeral before becoming ill? ☐ Yes ☐ No ☐ Unk
If yes, please complete one line of information for each funeral attended:

Name of Deceased Person	Relation to Patient	Dates of Funeral Attendance (D, M, Yr)	Village	County	Did the patient participate (carry or touch the body)?
		___/___/___ - ___/___/___			☐ Yes ☐ No
		___/___/___ - ___/___/___			☐ Yes ☐ No

3. Did the patient travel outside their home or village/town before becoming ill? ☐ Yes ☐ No ☐ Unk
If yes, Village: _____ County: _____ Date(s): ___/___/___ - ___/___/___ (D, M, Yr)

4. Was the patient hospitalized or did he/she go to a clinic or visit anyone in the hospital before this illness? ☐ Yes ☐ No ☐ Unk
If yes, Patient Visited: _____ Date(s): ___/___/___ - ___/___/___ (D, M, Yr)
Health Facility Name: _____ Village: _____ County: _____

5. Did the patient consult a traditional/spiritual healer before becoming ill? ☐ Yes ☐ No ☐ Unk
If yes, Name of Healer: _____ Village: _____ County: _____ Date: ___/___/___ (D, M, Yr)

6. Did the patient have direct contact (hunt, touch, eat) with animals or uncooked meat before becoming ill? ☐ Yes ☐ No ☐ Unk
If yes, please tick all that apply:

Animal:	Status (check one only):
☐ Bats or bat feces/urine	☐ Healthy ☐ Sick/Dead
☐ Primates (monkeys)	☐ Healthy ☐ Sick/Dead
☐ Rodents or rodent feces/urine	☐ Healthy ☐ Sick/Dead
☐ Pigs	☐ Healthy ☐ Sick/Dead
☐ Chickens or wild birds	☐ Healthy ☐ Sick/Dead
☐ Cows, goats, or sheep	☐ Healthy ☐ Sick/Dead
☐ Other, specify: _____	☐ Healthy ☐ Sick/Dead

Section 6. Case Report Form Completed by:

Name: _____ Phone: _____ E-mail: _____
Position: _____ County: _____ Health Facility: _____
Information provided by: ☐ Patient ☐ Proxy; if proxy, Name: _____ Relation to Patient: _____

Case
Name:

Outbreak
Case ID:

LIB-MONT

****If the patient is deceased or has already recovered from illness, please fill out the next section.**

****If the patient is currently admitted to the hospital, leave the next section blank (it will be completed upon discharge)**

Section 7. Patient Outcome Information

Please fill out this section at the time of patient recovery and discharge from the hospital OR at the time of patient death.

Date Outcome Information Completed: ____/____/____ (D, M, Yr)

Final Status of the Patient: ☐ Alive ☐ Dead

Did the patient have signs of unexplained bleeding at any time during their illness? ☐ Yes ☐ No ☐ Unk

If yes, please specify: _____

If the patient has recovered and been discharged from the hospital:

Name of hospital discharged from: _____ County: _____

If the patient was isolated, Date of discharge from the isolation ward: ____/____/____ (D, M, Yr)

Date of discharge from the hospital: ____/____/____ (D, M, Yr)

If the patient is dead:

Date of Death: ____/____/____ (D, M, Yr)

Place of Death: ☐ Community ☐ Hospital: _____ ☐ Other: _____

Village: _____ County: _____ District: _____

Date of Funeral/Burial: ____/____/____ (D, M, Yr) Funeral conducted by: ☐ Family/community ☐ Outbreak burial team

Place of Funeral/Burial:

Village: _____ County: _____ District: _____

Please tick an answer for ALL symptoms indicating if they occurred at any time during this illness including during hospitalization:

Headache	☐ Yes ☐ No ☐ Unk
If yes, Temp: _____ °C	Source: ☐ Axillary ☐ Oral ☐ Rectal
Diarrhea	☐ Yes ☐ No ☐ Unk
Anorexia/loss of appetite	☐ Yes ☐ No ☐ Unk
Chest pain	☐ Yes ☐ No ☐ Unk
Joint pain	☐ Yes ☐ No ☐ Unk
Cough	☐ Yes ☐ No ☐ Unk
Difficulty swallowing	☐ Yes ☐ No ☐ Unk
Jaundice (yellow eyes/gums/skin)	☐ Yes ☐ No ☐ Unk
Skin rash	☐ Yes ☐ No ☐ Unk
Pain behind eyes/sensitive to light	☐ Yes ☐ No ☐ Unk
Confused or disoriented	☐ Yes ☐ No ☐ Unk

Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk

If yes, please specify: _____

LABORATORY FORM (sample #2)

Outbreak
Case ID:

LIB-MONT

Patient's Surname: _____ Other Names: _____
 Age: _____ ☐ Years ☐ Months
 Gender: ☐ Male ☐ Female
 Permanent Residence:
 Village/Town: _____ County: _____ Country of Residence: _____
 Date of Initial Symptom Onset: ____/____/____ (D, M, Y)
 Status of Patient at Time Sample Collected: ☐ Alive ☐ Dead If dead, Date of Death: ____/____/____ (D, M, Y)
 Health Facility Submitting Sample: _____ Person Submitting Sample: _____
 Submitter's Phone Number: _____ Submitter's Email: _____

Section 5: Clinical Specimens and Laboratory Testing

- Specimen/shipping instructions:**
- Label sample with patient name, date of collection, and case ID
 - Send sample cold with a cold/ice pack, and packaged appropriately
 - Collect whole blood in a purple top (EDTA) tube – green or red top tubes acceptable if purple not available
 - Preferred sample volume = 4ml (minimum sample volume = 2ml)

Has this patient had a sample submitted previously? ☐ Yes ☐ No

Sample 1:

Do not complete
(LVR) Only

Sample Collection Date: ____/____/____ (D, M, Y)

Sample Type:

- ☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

Sample 2:

Do not complete
(LVR) Only

Sample Collection Date: ____/____/____ (D, M, Y)

Sample Type:

- ☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

LABORATORY FORM (sample #1)

Outbreak
Case ID:

LIB-MONT

Patient's Surname: _____ Other Names: _____
 Age: _____ ☐ Years ☐ Months
 Gender: ☐ Male ☐ Female
 Permanent Residence:
 Village/Town: _____ County: _____ Country of Residence: _____
 Date of Initial Symptom Onset: ____/____/____ (D, M, Y)
 Status of Patient at Time Sample Collected: ☐ Alive ☐ Dead If dead, Date of Death: ____/____/____ (D, M, Y)
 Health Facility Submitting Sample: _____ Person Submitting Sample: _____
 Submitter's Phone Number: _____ Submitter's Email: _____

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Sample 1:

Do not complete
(LVR) Only

Sample Collection Date: ____/____/____ (D, M, Y)

Sample Type:

- ☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

Sample 2:

Do not complete
(LVR) Only

Sample Collection Date: ____/____/____ (D, M, Y)

Sample Type:

- ☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

Chapter 5:

Investigation of a novel strain of Methicillin-resistant *Staphylococcus aureus* in a New South Wales local health district

“A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill”

Dr Margaret Chan
Director-General of the World Health Organization

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Abbreviations

AGAR	Australian Group on Antimicrobial Resistance
BT	Binary typing
CA – MRSA	Community-associated Methicillin-resistant <i>Staphylococcus aureus</i>
CEC	Clinical Excellence Commission
HA – MRSA	Hospital-associated Methicillin-resistant <i>Staphylococcus aureus</i>
HIE	Health Information Exchange
ICD-10 AM	International Classification of Diseases, 10 th edition, Australian Modified
ICU	Intensive care unit
LHD	Local health district
MLST	Multi-locus sequence typing
MRO	Multi-resistant organism
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NSW	New South Wales
OR	Odds ratio
PCR	Polymerase Chain Reaction
PCL	Panto-Valentine leucocidin
SCCmec	Staphylococcal cassette chromosome <i>mec</i>
Spa	Staphylococcal protein A
WGS	Whole genome sequencing

Chapter Prelude

My role

Health Protection New South Wales (NSW) was made aware of an outbreak of Methicillin-resistant *Staphylococcus aureus* (MRSA) in July 2014 through local clinicians who were concerned at the rate with which the bacterium was spreading in affected hospitals and by its unique anti-microbial resistance pattern. The antibiotic resistance pattern had not previously been seen in Australian hospitals. We had teleconferences with the infection control team at the local health district and with the Clinical Excellence Commission (CEC), a Ministry of Health agency who provide advice on healthcare associated infections, to discuss how best to approach the problem. The team thought further investigation was necessary and that an epidemiological study should be conducted.

A public health officer trainee of the NSW Public Health Officer training program, and I were set the task of conducting a case-control study to better understand this novel MRSA strain. We visited the affected hospital and discussed a study design protocol with the infectious diseases team, including information that should be gathered from medical records on cases and controls. I developed a data collection form, organised to get medical records from the medical records department and visited the hospital on and off for the next two months to gather data. Together with an epidemiologist from the local public health unit, the public health officer trainee worked on retrieving medical information from the hospital's electronic databases. I then developed a data analysis plan for the study and the data analysis was performed by a biostatistics trainee due to the complexity of the data sources and the need for timely results.

The next phase of the study was to analyse results of whole genome sequencing data. I did this by manually mapping patient movements through admitted hospitals in the local health district, down to ward and bed level and by looking at the 'treating medical officer' to identify potential links and transmission patterns.

We had ongoing teleconferences with the local team throughout the investigation and progress and results were discussed at these meetings. I presented the findings of the investigation at the

Communicable Diseases Control conference (organised by the Public Health Association of Australia) in Brisbane in June 2015. I also aim to publish these findings in a peer-reviewed journal.

Lessons learned

This study was a great way to learn about the processes involved in conducting an epidemiological study from beginning to end. Being involved in the study design and protocol, data extraction and recording, data analysis and reporting, helped me understand the requirements and constraints of each stage. In particular, the systematic extraction of data from medical records taught me the value in having a well-defined tool for data collection and standardised criteria for defining specific clinical variables – such as ‘infection’ and ‘medical treatment’, made it easier to gather information from medical records methodically. It was also an eye-opening experience to learn about what is possible through data linkage and electronic-based systems for data extraction.

I learned important epidemiological concepts relating to case-control studies and their advantages and disadvantages as a study design. It is often said that one of the biggest challenges in any case-control study is appropriate control selection and this was true in our study, as we had the possibility of over-matching. I also learned about alternative study designs such as the ‘case-case’ study type and the ‘self-controlled case series’, both of which could have applied to our study. However, ultimately, I learned that the investigation has to be tailored to what is practical and possible to be achieved in the allotted time frame. This was not only a research study, it was also conducted to determine whether further control measures were necessary to control an outbreak.

While whole genome sequencing is being hailed as a breakthrough technology in increasing our understanding of organisms, its application to real-time field investigations is in its infancy, especially in Australia. The utilisation of whole genome sequencing in our investigation may have been more useful if it could have been applied in real-time and there were more efficient means to analyse transmission pathways. In clinical medicine, we often get taught by seniors that we shouldn’t order a laboratory test unless we know what we will do with the result. I think the same lesson could be applied to public health laboratory methods. Before we invest in more advanced molecular tests we should know how the information gained will add to our investigation. With increased

understanding and utilisation of these methods, however, hopefully these teething problems will be resolved.

Public health implications

MRSA can result in significant morbidity and mortality for individuals infected with this organism. From a public health point of view, this can mean adverse health effects on the very young and the elderly, a prolonged hospital stay resulting in an increased cost of hospitalisation and the potential for ongoing spread of multi-resistant organisms. Therefore, understanding characteristics of emerging strains of MRSA through investigative methods is important in informing our decisions for ongoing infection prevention and control.

This is the first time that this MRSA strain has been reported in Australia and insight into its unique biological properties has implications for our understanding of the interaction between hospital-associated and community-associated strains of MRSA.

Whole genome sequencing is a rapidly progressing tool for characterising outbreaks and has been well described in MRSA investigations overseas, but this was the first time it has been used in an MRSA outbreak investigation in NSW. Lessons learned from this experience may assist in utilising this methodology in a more timely way in future MRSA outbreaks.

The World Health Organization released its first global report on antibiotic resistance in April 2014, with a concluding statement that antimicrobial resistance is an increasing threat to global public health (1). Adding to the body of knowledge on antibiotic-resistant organisms is therefore important in contributing to the global effort taken to address this growing public health concern.

Abstract

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important hospital-associated pathogen. A novel MRSA strain, characterised by its uncommon antibiogram of gentamicin resistance and co-trimoxazole sensitivity, was identified in a local health district (LHD X) in New South Wales (NSW) in August 2013. An outbreak ensued across nine hospitals and by June 2014, this strain accounted for 45% of all hospital-associated MRSA. We sought to describe the characteristics of patients identified with the novel strain and assess whether they were different from patients with existing endemic strains, with respect to risk factors for infection and clinical outcomes. We aimed to identify potential chains of transmission between patients with the novel strain.

Methods

We identified patients with the novel MRSA antibiogram from a database of routinely collected multi-resistant organisms at LHD X. We performed descriptive epidemiology on these patients. We defined cases in the case-control study as hospital in-patients with the novel MRSA strain and controls as those with endemic, hospital-associated MRSA strains, isolated between 29 August 2013 and 30 June 2014, who were admitted to a hospital at LHD X. We collected demographic, clinical and hospitalisation information on all patients and compared information on risk factors and clinical outcomes between cases and controls. Isolates were further characterised by binary typing, multilocus sequence typing and *spa* typing. Using whole genome sequencing (WGS), we attempted to identify common linkages between patients with respect to patient movements within hospitals and treating medical officer.

Results

Between 29 August 2013 and 30 June 2014, there were 84 patients with the novel MRSA strain identified at LHD X. The median age of patients was 77 years (range 46 - 96), 52 (62%) were male and 25 (30%) usually lived in a nursing home. In the case-control study, we compared 67 cases with 112 controls. Cases and controls had similar demographic features and medical co-morbidities. There were no differences in clinical outcomes relating to infection, colonisation or 30 day all-cause mortality. In the 90 days before diagnosis, cases, relative to controls, had 0.4 times the odds of visiting one rather than two hospitals (OR 0.4, 0.2 – 0.7). Acquiring the novel strain was not associated with having surgery prior to MRSA isolation or being admitted to a particular ward type. Further laboratory characterisation identified the novel strain to be an ST45-V clone, PVL positive and binary type 1296. Whole genome sequencing of 45 isolates identified eight unique clades. Although we did not collect information on all relevant factors implicated in the transmission of MRSA, analysis of the eight clades identified three clusters - two clusters related by a single ward and one cluster related by a medical officer.

Conclusion

Despite the lack of specific risk factors and indifference in clinical outcomes when compared with endemic hospital MRSA strains, the novel strain was rapidly transmitted through several health care facilities. Enhanced infection control measures had an effect on reducing all hospital-associated MRSA strains, including the novel strain. Whole genome sequencing may allow for better definition of transmission pathways and may assist in the characterisation of MRSA outbreaks in future.

Background

Methicillin resistant *Staphylococcal aureus* (MRSA) has become an increasingly common cause of nosocomial infections worldwide, with estimates that approximately 44% of all hospital-associated infections can be attributed to MRSA (2). Hospital-associated MRSA (HA-MRSA) strains usually cause infection in elderly, immuno-compromised patients, most with a history of surgery, indwelling devices and /or antimicrobial therapy (3, 4). MRSA is also prevalent in health care workers, suggesting that these individuals may serve as a reservoir for spreading MRSA infections in healthcare settings (5).

Common clinical manifestations of MRSA in the hospital setting include skin and soft tissue infections and respiratory infections (6). However, more invasive infections such as osteomyelitis, necrotising pneumonia and endocarditis are often associated with life-threatening bacteraemia, with mortality rates ranging from as low as 2.5% to as high as 40% (7-9). Vancomycin continues to be the treatment of choice for treating most MRSA infections in hospital due to multi-resistance to other beta-lactam antibiotics (10).

Although MRSA was first isolated in the hospital environment, community-associated MRSA (CA-MRSA) infections have been identified in patients without previous healthcare contact (4). These strains affect younger, healthy people and are rapidly spread in community settings (4). Community-associated MRSA strains appear to have arisen by the acquisition of a mobile staphylococcal cassette chromosome *mec* (SCC*mec*) gene (2). These strains are generally susceptible to non – beta lactamase antibiotics and many of them also produce the Panto-Valentine leucocidin (PVL), a toxin associated with increased virulence (2, 6).

Individuals can also be colonised with MRSA without symptoms; this occurs in approximately 1.5% of the general population (5). Transmission of MRSA occurs when a non-infected individual comes into direct skin-to-skin contact with an infected individual or it can occur via contaminated fomites in hospital and household settings (5). An individual is at higher risk of infection from his or her own colonising strain (11).

In an effort to understand the epidemiology of the various MRSA strains, a number of molecular methods are currently in place. While the phenotypic method of comparing isolate-susceptibility to a range of antibiotics (an antibiogram) allows for the identification of an outbreak caused by an unusual pattern of antibiotic resistance, this method has relatively poor discriminatory power (12). Genotypic methods which allow molecular changes in the bacterium to be detected are commonly used in Australia and include multilocus sequence typing (MLST), *SCCmec* typing and staphylococcal protein-A (*spa*) typing (8). A more recently introduced method of strain typing called binary typing (BT) is based on the detecting of a combination of genetic loci by polymerase chain reaction (PCR) (12). This method is proven to have high discriminatory power, results are reproducible and easily interpretable (12, 13).

A local health district (LHD) X in New South Wales (NSW), usually conducts surveillance for MRSA by keeping a database of all patients with multi-resistant organisms (MROs) isolated from each of the nine hospitals in their district. In August 2013, the main hospital laboratory in LHD X identified an MRSA isolate with a unique antibiogram pattern of gentamicin resistance and co-trimoxazole sensitivity. In November 2013, a cluster of six patients from four hospitals in the district were noted to be infected with this strain. Further characterisation by binary typing in March 2014 identified the strain as bt-1296. In May 2014, the first bacteraemia due to this strain was reported. Local surveillance suggested that the new strain was adding to rather than replacing usual HA-MRSA, and accounted for 45% of all HA-MRSA in the district by June 2014. No other hospitals in NSW reported the presence of this strain.

The nine hospitals of LHD X serve a population of approximately 390,000 people and comprise one major tertiary referral and teaching hospital with 500 beds, three smaller acute care facilities with medical and surgical capacity with between 100 to 200 beds and five 50 to 60 bed rehabilitation, aged care and palliative care facilities. Doctors, nurses and allied health staff work across these nine facilities. This region has a higher than average ageing population - 8.5% of the population are aged greater than 75 years compared to 6.9% for the rest of the state (14).

An outbreak investigation team was formed in July 2014 at the request of local clinicians to better understand the situation. The main goal of conducting the investigation served a public health purpose and that was to limit the spread of the novel strain and to potentially identify any additional

control measures that may be necessary to ensure that no new cases were infected. As such, we were limited by time and logistic capacity in our investigation. We were not able to collect information on all known risk factors for infection with MRSA – the information collected was that which was easily accessible and extractable via hospital medical records and local databases.

In this chapter, I present the findings from our epidemiological study which aimed to describe the characteristics of patients with the novel strain and compare their clinical features and risk factors for infection with patients infected with endemic MRSA strains. We also sought to identify chains of transmission, within the health care setting, between patients infected with the novel strain by using whole genome sequencing.

Methods

1) Case series

As part of routine surveillance for MROs, LHD X keeps a database of all patients isolated with multi-resistant organisms from each of the nine hospitals in their district. These isolates may be clinical samples, e.g. from infected wound sites or they may be reported from screening samples taken routinely on certain wards, e.g. aged care and rehabilitation wards.

We searched the MRO database at LHD X for all cases admitted to any of the nine LHD X hospitals with the novel MRSA antimicrobial resistance pattern of gentamicin resistance and co-trimoxazole sensitivity, between 29 August 2013 and 30 June 2014.

We used simple descriptive analysis to describe the demographic and clinical characteristics of the novel cases.

2) Case – control study

2.1 Case Definitions

We defined a case as a person admitted to a hospital at LHD X with the novel MRSA antimicrobial resistance pattern of gentamicin resistance and co-trimoxazole sensitivity, isolated between the period 29 August 2013 and 30 June 2014, where their MRSA was classified as hospital-associated.

In keeping with local and national protocols, hospital-associated MRSA was further defined as:

- an isolate identified after at least 48 hours of hospitalisation (attributed to the current facility) (15) OR
- an isolate from a patient who has had a hospital admission, of 48 hours or more, in one of the nine facilities in the previous 90 days (attributed to the most recent facility).

We defined a control as a patient admitted to a hospital at LHD X, consecutively listed on the LHD X, MRO database with an MRSA antibiotic resistance pattern that was non-novel and the MRSA was classified as hospital-associated, over the same time period.

If an individual patient had more than one MRSA isolate in the study period, only the first isolate was considered for both cases and controls.

2.2 Data collection and variables used

For cases and controls, we collected the following risk factor information related to the 90-day period before MRSA acquisition: 1) existing medical co-morbidities, 2) history of surgery prior to isolate identification, 3) number of hospitals visited and 4) type of ward the patient was admitted to during their hospital stay.

For cases and controls, we collected the following outcome information related to the 30-day period after MRSA acquisition. Firstly, we made an assessment of clinical infection or colonisation with MRSA. Clinical infection with MRSA was defined as having a medical treatment plan where strain-susceptible intravenous or oral antibiotics were administered for at least 48 hours or where there was a surgical treatment plan. This definition was used as it was not always clear from the medical records whether or not antibiotics were used specifically for MRSA or whether intervention was targeted at the treatment of another infection. Clinical infections were further classified according to site – primary (the most invasive site of infection) versus secondary, and type - sterile versus non-sterile (sterile sites were blood, cerebrospinal fluid, peritoneal fluid, bullae, lumbar disc fluid and lymph nodes). If a patient did not meet the criteria for infection, they were classified as having MRSA colonisation. Secondly, we collected information on admission to an intensive care (ICU) for any cause and lastly, we gathered information on in-hospital mortality, where this was recorded in the medical notes.

Information regarding history of antibiotic use, indwelling catheters and other devices, details of clinical and non-clinical staff involved in patient care were not easily extractable from hospital medical records and were therefore not collected.

We gathered information on cases and controls in two ways:

1. We used the Health Information Exchange (HIE), a data warehouse of all hospital admissions and discharges managed by NSW Health, to extract information electronically on the following variables: demographics, co-morbidities, admission to ICU, surgical procedures pre- and post-isolate and hospital and ward locations. Co-morbidities were extracted using codes from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) (16).
2. Using a standardised protocol, we used electronic and paper-based medical records to collect clinical information such as whether an individual was infected or colonised with MRSA and the site of infection.

2.3 Data analysis

Data gathered from the HIE and medical records were imported into SAS enterprise guide version 12 and merged using unique identifiers. We calculated frequencies of demographic and risk factor information for cases and controls. Single variable analysis of relevant exposures was conducted after categorizing exposures as binary variables. Odds ratios were used to calculate measures of association between cases and controls using SAS version 12. Fisher's exact tests were conducted for cell counts less than five. A result was determined significant at a p-value less than 0.05 with corresponding 95% confidence intervals also considered.

3) Identifying chains of transmission

To identify potential chains of transmission in acquisition of the novel strain, we conducted whole genome sequencing (WGS) on available isolates. We then analysed information on corresponding

patients, pertaining to hospitals and wards visited, bed location and treating medical officer in the 90-day period before and the 30-day period after MRSA was isolated. In this assessment, we were not able to collect information on other clinical and non-clinical staff who may have had contact with cases - such as nursing staff, physiotherapists, occupational therapists, cleaners, etc. We were also not able to collect information on environmental sources of infection such as shared medical equipment, shared equipment in the hospital-room, toilet facilities and others.

4) Laboratory methods

4.1 Antibigram

Isolates were identified as MRSA from clinical and screening specimens using standard laboratory methods and susceptibility testing was performed using the calibrated dichotomous sensitivity (CDS) method (17).

4.2 Binary typing

This method has been described in detail previously (12). Briefly, the 19 targets for this assay were chosen from 51 utilized in previous assays for toxin gene (18), phage-derived open reading frame (19) and *SCCmec* typing (20). Results of these assays using a diverse local and international collection of 165 MRSA isolates, were analysed by a specially designed computerized algorithm (AuSeTTS, available at <http://www.cidmaph.org.au/pages/AuSeTTS>) to identify the combination of targets with the highest discriminatory power, while maintaining concordance with MLST. Targets selected were four toxin genes and six *SCCmec* elements plus *nuc* and *mec A*. All targets were amplified in a single multiplex PCR reaction. Results were expressed as a 19-digit binary number, converted to a decimal code for ease of interpretation.

4.3 Multilocus sequence typing and Staphylococcal protein A typing

Multilocus sequencing typing was performed as described by Enright et al. (21) and *spa* typing was performed as described by Shopsin et al. (22).

4.4 Whole genome sequencing

Whole genome sequencing was conducted using previously described methods (23). Whole-genome pUC18 plasmid libraries were prepared in *Escherichia coli* DH5 α MCR (Life Technologies, MD, USA). Genomic DNA fragments of 1.0–2.2 kb in size were generated by random mechanical shearing. Random clones were sequenced using dye-terminator chemistry, analysed with an ABI PRISM 3700 DNA analyser (Applied Biosystems, CA, USA), and data were assembled by use of Phred/Phrap. Physical gaps were closed by combinatorial PCRs followed by sequencing of PCR products. The assembled contigs of the entire chromosome and plasmid sequence were edited by Sequencher (Gene Codes, Ann Arbor, MI, USA). The genome orientation was reconfirmed by doing 18-kb-long PCR walking for the genome sequence and by pulsed-field gel electrophoresis. The final genome sequences of N315 and Mu50 were based on about 64 000 and 63 000 sequences, respectively. Bootstrapping algorithms were used to construct the phylogenetic tree.

5) Ethics

This study was conducted as part of routine investigation of an outbreak and review by a human research ethics committee was not required.

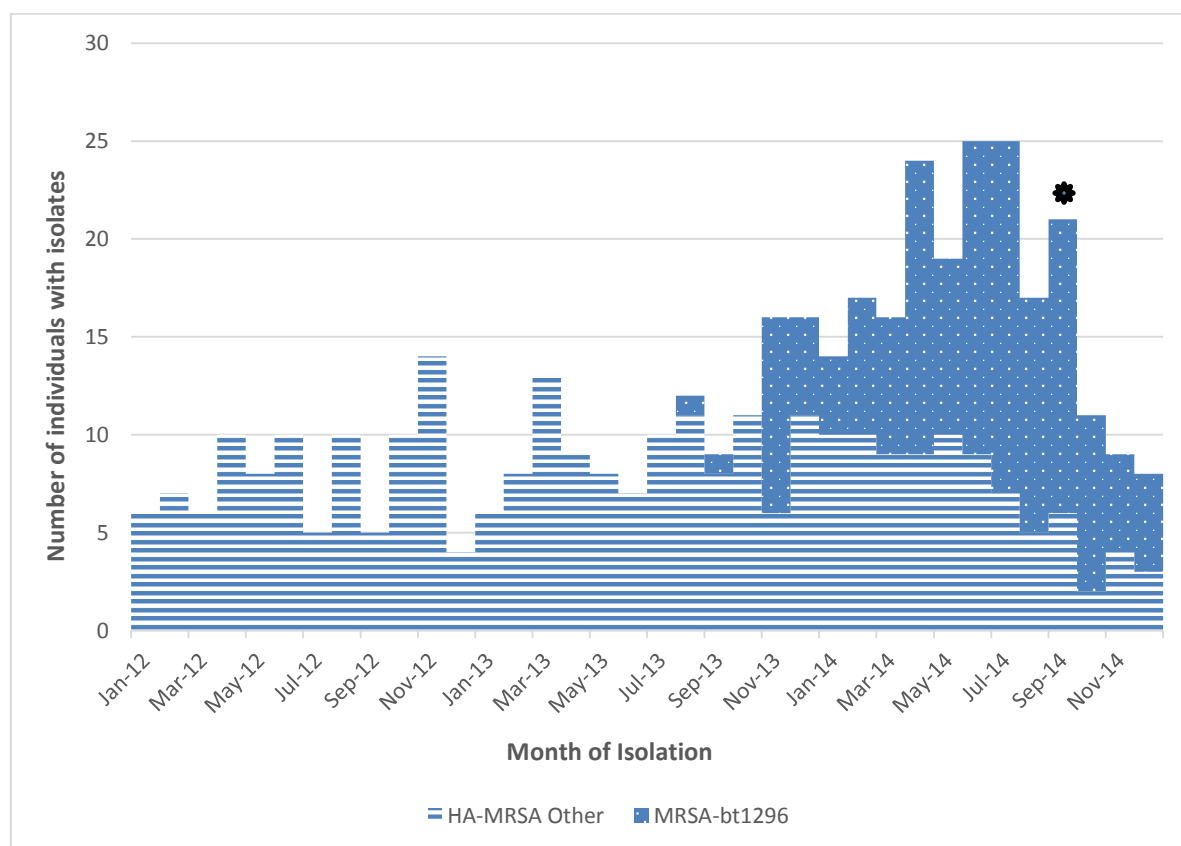
Results

1) Case series

1.1 Description of patients with the novel MRSA strain

Between 29 August 2013 and 30 June 2014, 179 HA-MRSA isolates were identified in inpatients at LHD X (Figure 1). Of these, 84 (47%) were the novel MRSA strain; 75 (89%) of which were isolated from hospitalised patients, five (6%) from residents in a nursing home, one (1%) from a hospice resident and four (5%) were community-associated. Of the 75 hospitalised patients with the novel strain, 24 (32%) were first identified with MRSA from the major tertiary facility, 11 (17%) from the smaller acute care facilities and 39 (52%) from the rehabilitation hospitals.

Figure 1: Inpatients with MRSA isolated between January 2012 and December 2014 in Local Health District X



✿ Enhanced control measures enforced at LHD X hospitals

The mean age of all patients with the novel MRSA strain was 77 years (range 46 - 96), 52 (62%) were male and 25 (30%) usually lived in a nursing home. The most common co-morbidities reported were endocrine disorders in 76 cases (90%), followed by renal disease in 62 (74%) and circulatory disorders in 56 (67%). Other conditions included lung disease in 29 (35%) and cancer in 14 (17%).

1.2 Laboratory features of novel MRSA isolates

In addition to gentamicin resistance and co-trimoxazole sensitivity, antibiotic susceptibility testing showed resistance to tetracycline, erythromycin and ciprofloxacin. Binary typing was conducted for 50 of the 84 (60%) novel isolates. Of these, 42 (84%) were characterised as *bt-1296*. The remaining eight isolates were represented by eight distinct binary types. Further MLST and *SCCmec* typing identified the novel strain as an ST45-V clone and PVL positive.

2) Case-control study

2.1 Criteria for inclusion

Of the 84 novel isolates, nine were excluded from the case control study as their MRSA was community-associated or acquired in a nursing home. Eight duplicate isolates were excluded as they belonged to an individual known to have acquired the novel strain at an earlier time point. Seven duplicate isolates from the control group were also excluded for the same reason. Sixty-seven individuals with the novel MRSA strain were compared to 112 with endemic MRSA strains.

2.2 Description of cases and controls

The mean age of cases included in the case-control study was 79 years (range 46 – 97 years), 44 (62%) were male and 16 (24%) usually lived in a nursing home (Table 1). The most common co-morbidities reported were endocrine disorders in 62 cases (93%), followed by renal disease in 50 (75%) and circulatory disorders in 44 (66%). Other co-morbidities included lung disease in 23 (34%)

and cancer in 13 (19%) (Table 1). Control patients with endemic MRSA strains had similar demographic features and history of medical co-morbidities. There were no statistically significant differences in age, sex, nursing home residence or co-morbidities between the two groups (Table 1).

Table 1: Comparison of novel MRSA isolates to endemic hospital-associated MRSA strains

Characteristic	Cases, n = 67	Controls, n = 112	OR (95% CI)
Age, median (range), years	79 (46 – 97)	77 (20 – 100)	1.0
Sex, % male	44 (66%)	64 (57%)	1.4 (0.8 – 2.7)
Nursing home as primary place of residence	16 (24%)	20 (18%)	1.4 (0.7 – 3.0)
Co-morbidities			
Endocrine disorders	62 (93%)	100 (89%)	1.5 (0.5 – 4.4)
Renal disease	50 (75%)	74 (66%)	1.5 (0.8 – 3.0)
Circulatory disorders	44 (66%)	83 (74%)	0.7 (0.4 – 1.3)
Lung disease	23 (34%)	52 (46%)	0.6 (0.3 – 1.1)
Cancer	13 (19%)	20 (18%)	1.1 (0.5 – 2.4)
Influenza	21 (31%)	41 (37%)	0.8 (0.4 – 1.5)
Clinical Outcomes			
Colonisation	43 (64%)	69 (62%)	1.0
Infection	24 (36%)	43 (38%)	0.9 (0.5 – 1.7)
- Antibiotics received	23/24 (96%)	43/43 (100%)	0.9 (0.5 – 1.7)
- Surgery for infection	5/24 (21%)	7/43 (16%)	1.2 (0.4 – 3.9)
Intensive care unit admission for any cause	2 (3%)	10 (9%)	0.3 (0.1 – 1.5)
Mortality 30 days post isolate	11 (16%)	7 (6%)	2.9 (1.1 – 8.0)
Risk factors			
Surgery prior to isolate	5 (7%)	13 (12%)	0.6 (0.2 – 1.8)
No. of hospitals visited			
1	18 (26%)	55 (49%)	Reference group
2 or more	49 (73%)	56 (50%)	3.0 (1.6 – 5.9)
Unit type			
Geriatric	34 (51%)	40 (36%)	1.9 (1.0 – 3.4)
Medicine	61 (91%)	97 (87%)	0.6 (0.2 – 1.7)
Rehabilitation	20 (30%)	32 (29%)	1.1 (0.6 – 2.1)
Renal	3 (4%)	9 (8%)	0.5 (0.1 – 2.1)
Surgical	17 (25%)	45 (40%)	0.5 (0.3 – 1.0)

2.3 Clinical outcomes

Forty-three cases (64%) were colonised with MRSA, while infection occurred in 24 (36%). Of those infected, twenty (85%) were in non-sterile sites with skin/soft tissue infections accounting for 13 cases (65%), followed by three urinary tract infections (15%) and two respiratory tract infections (10%). The two other non-sterile infections were catheter-associated with one related to a central venous catheter for dialysis and the other to a urinary catheter. There were four (17%) sterile site infections caused by the novel MRSA strain, being septicaemia, osteomyelitis, empyema and two muscle infections. A secondary infection in a patient with malignant muscle infection who later developed a surgical wound infection was also reported.

Rates of colonisation and infection were comparable in the two groups (Table 1). There were no differences in admission to the intensive care unit or having surgery for infection between cases and controls (Table 1). There was evidence of a difference in mortality in case-patients compared with controls (OR 2.9, p-value < 0.05) (Table 1). However, looking further into the cause of death in patients with the novel strain, we found that seven of the 11 deaths were in patients colonised with the strain and their cause of death was unrelated to MRSA. In the four patients with infection, two were known to palliative care services.

2.4 Risk factor information

In the 90 days before MRSA acquisition, 49 cases (73%) visited two or more hospitals while 18 (26%) visited just one, compared to 56 controls (50%) who visited two hospitals and 55 (49%) who visited one hospital (Table 1). Cases, relative to controls, had three times the odds of visiting two or more hospitals rather than one (Table 1).

Patients admitted to a surgical unit were less likely to acquire the novel strain (OR 0.5; 95% CI 0.3 – 1.0), although statistical significance was marginal (Table 1).

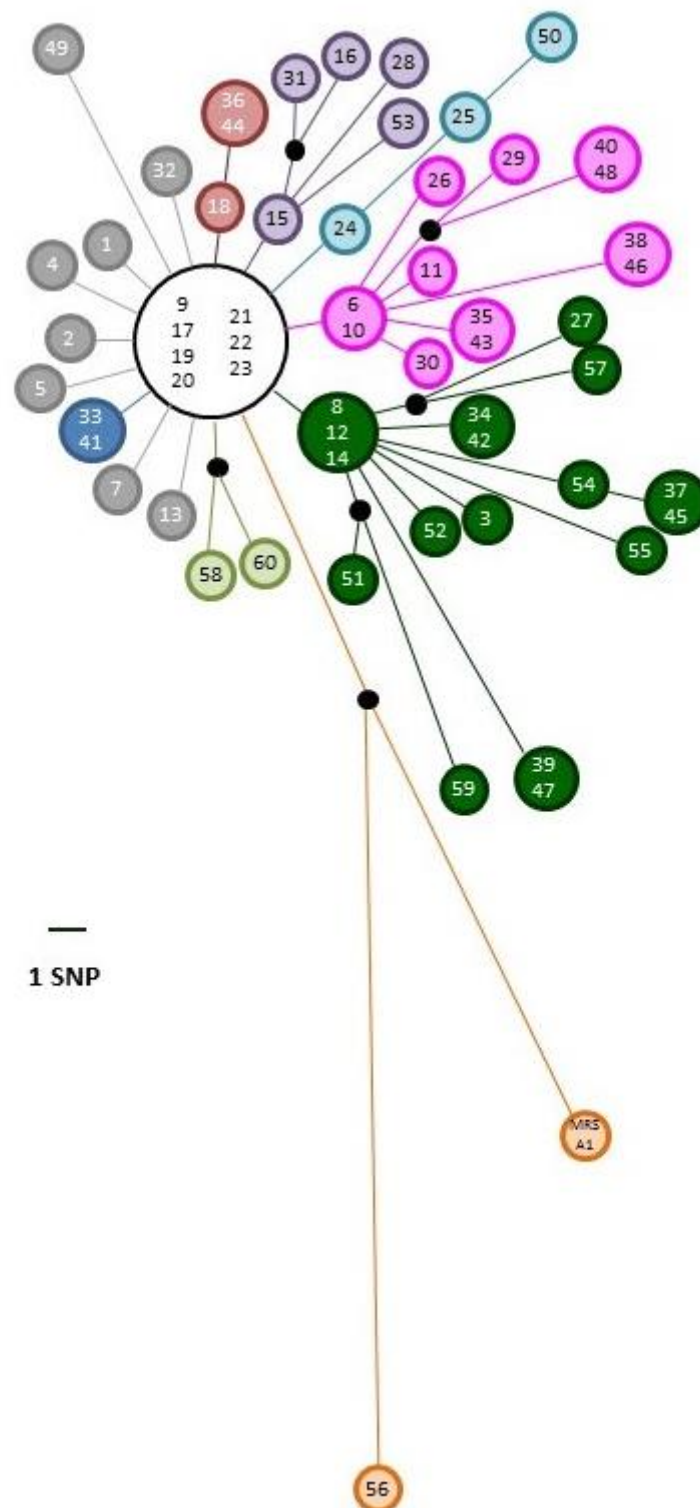
3) Identifying chains of transmission

Whole genome sequencing was performed on 45 novel MRSA isolates collected between 11 November 2013 and 30 June 2014.

Isolates could be defined into eight distinct clades: A – H (Figure 2). Isolates within clades were closely related with at most 12 single nucleotide polymorphism (SNP) difference between isolates. Isolates within a single circle of a clade had indistinguishable SNP profiles.

Examining the hospitalisation information for each of the isolates, we found that within clade A, two patients shared the same medical officer (isolates 20 and 22) and three patients were on the same ward at the same time (isolates 17, 19 and 21). Within clade B, three patients (isolates 8, 12 and 14) were all admitted on the same ward at the same time and appeared to have shared a four-bedded room.

Figure 2: Whole genome sequencing analysis of 60 novel MRSA strain isolates collected from LHD X, 11 November 2013 – 27 July 2014



4) Infection control interventions

During the course of the outbreak, the following additional control measures were implemented: (i) an improved hand hygiene project by junior doctors aiming to increasing adherence to the '5 moments for hand hygiene' protocol, (ii) the 'bare below elbows' policy, which required that all medical staff had no clothing or personal items (including watches) below the elbow, (iii) enhanced environmental cleaning of surfaces regularly in contact with patients such as bed rails, medical equipment, hospital furniture, etc., (iv) improved access to detergent wipes for healthcare workers, (v) improved signage at entrances to wards reminding visitors and staff to clean hands on entry, (vi) emails sent out to responsible medical officers of patients, alerting them of their patient's MRSA strain, (vii) notification of all medical staff of the outbreak and reminding them of infection control measures.

Discussion

Routine hospital-based surveillance for MROs allowed the identification of a novel strain of hospital-associated MRSA in a single LHD in Australia. Between April and October 2014, this novel strain accounted for over half of all HA-MRSA strains in the nine hospitals across LHD X. Although this strain affected hospitalised elderly patients with multiple medical comorbidities, there were no clinically significant differences between this strain and endemic HA-MRSA strains. Being admitted to two hospitals compared to one was significantly associated with acquiring the novel strain. No other unique risk factors for transmission were identified in the variables examined.

The Australian Group on Antimicrobial Resistance (AGAR) performs periodic prevalence surveys on antimicrobial resistance. The 2011 AGAR survey analysed *Staphylococcus aureus* isolates from 29 laboratories across all states and territories in Australia (6). In this report, 18.2% of all *Staphylococcus aureus* were HA-MRSA and four different HA-MRSA clones were identified (6). The two most prevalent strains were ST22-IV accounting for 49.5% and ST239-III accounting for 49.3% of all HA-MRSA (6). Typically, these two strains are PVL-negative, although a small number of PVL-positive isolates were reported in the 2012 survey (24). The novel strain that caused the outbreak in LHD X was identified as ST45-V – a clone of HA-MRSA that has not previously been isolated in hospital settings in Australia or been associated with nosocomial transmission. This strain, however, has been reported as a community MRSA strain in Western Australia where it accounted for 5.9% of CA-MRSA clones in 2012 (24).

The novel strain having the features of a CA-MRSA strain may have necessitated the application of specific control measures applicable to features of this strain-type. The introduction of enhanced control measures in July 2014 such as increasing access to alcohol wipes, enforcing a 'bare below elbows' policy and improving environmental cleaning saw a reduction in all HA-MRSA, including the novel strain. The application of these standard infection control measures suggest that the novel strain was equally susceptible to these methods. This is consistent with what is known about control measures applied to outbreaks of CA-MRSA in healthcare settings (4). However, an important measure to consider in an outbreak of this type in future is to routinely screen healthcare workers involved in patient care, as it has been reported that healthcare workers are more commonly the source of outbreaks of CA-MRSA outbreaks in healthcare facilities (25-27).

The detection of PVL in the novel strain is of particular concern due to the increased virulence associated with PVL-positive strains (4, 28). The PVL toxin is absent in HA-MRSA but present in most CA-MRSA lineages (4). It is associated with skin and soft tissue infections and with severe infections such as necrotising pneumonia and septic shock (28, 29). An increasing number of reports from around the world indicate that CA-MRSA strains may be gradually replacing HA-MRSA strains in hospitals, with most reported healthcare outbreaks being caused by PVL-positive CA-MRSA strains (4). Studies suggest that CA-MRSA strains may behave more like HA-MRSA when inside hospitals with similar rates and severity of infection as HA-MRSA (30, 31). The additional challenge presented by community strains is that the reservoir may extend outside hospital walls to visitors, healthcare workers and other patients, who can facilitate transmission of CA-MRSA within hospitals.

The antibiotic susceptibility pattern of gentamicin-resistance and co-trimoxazole-sensitivity is uncommon and rarely seen in Australia (6). However, this resistance pattern has been described in hospital settings overseas (32, 33). A study in Israel in 1997 showed that of 270 MRSA isolates from a single hospital, 92% were sensitive to co-trimoxazole (32). At the same hospital in 1988, the co-trimoxazole sensitivity rate was 31% (32). The authors suggested that one possibility for this increase may have been a reduced usage of this drug in their institution. In support of this theory, in settings where co-trimoxazole is extensively used, an increase of MRSA resistance to co-trimoxazole has been observed (34). The reasons for the emergence of this antibiotic pattern in our facilities needs further exploration and it may be useful to consider in informing future guidelines around antibiotic usage in LHD X facilities.

In our study, we were able to show by WGS that the number of SNP differences between outbreak-related isolates were less than 15 (except in one case isolated from the community) indicating close genetic relatedness. We were also able to identify retrospective epidemiological links in eight isolates within clades with indistinguishable SNP profiles. This relatedness between isolates suggests that this may have been a point-source outbreak. However, we were not able to identify more definite chains of transmission between patients infected with the novel strain, partly because isolates analysed by WGS were those collected approximately three months after the outbreak commenced. It is possible that early, uncollected isolates not included in the WGS analysis may have acted as links in the chain, connecting the isolates that were included in our study. Whole genome sequencing methods have been used successfully in MRSA outbreak investigations in the United Kingdom (35) and Denmark (36) to identify chains of transmission and to pinpoint sources of infection. Perhaps if we expanded our criteria for mapping to more than just ward of admission and treating medical

officer, we may have been able to identify other epidemiological links. Due to time constraints and the manual way in which mapping of transmission pathways had to be done, we did not further pursue this.

MRSA outbreak investigations have typically been described on neonatal wards and localised facilities where transmission events are relatively easy to follow and dates of MRSA acquisition are more reliable. This investigation was different in that it investigated an elderly population with movements between multiple hospitals and the community, occurring over a ten month period. With this level of complexity and given our public health goal of controlling the outbreak, there were several limitations to our investigation. Firstly, we were not able to obtain information on all common risk factors for MRSA acquisition such as history of antibiotic use and presence of indwelling devices, due to time constraints. Secondly, our controls, being those with endemic strains of HA-MRSA, may have been closely matched to those with the novel strain, biasing the odds ratio towards the null. However, this control group was appropriate in answering our research question which was to determine the significance of the novel strain compared to usual MRSA strains seen in hospital.

Thirdly, although there was a significant finding with the novel strain more likely in those who stayed in two hospitals prior to MRSA acquisition compared to those who only stayed at one, we did not adjust for the length of stay in hospital. It is conceivable that elderly patients with MRSA may have stayed longer in hospital due to complications arising from their admission. This may also have necessitated the transfer of such patients to a rehabilitation facility. In effect, these considerations make hospitalisation in two facilities a confounder. Fourthly, we did not assess other factors such as carriage amongst healthcare workers and environmental contamination in our assessment of transmission pathways.

Another limitation in the study may have been the laboratory criteria used to define cases in the case definition. We used the novel antibiogram to define cases in our case definition. However, binary typing was able to better characterise novel isolates and showed that 84% of isolates with the novel antibiogram were bt1296 – a strain type not previously seen in the main reference laboratory. Binary typing has been used in outbreak investigations before (13) and using the binary type in our

case definition instead of the antibiogram may have allowed us to exclude some isolates that may not have been a part of the outbreak.

Our investigation of a novel strain of MRSA within nine facilities in a single local health district in NSW allowed us to determine that novel MRSA strains can emerge, but their clinical significance may not differ from endemic strains. The appearance of a community MRSA strain within hospital facilities with the ability to spread rapidly provides impetus for ongoing surveillance and monitoring of MRSA within hospitals and laboratories. We also found that whole genome sequencing has the potential to be useful in investigating MRSA outbreaks if combined with appropriate epidemiological information in a timely way.

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Chapter 6:

Lessons from the field

and

Teaching

“When one teaches, two learn”

- Robert Heinlein

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Abbreviations

EVD	Ebola virus disease
LFF	Lessons from the field
MSF	Medecins sans Frontieres
PVN	Predictive value negative
PVP	Predictive value positive

Chapter Prelude

My role and lessons learned

The MAE requires trainees to conduct two main teaching exercises. These are a 'lesson from the field' (LFF) and a teaching session for the first year MAE cohort at course block.

My lesson from the field stemmed from my observations and frustration of the international response to the Ebola virus disease (EVD) epidemic in West Africa in 2014. The international response was criticized by organisations like Medecins sans Frontieres (MSF) for being late and uncoordinated. It also seemed that some developed countries bore the brunt of the response while others stood on the sidelines. I had lively discussions with my MAE colleagues about this at course block and we thought it might be interesting to flesh out some concepts around policy-making, using the Australian response to the EVD epidemic in West Africa as an example. The questions and answers to this LFF from the MAE class are in Appendix 1.

It was great to have my supervisor, Jeremy McAnulty, participate in the LFF teleconference as well to share some of his knowledge and experience relating to the general development of policy on communicable disease control. Summary points of Jeremy's talk on what should be considered in policy development are in Appendix 2.

I conducted the teaching session for the first year MAE cohort with two other MAE colleagues – Fiona and Zoe. In our placements and projects, we all had experience dealing with the concepts of sensitivity, specificity and predictive value positive/negative relating to case definitions and/or laboratory tests. In particular, I learned a lot about these concepts in my time in Liberia working at an Ebola transit centre. When evaluating the positivity rate of EVD confirmed patients at the transit centre, I was puzzled as to why the positive value predictive (PVP) was so much lower than when I compared it to data from just a few months earlier. I was afraid that I was not doing a good job of triaging patients and I may be admitting individuals to an environment where they are unnecessarily exposed to EVD confirmed patients. However, I realised later that this difference in PVP was due to

the much reduced prevalence of EVD in Liberia when I was there, compared to just a few months ago. It was great to be able to derive this epidemiological concept from first principles and from thinking it through logically.

Previously, I had not fully comprehended the concept of predictive value negative (PVN) or been able to apply it in a meaningful way to a public health problem. However, again with patient-triage, I was able to understand that PVN has important implications when applied to a case definition, especially in the context of Ebola. By understanding these concepts better myself from having used them practically, I could use real-life examples to teach these concepts to my peers.

Zoe, Fiona and I shared the load of teaching to the first years. We agreed that Zoe would introduce the concepts of sensitivity, specificity, predictive value positive and predictive value negative from a theoretical perspective, I would talk about the application of these concepts using my experience in Liberia as an example and Fiona would coordinate an activity which required students to apply these concepts to an exercise. My aspect of the teaching presentation is in Appendix 3.

The lesson plan and activity session with questions and answers are provided in Appendix 4. We added an element of fun to the activity with the use of party hats and red dots. We did not ask the class to do a formal evaluation of our session, but we thought we did relatively well as the students stayed well past the end of the class to finish the exercise and ask questions, and several requested that our PowerPoint presentation be made available on the university web-portal for future reference.

Teaching others is a great way to learn and consolidate concepts yourself. I learned the value of having a lesson plan and being quite specific with learning objectives. I also learned that it is important to keep to time and only teach what is possible in the allotted time slot. When teaching concepts, especially potentially confusing ones, it is very valuable and useful for students to have examples that they can refer to for clarification. I have always enjoyed teaching and will hopefully have the opportunity to continue to do this in future.

Appendices

Appendix 1: Lessons from the field Questions and Answers

Australia's response to Ebola: A lesson in policy making

Learning Objectives

At the end of the session, you should be able to:

- Discuss Australia's response to the Ebola crisis of 2014/15
- Identify aspects of the Australian response that could have been improved and comment on alternative actions
- Identify areas for improvement in Australia's global health intervention framework
- Gain an understanding of the steps to be considered when developing a policy related to health protection

Possible resources to use:

- 1) Centre for Disease Control and Prevention Global Health Strategy framework
- 2) United States Presidential Commission for the study of bioethical issues – Ethics and Ebola
- 3) AusAID humanitarian policy
- 4) Papers on global public goods
- 5) Commonwealth budget for biosecurity and preparedness
- 6) Summary of the WHO response to EVD: <http://www.who.int/csr/disease/ebola/who-activities-report/en/#>
- 7) Summary of the US response to EVD: <https://www.whitehouse.gov/the-press-office/2015/02/11/fact-sheet-progress-our-ebola-response-home-and-abroad>
- 8) Summary of the Canadian response to EVD: <http://www.healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/ebola/response-reponse/index-eng.php>
- 9) Summary of the UK response to EVD: <http://www.parliament.uk/business/committees/committees-a-z/commons-select/public-accounts-committee/news/report-uks-response-to-the-outbreak-of-ebola-virus-disease-in-west-africa/>

Questions:

1. What do you think Australia's role should have been in response to the Ebola virus disease epidemic in West Africa? Did the government meet its requirements as a member of the global health community and in keeping with the World Health Organization's International Health Regulations? Justify your reason using ethics, laws, and principles, as they apply.

Answer from Colleague 1:

I think our role should be:

- to provide timely on the ground assistance to the EVD response in the form resources and personnel
- to ensure Australia is prepared to detect any incoming cases
- to assist with preparedness in the Pacific region
- to assist with research and the development of a vaccine

We provided \$37 million to the global response to Ebola in West Africa and with Aspen Medical managed and ran a 100-bed Ebola treatment facility in Sierra Leone which started in November 2015.

Relevant statements from IHR documents:

- *"International public health security relies on the appropriate and timely management of public health risks, which in turn depend on effective national capacities and international and inter-sectoral collaboration. The IHR comprise a legal instrument specifically designed to support the attainment of this goal"*
- *"Implementing IHR (2005) is an obligation for WHO and States Parties to the Regulations"*
- *"Timely and effective coordinated response to international public health risks and public health emergencies of international concern"*
- *"States have a legal duty under the International Health Regulations to respond promptly to a "public health emergency of international concern."*
- *"the Regulations essentially impose a universal duty on all states to prevent the spread of disease domestically and internationally and to respond to infectious outbreaks"*

Relevant statement from 'Australian Aid: promoting prosperity, reducing poverty, enhancing stability' that

- *'in line with our global responsibilities, Australia will respond promptly and effectively to humanitarian disasters'*

Relevant statement from 'Protection in Humanitarian Action Framework for the Australia Aid Program':

- Our humanitarian action goal is *"to save lives, alleviate suffering and enhance human dignity during and in the aftermath of conflict, natural disasters and other humanitarian crises, as well as to strengthen preparedness for the occurrence of such situations"*

I don't think we contributed enough in terms of on the ground support in the form of personnel and our response was not timely. I am not sure how effective our specific small response was. It would require a proper evaluation.

2. If you felt that Australia's response could have been better, how do you think this could have been achieved? When should this have been done?

Answer from Colleague 2:

As a well-resourced nation Australia should have played a more pro-active role in the West Africa Ebola response. Following the Declaration of the Public Health Emergency of International Concern, our response was focussed entirely on our own internal security. It was not until two other developed nations were affected by Ebola importations, that Australia took notice.

We should have acted earlier, and provided more practical assistance in the form of human resources as this is what was needed and requested. The argument that it was not possible to safely repatriate affected Australians is not satisfactory – it is a global community so we need to mount a global response to global public health threats. This includes, where necessary, negotiating agreements with allies to provide healthcare to Australians responding to international disasters. Such agreements were eventually made but took way too long.

Answer from Colleague 3:

- I think Australia could have played a role in lobbying WHO for an emergency response on the back of information from NGO's in mid-2014.
- I think Australia could have provided money and staff for the global response inside affected countries.
- I think Australia should be looking at ways to fund and support recovery projects.

3. In thinking about the general approaches to outbreak response and control and considering the concept of the global public good, how might Australia's public health practitioners have convinced the government that it might be in Australia's best interests to respond to EVD in West Africa?

Answer from Colleague 2:

Addressing an outbreak at the source, and early, is the most effective way to reduce the risk of importation into Australia. There was a significant delay before Australia provided human resources necessary for contact tracing and other essential control measures. Australia lagged well behind other nations before committing to provide an ETC. This delay contributed to the escalation of the outbreak, a tragic loss of life, devastating impacts on local economies and social structures, and an elevated risk of spread to other countries. The delay in international response (including, and most notably Australia) resulted in a large resource burden in "preparedness" planning in Australia.

Preparing to detect and respond to a possible importation of Ebola Virus disease required a huge amount of resources in my Jurisdiction. The hard work, dedication and leadership shown by the individuals tasked to do this work was commendable and at the time the response commenced, it was necessary. This planning and preparation was consistent with the guidelines provided by WHO when the situation was declared a Public Health Emergency of International Concern:

"States should be prepared to detect, investigate, and manage Ebola cases; this should include assured access to a qualified diagnostic laboratory for EVD and, where appropriate, the capacity to manage travelers originating from known Ebola-infected areas who arrive at international airports or major land crossing points with unexplained febrile illness." (1)

However if Australia (and the world) had played a more active role at the source of the outbreak earlier during the course of the outbreak, the actual risk to Australia (and other states) would have been significantly lower and the huge resources involved with this response could have been avoided.

Answer from Colleague 4:

Responding directly to the Ebola outbreak in West Africa, is the most effective method for protecting Australia from external threats. Border measures and travel restrictions have limited effectiveness and social and economic consequences.

Whilst early recognition and response to outbreaks are important, prevention is better. Multiple commentaries on the Ebola epidemic have highlighted that underlying structural health system weaknesses, political instability, and poverty that contributed to the spread of disease. Indeed, some sources have suggested that the global community bears some responsibility in perpetuating to an environment suitable for the spread of disease.

The second, more pragmatic reason, is self-interest. In an increasingly globalised world, disease can quickly and easily cross national borders. In an interconnected world, it is in Australia's self-interest to respond quickly and efficiently to global outbreaks in order to protect Australia from disease as well as mitigate the inevitable global social and economic consequences as a result of disease epidemics.

Other advantages include, strengthening Australia's public health and emergency response capabilities and improving international relations should Australia be in a position to require assistance in the future.

4. What has Australia learnt from other public health emergencies of international concern and how can these lessons learnt be applied to the current EVD epidemic?

Answer from Colleague 4:

In the aftermath of the H1N1 'swine flu' pandemic, Australia made significant adjustments in approach to its pandemic plan drawing on lessons learned and developments in approach to pandemic response following extensive consultation with states and territories. (1) The plan outlines legal and ethical frameworks, governance and decision-making structures (with whole of government decision-making as well as health sector advisory groups and consultative forums) to guide the selection of public health measures including coordinating the provision of Australia Medical Assistance Teams in response to requests for international assistance. Similar structures and guidelines need to be in place to respond to the wide range of emerging infectious diseases with pandemic potential and will increase the efficiency, timeliness and appropriateness of Australia's response to future outbreaks.

1. <http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-ahmpipi.htm>

Answer from Colleague 2:

Not much!

The 2009 H1N1 pandemic clearly demonstrated that temperature screening at airports is not very effective, and is very resource intensive. Out of 15,457 H1N1 infected passengers detected by airport screening measures in Australia, only 0.5% were detected by thermal scanners (2). But we did it this time anyway, even though the effectiveness was found to be poor (3). The local argument is that political and public pressure insists upon it. But perhaps we should challenge this paradigm, and use evidence to inform our decisions.

5. Should Australia have a global health policy? What should it look like?

Answer from Colleague 1:

Similar to the CDC global health strategy we should:

Contribute to improving the health of people around the world (with a focus on developing countries within our region) by working with countries to provide:

- a. Research into the neglected tropical diseases and be involved with translation of that research to the people who need it
- b. Help strengthen health systems in developing countries. Help build the capacity of other countries to detect, respond, manage public health emergencies
- c. Be prepared and available to activate/deploy our own resources and personnel to respond to an international crisis in a way that is coordinated with other agencies, NGOs
- d. incorporate preparedness exercises to identify the ways in which the response system needs to improve
- e. Resources
- f. Technical expertise
- g. Personnel

Answer from Colleague 2:

Australia needs a Global Health Policy that recognises that national and global health are linked and that Australia cannot protect the health of its citizens in isolation from the rest of the world (4).

The policy should include provisions for:

- A vision to be a global leader in international health preparedness
- Ongoing support for health system strengthening in our region and beyond, including ongoing budgetary support for this outside of the AusAID budget.
- Preparedness to assist in the global response to Public Health Emergencies of International Concern, including provision of supplies and personnel (not just budgetary assistance).
- Clarification of how such personnel should be sourced at short notice. Potentially roles could be filled by individuals on a National Trauma Critical Care and Response Centre/AusMAT database.
- Developing and strengthening partnerships with nations from around the world that include agreements to provide healthcare to Australians who are affected by Global Health Emergencies during the course of responding to such an Emergency
- A clear framework articulating roles for Whole-of-Government when responding to Public Health Emergencies of International Concern, including a central role for Department of Health and Ageing.

Answer from Colleague 3:

- Big question.
- Fundamentally I think it needs to shift from a position of self-interest to a position of global contribution. I think it should reflect a responsibility to participate and support interventions to improve access to quality health care and medicine internationally. It should reflect a responsibility to respond to in global health emergencies.

Answer from Colleague 4:

Australia has the expertise and the capacity to respond to outbreaks however a number of factors have contributed to deficiencies in its response. Australia's actions did not occur in a vacuum – many other countries and international health organisations failed to recognise the magnitude and implications of the epidemic until too late. International responses only really ramped up when the outbreak spread outside of Africa.

The climate of fear surrounding, propagated by some media outlets, led to the development of policies aimed more at addressing public perceptions of risk despite scientific advice recommending otherwise. (1) Some examples include the excessive use home quarantine for returning healthcare workers in several states in the US, and the suspension of the humanitarian visa program by Australia and Canada.

In Australia, the lack of a plan meant that policy makers were developing policy in the midst of the outbreak. We suggest national governance structure and policy to guide the response to epidemics of emerging infectious diseases. The policy should have clear guidelines on groups responsible for the development and then monitoring and evaluation of policy. It should have clear guiding ethical philosophies protecting the rights of citizens in Australia and abroad.

Appendix 2: Considerations for developing policy related to health protection, Dr Jeremy McAnulty – Director of Health Protection, NSW Health

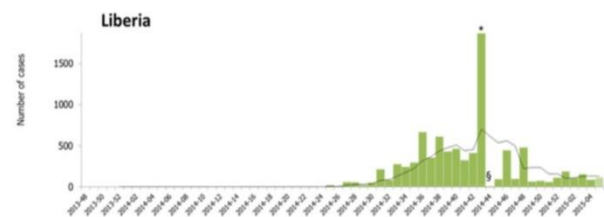
- Analysing the problem, i.e. Who are you protecting? What is the risk to your population?
What are the risk factors?
- What tools are available to protect the population?
- Consultation - depending on the population of interest, and structures, this can involve local public health units, CDNA, AHPPC, AHMC, media, clinicians, labs, etc.
- Writing down protocols and procedures
- Involving the workers in the development of these protocols and procedures
- Communicating and training people up in how to make it work
- How should a program of protection be implemented?
- Evaluation of whether what you did worked
- Sharing intelligence regularly, through regular meetings, both data from surveillance and stories of what works and what doesn't
- Feedback loop

Appendix 3: My teaching presentation

Example 1: Measuring test performance for EVD in Monrovia, Liberia



Epi curve for EVD notifications in Liberia, Dec 2013 – Jan 2015



Source: ECDC epidemiological update 30th Jan 2015

Symptoms of Ebola:



- Fever
- Severe headache
- Muscle pain
- Lethargy
- Anorexia
- Diarrhea
- Vomiting
- Abdominal pain
- Unexplained bleeding or bruising

Transit Centre



Epi curve for EVD notifications in West Africa, Dec 2013 – Jan 2015



Source: ECDC epidemiological update 30th Jan 2015



Triage



LIBERIA VIBRIAL MEMORANDUM FEVER CASE INVESTIGATION FORM

Case ID: LIB-M-101
 Patient Name: FTU-101

Section 1: Patient Information

Patient's Name: _____ Age: _____ Sex: _____
 Gender: ☐ Male ☐ Female Phone Number of Patient's Family Member: _____
 Date of Report of Case of This Case Report: ☐ Date ☐ Date of Death (D.M.Y.) _____
 Requested Residence: _____
 Date of Residence: _____
 Country of Residence: _____

Section 2: Clinical Signs and Symptoms

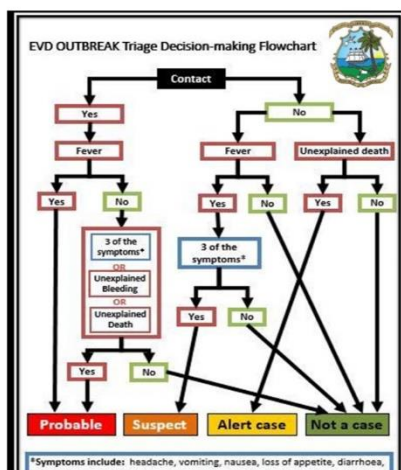
Date of Initial Symptom Onset: _____ (D.M.Y.)

Please tick an answer for ALL symptoms indicating if they occurred during the illness between symptom onset and case detection:

Symptom	Yes	No	Other
Fever	☐	☐	☐
Headache	☐	☐	☐
Vomiting	☐	☐	☐
Diarrhea	☐	☐	☐
Abdominal pain	☐	☐	☐
Joint pain	☐	☐	☐
Dysphagia	☐	☐	☐
Hiccups	☐	☐	☐
Rash	☐	☐	☐
Conjunctivitis	☐	☐	☐
Unexplained bleeding	☐	☐	☐
Unexplained death	☐	☐	☐

Section 3: Hospitalization Information

At the time of this case report, is the patient hospitalized or currently being admitted to the hospital? ☐ Yes ☐ No



Case definitions for EVD

SUSPECT:

Fever AND 3 symptoms from list of 20

Headache, vomiting, anorexia, diarrhea, asthenia, abdominal pain, joint pain, dysphagia, hiccups, dyspnea, rash, conjunctivitis,

PROBABLE:

Fever AND Contact

CONFIRMED:

PCR based lab test for Ebola positive

	Truth (Gold Standard)		
Case definition Test Result	Disease	Non-Disease	Total
Positive	True positive a	False positive b	People who meet case definition People who test positive a + b
Negative	False negative c	True negative d	People who don't meet case definition People who test negative c + d
Total	All true disease	All non-diseased	Total tested

Answer to my question:

The chance that someone I admitted who met the case definition actually had Ebola was 45%

What I wanted to know was:

What was the chance that a person who met the case definition truly had Ebola?

In Aug/Sept in Monrovia

	Truth (Gold Standard – PCR based test)		
Case Definition	Ebola Pos	Ebola Neg	Total triaged
Positive	455	125	600
Negative	? (45)	? (75)	100
Total	500	200	700

PVP → 455/600 → 76% Sensitivity → 455/500 → 91%

NVP → 75/100 → 75% Specificity → 75/200 → 37%

In Nov/Dec in Monrovia:

	Truth (Gold Standard – PCR based test)		
Case Definition	Ebola Pos	Ebola Neg	Total triaged
Positive	21	30	51
Negative	? (2)	? (17)	19
Total	23	47	70

PVP → 21/51 → 41% Sensitivity → 21/23 → 91%

NVP → 17/19 → 89% Specificity → 17/47 → 36%

In August/September, the chance that someone whom my colleague admitted who met the case definition actually had Ebola was 76%

What was going on??

Remember....



PREVALENCE OF EBOLA!!

- Sensitivity & Specificity are characteristics of the case definition/test and stay the same regardless of the underlying prevalence
- PVP & PVN are affected by the prevalence of disease
 - High prevalence - high PVP, low PVN
 - Low prevalence - low PVP, high PVN

Prevalence of Ebola in Nov/Dec in Monrovia:

Case Definition	Truth (Gold Standard – PCR based test)		
	Ebola Pos	Ebola Neg	Total triaged
Positive	21	30	51
Negative	?(2)	?(17)	19
Total	23	47	70

Prevalence → 23/70 → 33%

Prevalence of Ebola in Aug/Sept in Monrovia

Case Definition	Truth (Gold Standard – PCR based test)		
	Ebola Pos	Ebola Neg	Total triaged
Positive	455	125	600
Negative	?(45)	?(75)	100
Total	500	200	700

Prevalence → 500/700 → 71%

Appendix 4: Lesson Plan for teaching session to first year Masters of Philosophy in Applied Epidemiology cohort

Title: Analysing 2 x 2 tables in surveillance systems and diagnostic tests

Time required: 50 minutes

Materials required:

- PowerPoint
- Activity handout
- Red dot stickers and party hats

Learning Objectives:

By end of this session, students will be able to:

- Explain the concepts of sensitivity, specificity, positive predictive value and negative predictive value
- Calculate and interpret sensitivity, specificity, positive predictive value and negative predictive value both for case definitions and for diagnostic tests
- Explain how these concepts differ with varying prevalence of the disease in the population

Instructions:

Session 1 (Zoe): Overview of the concepts of Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value (10 mins)

Students will be shown:

- A PowerPoint presentation explaining each of the concepts
- 2 x 2 tables

Session 2 (Chatu): Explain each of the concepts in the context of a surveillance system using Ebola as an example (10 min)

Students will be shown:

- A PowerPoint presentation explaining the differences between a sensitive and a specific case definition and how PPV and NPV apply to surveillance systems
- Illustrations of how these would be applied in settings of low and high disease prevalence, for an example in West Africa and Australia

Session 3 (Fiona): Explain each of the concepts in the context of diagnostic testing using Ebola as an example (10 mins)

Students will be shown:

- A PowerPoint presentation explaining how different types of diagnostic tests provide different levels of sensitivity, specificity, positive predictive value and negative predictive values
- Illustrations of why knowing these values is important in diagnosis, and why you might choose one test over another in different situations.

Activity (all): Apply the concepts in a simulated exercise using Measles as an example (15 mins)

Students will be given an activity where the class will be given stickers and party hats to indicate the actual prevalence of disease and detection of disease by case definition. We will simulate both high and low prevalence of measles, and students will calculate sensitivity, specificity, PPV and NPV in each of these situations.

Summary (5 mins):

The following will be emphasized:

- The situations in which a sensitive and specific case definition is important in a surveillance system
- The pros and cons of a highly sensitive/specific lab test
- How sensitivity/specificity, PPV and NPV change with varying prevalence of disease

Activity Session – Questions and Answers

Resources required:

1. Activity sheet for each student
2. Answer sheets for teaching team
3. Stickers – to represent measles case definition
4. Party hat – to represent true measles

Activity 1

You are working in a public health unit (PHU) in Canberra. There has been a report of a case of measles who attended your MAE graduation at ANU. Your PHU has been tasked with finding all new cases of measles in an effort to stop transmission. Your supervisor hasn't done the MAE, and insists that the case definition should only include rash as confirmation of a measles case. You decide to see how accurately this case definition identifies cases of measles by doing a mini study of your fellow MAE attendees.

Case definition positive = Anyone in this room with rash today (*red spots*)

Truth positive = Anyone who actually has measles as determined by super accurate lab testing (*party hats*)

1. Count the number of lab confirmed measles cases in the group and the number of cases determined positive by the case definition to complete the two by two table below.

		Truth (super accurate lab test)		Total
		Positive	Negative	
Case definition	Positive	3	2	5
	Negative	1	8	9
Total		4	10	14

- a) What is the prevalence of measles in this group? 28.6%

- b) What is the:
- a. Sensitivity of the case definition? 75%
 - b. Specificity of the case definition? 80%
 - c. Predictive value positive of the case definition? 60%
 - d. Predictive value negative of the case definition? 88.9%

Activity 2

Since measles has been eliminated in Australia and cases are rare, you want to compare our case definition with how it would work in a country where measles is endemic and therefore has a higher prevalence. You are thrilled to learn there is an ongoing outbreak of measles in the Philippines. You are assigned to a GOARN group to go over and help out with diagnosis. You decide to test out how the Australian case definition would work applied in this situation.

		Truth (super accurate lab test)		Total
		Positive	Negative	
Case definition	Positive	6	1	7
	Negative	2	4	6
Total		8	5	13

- a) What is the prevalence of measles in this group? 61.5%
- b) What is the:
- a. Sensitivity of the case definition? 75%
 - b. Specificity of the case definition? 80%
 - c. Predictive value positive of the case definition? 85.7%
 - d. Predictive value negative of the case definition? 66.7%
- c) How does performance of the case definition differ in this different setting? In what ways is it the same? Explain why it differs?

