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Prevention and control of sexually transmissible infections and other infectious diseases across multiple settings

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Authorship declaration

This thesis is composed of the authors' original work. For projects that were undertaken collaboratively with multiple stakeholders, the author has clearly stated the contribution made by each of the stakeholders in the respective chapter. The author certifies that this work contains no material which has been accepted for the award of any other degree or diploma, in any university or other tertiary institution and, to the best of my knowledge, contains no material previously published or written by another person, except where due reference has been made in the text.

Jana Sisnowski

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Abstract

This thesis summarises the results of five discrete projects completed from February 2017 to November 2018 to meet the requirements of the Master of Philosophy in Applied Epidemiology (MAE), the Australian Field Epidemiology Program. The majority of the work presented here was completed at the Kirby Institute for infection and immunity at the University of New South Wales, with two additional projects carried out at the Communicable Disease Control Branch, South Australia Department for Health and Wellbeing (SA Health).

Chapter 1 provides an introduction to the primary field placement at the Kirby Institute and an overview of activities undertaken over the course of the MAE program.

Chapter 2 presents an epidemiological research project investigating gaps in the adolescent vaccination program for human papillomavirus (HPV), a sexually transmissible infection (STI), with a view to informing interventions to improve coverage. The study examined school-level correlates of low initiation and completion of the vaccination course in several school-based programs in three jurisdictions, using a dataset built from several data sources, including the Australian Bureau of Statistics, the Australian Curriculum, Assessment and Reporting Authority, and the National HPV Program Register. Univariable and multivariable logistic regression analyses were conducted to determine characteristics of schools and school populations associated with low vaccination initiation and completion.

Chapter 3 has a methodological focus, describing the development of geographical maps at the small area level for the Kirby Institute's *2017 Annual Surveillance Report of HIV, viral hepatitis and sexually transmissible infections*. This project involved an iterative process to define the most appropriate methodological approach to show differences in age-standardised notification rates that could be applied in future reports. The chapter documents the investigation of the effects of administrative areas of different size, different classification methods of notification rates, and several

suppression methods using maps developed for HIV and chlamydia as two diseases with contrasting epidemiology.

Chapter 4 presents a full evaluation of the operations of the South Australian surveillance system for *Neisseria gonorrhoeae* antimicrobial resistance since 2016, using the United States Centers for Disease Control and Prevention (CDC) guidelines for the assessment of disease surveillance systems. Also within the CDC framework, chapter 5 describes work undertaken to support the introduction of HIV subtype and drug resistance surveillance at the national level.

Finally, chapter 6 outlines a descriptive case series investigation of a *Salmonella* Typhimurium phage type 44 cluster in South Australia which did not identify a common source of infection, but contributed evidence that *Salmonella* Typhimurium is an important cause of foodborne illness in the community.

Collectively, the majority of projects within this thesis contribute to strengthening STI surveillance in Australia, and the identification of factors associated with low uptake of HPV vaccination has the potential to guide future research and public health programming to improve prevention.

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Abbreviations and acronyms

ABS	Australian Bureau of Statistics
ACARA	Australian Curriculum, Assessment and Reporting Authority
AIHW	Australian Institute of Health and Welfare
AMR	Antimicrobial resistance
ANU	Australian National University
ASHM	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
BBV	Blood-borne virus
CDC	United States Centers for Disease Control and Prevention
CDCB	Communicable Disease Control Branch, SA Health
CDNA	Communicable Diseases Network Australia
DSIS	Disease Surveillance and Investigation Section, Communicable Disease Control Branch, SA Health
ERP	Estimated Resident Population – yearly ABS estimate of population numbers by various geographical units
FSS	Food Standards Surveillance, SA Health
GIS	Geospatial information system
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
MAE	Master of Philosophy in Applied Epidemiology
MIC	Minimum inhibitory concentration
MLVA	Multiple Locus Variable Number of Tandem Repeats Analysis
MSM	Men-who-have-sex-with-men
NAT	Nucleic acid testing
NHPVR	National HPV Program Register
NIDS	Notifiable Infectious Disease Surveillance database (SA Health)
NNDSS	National Notifiable Diseases Surveillance System
NSW	New South Wales
PCR	Polymerase chain reaction (NAT)
PrEP	Pre-exposure prophylaxis (HIV)
SA	South Australia
SA Health	South Australia Department for Health and Wellbeing

SDRM	Surveillance drug resistance mutation (HIV)
STI	Sexually transmissible infection
TAS	Tasmania
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNSW	University of New South Wales
WA	Western Australia
WHO	World Health Organization

1. Introduction

This thesis documents a series of projects undertaken between February 2017 and November 2018 as part of the Australian Field Epidemiology Training Program, the Master of Philosophy in Applied Epidemiology (MAE) program. The majority of projects were carried out at the primary MAE field placement, the Kirby Institute for infection and immunity in society (Kirby Institute) at the University of New South Wales (UNSW), Sydney. The placement was situated across the Surveillance, Evaluation and Research Program headed by Professor Rebecca Guy and the Public Health Interventions Research Group led by Professor John Kaldor. The outbreak investigation component and part of the surveillance evaluation requirement were completed externally at the Communicable Disease Control Branch, South Australia Department for Health and Wellbeing (SA Health).

The Kirby Institute is named after Michael Kirby, a former Justice of the High Court of Australia with a long-standing commitment to health and human rights. (1) The institute was founded in 1986 as the NHMRC Special Unit in AIDS Epidemiology and Clinical Research and became the National Centre in HIV Epidemiology and Clinical Research in 1990. (1,2) The latest name change in 2011 reflects the shift from a narrow initial research focus on HIV/AIDS to a broader focus on diseases and health system issues affecting marginalised populations in Australia and in the region. In addition to its research activities, the Kirby Institute also fulfils an operational public health role, primarily through the coordination of national HIV surveillance (2) and annual reporting on the epidemiology of HIV and other blood-borne viruses (BBV) and sexually-transmissible infections (STIs).

I completed three projects during my MAE placement at the Kirby Institute and carried out two additional projects at SA Health. The following two sections outline how these workplace-based projects (section 1.1) and a number of course-related activities outside the workplace (section 1.2) collectively meet the MAE requirements. In addition, I contributed to a number of additional workplace-based projects which are not included in the thesis, but are summarised briefly in section 1.3.

1.1. Fulfilment of project-based MAE requirements

Chapters 2-6 each describe a major project conducted to collectively meet the core workplace-based MAE requirements. Each chapter is preceded by a short overview of the respective work in the context of the MAE program requirements, detailing contributions by myself, workplace supervisors, and other collaborators; describing lessons learned; and highlighting the public health implications of the work undertaken.

- Chapter 2 presents an epidemiological research project which is part of a large National Health and Medical Research Council-funded grant known as the HPV Partnership project. This component of the HPV Partnership project investigated school-level correlates of low initiation and completion of the HPV vaccination course in the school-based programs in New South Wales, Tasmania, and Western Australia, meeting the MAE core requirement to design and conduct an epidemiological study. In addition, this work also included a substantial data analysis component.
- Chapter 3 documents the development of geographical maps for the Kirby Institute's *2017 Annual Surveillance Report of HIV, viral Hepatitis and sexually transmissible infections* based on an analysis of notification data at the small area level. The project meets the MAE core requirement to analyse a public health dataset.
- Chapters 4 and 5 consist of two projects related to STI surveillance. Chapter 4 presents an evaluation of the operations of the South Australian surveillance system for *Neisseria gonorrhoeae* antimicrobial resistance, while chapter 5 describes work undertaken to support the introduction of HIV subtype and resistance surveillance at the national level. In combination, these two projects meet the MAE core requirement to establish or evaluate a surveillance system or other health information system.
- Chapter 6 summarises a descriptive case series investigation of a *Salmonella* Typhimurium phage type 44 cluster in South Australia. This project meets the MAE core requirement to investigate an acute public health problem.

In addition, the following MAE requirements were met through activities related to the five core MAE projects:

- An advanced draft of an article for a peer-reviewed publication, entitled “School-level characteristics associated with low adolescent HPV vaccination initiation and completion coverage in the school immunisation programs of three Australian states”, makes up the body of chapter 2 which presents the MAE epidemiological project component.
- A communication to a lay audience is provided as an appendix to chapter 5. This Frequently Asked Questions (FAQ) document was drafted in response to community concerns regarding the collection and public reporting of HIV subtype and drug resistance data and is also available online on the Kirby Institute website. (3)
- A critical review of the scientific literature is included in each of the four project-based chapters 2-6.
- A presentation given at the National Immunisation Conference in Adelaide in June 2018, entitled “The state of school-based HPV vaccination in three states: where are the gaps?”, is included as an appendix to chapter 2. This presentation summarises early findings from the HPV Partnership project.

1.2. Fulfilment of non-project based MAE requirements

Activities undertaken as part of the peer-to-peer teaching and learning requirements of the MAE program are documented in chapter 7. These include the preparation of a lesson from the field focused on the use of causal diagrams in epidemiological research and the development of a teaching module the MAE 2018 cohort on logic models for public health program evaluation. In addition, I had the opportunity to give a presentation on spatial mapping of health information as part of the “Issues in Applied Epidemiology” course held during the third MAE 2017 courseblock in March 2018.

1.3. Additional activities

Over the course of the MAE program, I was involved in a number of workplace activities in addition to the projects designed to meet the core requirements. At the Kirby Institute, this included an analysis of gonorrhoea treatment and testing patterns in general practice using data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood Borne Viruses and Sexually Transmitted Infections (ACCESS), led by Dr Denton Callander. Also at

the Kirby Institute, I contributed to the initial protocol for a case-control study investigating a rise in notifications of heterosexually acquired gonorrhoea in metropolitan Perth, led by Professor Rebecca Guy.

At SA Health, I had the opportunity to participate in the Disease Surveillance and Investigation Section's (DSIS) routine surveillance and disease investigation activities. The DSIS is managed by Emma Denehy and comprises of public health officers, public health nurses, and two OzFoodNet epidemiologists who receive medical notifications, perform surveillance activities, and undertake public health follow-up. I was involved in the following activities:

- Receiving medical notifications for notifiable diseases.
- Providing information to the public about notifiable diseases.
- Presenting epidemiological summaries at weekly surveillance review meetings.
- Contributing to surveillance data quality assurance activities.
- Responding to internal and external data requests.
- Participating in public health follow-up for a range of notifiable diseases.
- Leading the data management and data analysis aspects of a case-control study investigating an outbreak of *Salmonella* Oranienburg in South Australia in September-October 2018.

1.4. Public health significance

The public health implications of the five major projects are discussed in more detail in the preface and discussion of each chapter. Collectively, the work undertaken over the course of the MAE program may contribute to improving aspects of public health in the long term. The most immediate public health outcomes result from the work undertaken in an operational public heath setting, including the *Salmonella* cluster investigation as a major MAE project and additional work contributing to public health follow-up for notifiable diseases in South Australia. The project to develop geographical maps of notifications for the 2017 Annual Surveillance Report provides a methodology that can be adapted for use in future reports. The two surveillance-related projects have the

potential to strengthen STI surveillance in Australia by contributing to the introduction and improvement of data collection to monitor drug resistance and enable public health action where required. The results of the data analysis undertaken as part of the HPV Partnership project will guide future research and may help design and target interventions to increase HPV vaccination uptake in schools across the three participating jurisdictions.

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Thesis access restrictions are in place for chapters 2-4 due to public health confidentiality considerations.

5. Description of the first stage of the introduction of national surveillance for HIV subtype and transmitted drug resistance

Preface

This chapter describes additional work carried out under the MAE core competency 'Evaluation or establishment of a surveillance system'. In 2017-18, the introduction of national surveillance for HIV subtype and transmitted drug resistance (i.e. drug resistance present at the time a person first starts treatment) was progressed by the Kirby Institute in collaboration with jurisdictions, but at the time of writing had not yet reached the implementation stage. As a result, this is an abridged chapter summarising the work undertaken to date (August 2018) towards the establishment of the system. The proposed new system will eventually allow for HIV subtype and transmitted drug resistance information from all Australian jurisdictions to be systematically recorded in the National HIV Registry and reported in the *Annual Surveillance Reports of HIV, viral hepatitis and sexually transmissible infections in Australia* (hereafter referred to as the Annual Surveillance Reports).

Student role

This project was overseen by Professor Rebecca Guy as the head of the Surveillance Evaluation and Research Program at the Kirby Institute. Dr Muhammad Jamil and Dr Skye McGregor were responsible for project management in their roles as National HIV Surveillance Officers and Dr Angie Pinto provided clinical advice in her role as HIV infectious disease physician and researcher in the Immunovirology and Pathogenesis Program, also at the Kirby Institute. Advice on ethical aspects of HIV subtype and drug resistance surveillance was provided by Dr Bridget Haire, a research fellow in the Kirby Institute's Public Health Interventions Research Group, in her role as president of the Australian Federation of AIDS Organisations. My role encompassed the following components:

- Development of a practical guide for jurisdictional surveillance officers and laboratories outlining the data required, how to enter and record these data, and how to report them centrally to the Kirby Institute for national reporting.
- Participation in consultation meetings with jurisdictions.

- Development of a Frequently Asked Questions (FAQ) document aimed at community organisations to explain the need for HIV subtype and transmitted drug resistance surveillance and address possible concerns regarding the use of these data (provided in appendix 8.3).
- Descriptive analysis of retrospective subtype and resistance data from South Australia and New South Wales for the 2017 Annual Surveillance Report, and more detailed analysis of the same data to inform future data presentation once national data are available.
- Assessment of the proposed design of the HIV subtype and drug resistance surveillance system components against the United States Centers for Disease Control and Prevention surveillance system attributes. (1)

Lessons learned

Central to the lessons learned from this project is the sensitive nature of collecting and reporting HIV surveillance data. Community organisations representing people affected by HIV were concerned about the risk of this type of information being subpoenaed and used as evidence in criminal proceedings regarding alleged transmission events. They were also mindful that subtype information could highlight further that a proportion of HIV diagnoses each year occurs among people who have migrated to Australia, in a climate where there are critical political views on immigration. From an implementation point of view, the importance of close consultation with key jurisdictional stakeholders was highlighted in a political system where states and territories are the primary holders of operational public health powers. Finally, implementing substantial new surveillance arrangements takes time and requires extensive consultation as jurisdictions need to carefully consider the implications for their workload.

Public health impact

The public health implications of introducing national surveillance that captures internationally agreed HIV drug resistance mutations are evident at different levels. At the global level, collecting this information allows Australia to meet the expectations placed on developed country WHO member states. At the national level, consistent, centrally collated data and timely dissemination of information on the prevalence of transmitted drug resistance provides an indication of whether standard current first-line regimens and current pre-exposure prophylaxis formulations (PrEP) remain suitable or may need to be revised at a

future time. Finally, evidence of changes in subtype distribution may help identify shifts in key populations that require enhanced public health and policy responses at the national and jurisdictional levels.

Abstract

Background: In Australia, there has been no ongoing national surveillance of HIV subtype and transmitted drug resistance. Transmitted HIV drug resistance has important implications for the long-term viability of current first-line HIV treatment recommendations and new biomedical prevention approaches such as pre-exposure prophylaxis. Similarly, changes in the distribution of subtypes may be indicative of epidemiological shifts. Therefore, the Communicable Diseases Network Australia National Blood Borne Virus and Sexually Transmissible Infections Surveillance Subcommittee decided to progress the introduction of national surveillance of subtype and transmitted drug resistance.

Process: The surveillance approach chosen was a system that integrates subtype and drug resistance data into national HIV case reporting, coupled with the development of subtype and resistance-specific arrangements where necessary to accommodate reporting and data management processes specific to molecular laboratory data. An initial proposal outlining processes and data specifications was developed by the Kirby Institute and discussed with jurisdictional surveillance officers. Jurisdictions were asked to consult internally and with their respective laboratories about the general feasibility of the proposal and define the implementation steps to be taken at the jurisdictional level; this process was still ongoing at the time of writing. Using subtype and resistance surveillance data from two states and information obtained from key stakeholders through the consultation process, an assessment of key attributes of the proposed system and its anticipated overall usefulness was undertaken based on the United States Centers for Disease Control and Prevention guidelines for the assessment of disease surveillance systems.

Conclusion: The proposed introduction of routine surveillance of subtype and transmitted drug resistance represents an important and timely response to rapid changes in the biomedical approach to HIV treatment and prevention in Australia. The integration of laboratory data with epidemiological information from national case reporting enables monitoring of the distribution of subtype and transmitted drug resistance over time and in key populations. The introduction of subtype and drug resistance surveillance also improves the ability of the overall national HIV surveillance system to meet its purpose of monitoring the characteristics of new diagnoses of HIV and assessing the impact of prevention and treatment

programs. As all jurisdictions have indicated a willingness to participate, and subtype determination and resistance testing are already routinely performed in all Australian HIV reference laboratories, it is anticipated that surveillance data for subtype and resistance-related information will be representative of all new HIV diagnoses across jurisdictions and populations, and that data completeness and quality will be high once all jurisdictions have implemented locally appropriate structures. Specific aspects of data collection and data management at the jurisdictional level may require further consultation prior to implementation. In the long term, two of the main challenges are expected to relate to continued system flexibility and the acceptability of molecular surveillance to different groups of stakeholders.

1. Introduction

1.1. Epidemiology and public health importance of HIV in Australia

Human immunodeficiency virus (HIV) is a retrovirus that is transmissible person-to-person through unprotected sexual intercourse, sharing of contaminated injecting drug and other skin-piercing equipment, and vertically between mother and child. (2) During the acute phase, with onset within a few weeks of infection, HIV infection may present as a flu-like self-limited illness. Although HIV antibodies are generally detectable within one month from infection, the incubation period until the development of symptoms of Acquired Immunodeficiency Syndrome (AIDS) can last up to 15 years and longer. (2) In the absence of treatment, an estimated 90% of HIV-positive people eventually develop AIDS, characterised by progressive, usually fatal immune system dysfunction and associated opportunistic infections and malignancies. (2)

Disease progression can be measured by the decline in CD4+ cells. (2) A CD4+ cell count above 500 cells/μL is expected in most people without HIV, and late HIV diagnosis is defined as a CD4+ cell count of less than 350 cells/μL. (3) In countries with reliable, publicly subsidised access to combination antiretroviral therapy (ART), HIV has largely become a manageable chronic disease. (2, 4, 5) Nevertheless, the infection remains associated with potentially serious co-morbidities due to persistent inflammation and immune dysfunction despite viral suppression, as well as the side effects of life-long antiretroviral treatment. (5-7) Recent biomedical interventions for HIV such as Treatment as Prevention and pre-exposure prophylaxis (PrEP), described in more detail in section 1.2, have been shown to be effective in preventing HIV transmission (8-11), but also expose a larger number of individuals to ART for longer periods of time.

Australian national surveillance data show that the number of new HIV infections has been stable at just over 1,000 notifications per year since 2012. (3) In 2016, the latest year for which national data was publicly available at the time of writing, there were 1,013 notifications of newly diagnosed HIV infection in Australia, or 4.2 notifications per 100,000 population. (3) The age-specific notification rate ranged from 9.2 notifications per 100,000 population in the 20 to 29 year old age group to less than one notification per 100,000 population in the age groups 0 to 14 and 15 to 19 years. (3) HIV in Australia remains highly concentrated among

key populations, predominantly men-who-have-sex-with-men (MSM). Of all new diagnoses notified in 2016, 70% were attributed to male-to-male sexual contact. (3) The role of male-to-male sex as the predominant risk exposure is also reflected in the notification rate in males being 11 times as high as in females in 2016. (3) Recent increases in notification rates in Australia have been seen among MSM born in Southeast Asia and Northeast Asia. (3) These changes in the epidemiology of HIV are concerning and may relate to changing risk behaviours, lower health literacy, health care engagement, and potentially increased migration from these countries. (12) Increases have also been observed in the HIV notification rate among the Indigenous population, for whom the notification rate was 2.2 times as high as in the Australian born non-Indigenous population in 2016. (3) The public health importance of HIV is also highlighted by the estimated 26,444 people currently living with HIV in Australia. Further, an estimated 11% of these HIV positive individuals are unaware of their infection (3) and are at risk of adverse health outcomes and may unknowingly transmit the virus.

1.2. Policy implications of recent advances in HIV treatment and prevention

HIV treatment and prevention have evolved rapidly in recent years. In 2012, the World Health Organization (WHO) endorsed the scientific consensus that an undetectable viral load, or viral suppression, achieved through consistent combination antiretroviral treatment (ART) reduces the risk of onward transmission of HIV to near zero. (13) As a result, the approach of ‘treatment as prevention’ has become established. (13) At the same time, in response to evidence of early treatment leading to improved clinical outcomes, progressively earlier initiation of ART has been enshrined in guidelines. Since 2016, WHO has recommended immediate treatment initiation regardless of CD4 count, also known as the ‘treat all’ strategy. (14) Australia uses the US Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents with a commentary by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). (15) These guidelines have recommended immediate initiation of antiretroviral treatment regardless of CD4 cell count since 2015.

The most recent WHO guidelines also recognise PrEP globally as a component of HIV prevention. (14) ASHM has recommended PrEP for individuals at high risk of HIV infection since 2015 (16), including for MSM, transgender men and women, heterosexual men and women, and people who inject drugs meeting population-specific definitions of high risk. (17) PrEP formulations, including the tenofovir/emtricitabine combination Truvada which is currently the only drug approved by the Australian Therapeutic Goods Administration for HIV PrEP, contain some of the same antiretroviral agents that are routinely used in first line treatment regimens. Originally made available in 2016/2017 through state-funded PrEP demonstration trials in all jurisdictions except the Northern Territory, Truvada was listed on the Pharmaceutical Benefit Schedule (PBS) effective 1 April 2018. At the time of the PBS listing, over 14,000 people were accessing PrEP through the demonstration trials. (18)

In parallel with these changes in treatment recommendations and the introduction of new biomedical prevention options, global policy goals and implementation targets have evolved. In 2014, UNAIDS published their global 90-90-90 targets which set three indicators along the care continuum from diagnosis to viral load suppression: by 2020, 90% of all people living with HIV should be diagnosed, 90% of those diagnosed as HIV positive should be receiving ART, and 90% of those on ART should achieve viral suppression. (19) Meeting these targets would translate into at least 73% of the HIV positive population being virally suppressed. By 2030, the targets are 95-95-95, which, if met, would see at least 86% of people living with HIV achieve an undetectable viral load. The two targets combined underpin the policy goal of ending the AIDS epidemic by 2030, which UNAIDS define as a reduction of the annual number of new HIV infections by 90% and a reduction of AIDS-related mortality by 80% by 2030. (19) Sweden was the first country to achieve all three 90-90-90 targets. (20) Meanwhile, modelling to the end of 2016 suggests that Australia has surpassed the 2020 target for the clinical indicator of viral suppression, but remains slightly below the 90% targets for diagnosis and ART coverage, translating into 72% undetectable viral load coverage. (3) At the policy level, Australia has made the virtual elimination of HIV transmission by 2020 the central goal of the Seventh National HIV Strategy 2014-2017 (21), with similar goals set at the jurisdictional level. (22-24) While ‘virtual elimination’ is not clearly defined in the National HIV Strategy, an Australian target

similar to the one proposed by UNAIDS would require a sustained decline in annual notifications of newly acquired infections.

1.3. Rationale for surveillance of HIV subtype and transmitted HIV drug resistance in Australia

Laboratory testing to determine HIV subtype and the presence of drug resistance mutations is routinely performed by reference laboratories across Australia. Both subtype and drug resistant mutations are determined by sequencing one or more portions of the viral genome, generally the protease and reverse transcriptase regions of the *pol* gene. (25) These gene regions code for enzymes that are targeted by three major antiretroviral drug classes, Nucleoside Reverse Transcriptase Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors. In Australia, genotypic HIV drug resistance testing is recommended for all treatment-naïve persons at diagnosis to inform the selection of the initial antiretroviral treatment regimen. The surveillance of characteristics derived from genotyping is known as molecular surveillance. The extent to which these data are linked to epidemiological data, including temporal, clinical, demographic, behavioural, or geographic information (26), depends on the degree of integration with case-based HIV surveillance systems. In Australia, this is the National HIV Registry which does not currently require reporting of subtype and HIV drug resistance data.

HIV is characterised by substantial genetic variability which is reflected in a complex classification system based on similarities in key regions of the HIV genome. The HIV-1 virus type is comprised of our broad groups, M, N, O, and P. The major group M is responsible for almost all HIV infections globally and is further broken down into nine subtypes, also known as clades, which are denoted by one of the letters A, B, C, D, F, G, H, J, or K. In addition, there are several recognised circulating recombinant forms (CRFs), viruses that combine genetic material from several subtypes. (27) Certain subtypes have been associated with particular geographical areas: in Australia, North America, and Western Europe, subtype B was historically the main subtype across all risk groups and remains predominant. By contrast, subtype C, which accounts for a majority of infections worldwide, is associated with southern Africa and India, subtype A with parts of

central and eastern Africa and the former Soviet Union, CRF01-AE with Southeast Asia, and CRF02-AG with West Africa. (28)

In combination with demographic data, public health surveillance of subtype distribution can give an indication of transmission patterns and the impact of treatment and prevention programs on HIV infections in different populations. (29) There is also evidence of clinical and diagnostic differences between HIV subtypes, with studies suggesting that disease progression (30, 31), response to antiretroviral treatment and development of resistance mutations (32-34), and the accuracy of viral load tests (35) may vary between different subtypes. As a consequence, substantial shifts in the distribution of subtypes in Australia may have implications for HIV management and the direction of future research related to testing, treatment, and prevention for different subtypes.

HIV drug resistance due to mutations in the gene regions targeted by antiretroviral drugs generally arises while individuals are on antiretroviral treatment. This is acquired drug resistance, which is distinguished from transmitted drug resistance. Transmitted drug resistance is the focus of public health surveillance and refers to drug resistance that is present prior to the start of treatment and likely to have been transmitted from a person with acquired resistance at the time of infection. (36) Transmitted drug resistance increases the risk of subsequent treatment failure (37-39) and may require the use of more expensive antiretroviral agents with greater toxicity, particularly in resource-limited settings. (40) Increases in transmitted drug resistance can also compromise the effectiveness of new biomedical interventions such as PreP, for which only the tenofovir/emtricitabine combination has current regulatory approval internationally and in Australia. At the time of writing, reports of PreP failure in adherent patients suspected to have acquired a virus with transmitted resistance to PrEP components have been reported from Canada (41) and the United States. (42, 43) In addition, one case of HIV infection without any drug-resistant mutations in a PrEP-adherent patient was reported from the Netherlands (44). At the population level, changes in the prevalence of transmitted drug resistance can help assess HIV treatment and prevention efforts and can inform treatment guidelines or strategies to improve retention in care for HIV-positive individuals at risk of acquiring and transmitting drug resistant mutations. (45)

WHO therefore recommends that all member states integrate drug resistance assessment into routine surveillance activities and disseminate these data through nationally and internationally. (46) To ensure comparability of HIV drug resistance data internationally, WHO has endorsed (47) a list of standard surveillance drug resistance mutations (SDRMs) which are:

- Associated with transmitted drug resistance; nonpolymorphic (i.e. not mutations that occur naturally in a certain percentage of the population without drug pressure);
- Applicable to B and non-B subtypes;
- Relevant to clinicians and epidemiologists.

The list was revised in 2009 and comprises 93 Nucleoside Reverse Transcriptase Inhibitor (NRTI), Non-Nucleoside Reverse Transcriptase (NNRTI), and Protease Inhibitor (PI) resistance mutations. (48) Online tools such as the Stanford HIV Drug Resistance Database (49) match user-submitted nucleotide sequences to SDRMs. In 2017, WHO released guidelines on public health responses to pre-treatment HIV drug resistance, including for the first time a recommendation that countries adjust their first-line regimens once they exceed a threshold of 10% pre-treatment[1] resistance to Non-Nucleoside Reverse Transcriptase inhibitors. (50)

1.4. International and previous Australian approaches to surveillance of HIV subtype and transmitted drug resistance

Internationally, molecular surveillance based on gene sequences generated for drug resistance testing takes different forms and the level of detail collected from laboratories varies. Options include:

- Repeat cross-sectional surveys,
- Sentinel surveillance,
- Routine collection and reporting of laboratory data only,
- Full integration of laboratory data and routine surveillance data.

[1]WHO defines pre-treatment drug resistance differently from transmitted drug resistance: individuals reinitiating first-line ART and individuals having had previous exposure to first-line ART through preventive treatment such as PrEP or PMTCT are included in the definition of pre-treatment drug resistance in addition to those who are treatment-naïve.

To monitor transmitted drug resistance in low resource settings, WHO recommends regular surveys which would provide aggregated estimates of drug resistance prevalence by drug class. By contrast, many high resource-settings appear to have implemented a mix of case-based surveillance integrated into existing HIV surveillance systems and large-scale research projects with varying degrees of either linkage to epidemiological data or project-specific data collection.

In the United States since 2001, just under half of states have received funding from the US Centers for Disease Control to collect HIV sequence information under different drug resistance surveillance programs and report these data to the US National HIV Surveillance System. (3) The system was estimated to capture 72% of new HIV diagnoses in 2013-2017. (3) As a result of the integration of sequencing data with epidemiological information, the CDC have been able to determine and characterise transmission networks using national surveillance data. (3) Some of the US states reporting molecular data have permanently integrated the collection of nucleotide sequence data into their regular surveillance systems. (51)

Switzerland is an example of a country that collects sequence data separately from the national surveillance system as part of a research study: an ongoing cohort study, covering approximately 70% of persons living with HIV according to the national HIV surveillance system, collects the viral genotype and detailed demographic and behavioural data. (52, 53) In the UK an ongoing study collects nucleotide sequences from all laboratories performing resistance tests (54) and 83% of sequences are successfully linked to patient data from at least one cohort study and the national HIV/AIDS Reporting System. (55) Research projects rather than permanent routine surveillance have also recently been carried out in several European Union countries (56-59), some associated with the European Union SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) program which collected sequences and demographic and clinical information from a sub-set of newly diagnosed HIV infections in all European Union countries for over a decade. (60, 61) A survey of European countries about HIV drug resistance surveillance in the region following the end of European Union funding for the SPREAD program showed that almost two thirds of responding countries collected sequence data for national molecular surveillance, including for subtype

and drug resistance surveillance and phylogenetic analyses of transmission clusters. (61) Of these, just over half reported full integration of sequence or sequence-derived data with epidemiological data at the case level and 85% reported recording full sequence data. A larger percentage of countries indicated use of lists of clinically relevant mutations than use of the WHO SDRM list. (61)

In Australia, South Australia is the only jurisdiction to routinely integrate molecular data into case-based notifiable disease surveillance. Subtype and transmitted drug resistance data have been reported in the South Australian annual surveillance reports since at least 2011. (62) A research study drawing on several years of surveillance data was able to show that compared to subtype B infections, non-B infections in the state were more likely to be acquired overseas, attributed to heterosexual transmissions, and in non-Australian born persons. (63) Research studies in Western Australia (64) and Victoria (65) have also assessed trends in subtype distribution and collected limited demographic data. Resistance data have previously been published by laboratories in New South Wales and Victoria (66-68) In New South Wales, a more comprehensive analysis of transmitted drug resistance patterns was undertaken through data linkage of notification and laboratory data. (69) At the national level, reporting of both subtype and transmitted drug resistance data has been very limited in scope and frequency. The Kirby Institute's 2014 Annual Surveillance Report reported the percentage of non-B subtypes and drug resistance prevalence in approximately 100 newly acquired HIV infections per year sequenced over several years at the New South Wales State Reference Laboratory for HIV/AIDS and the Victorian Infectious Diseases Reference Laboratory. (70) The Australian Molecular Epidemiology Network-HIV (AMEN-HIV), a collaboration of HIV reference laboratories, has previously provided a snapshot of subtype diversity in Australia overall and by jurisdiction. (25) AMEN-HIV has also collated laboratory data on drug resistance nationally, but no reporting is currently available in the public domain.

The international examples highlight that a large number of high resource countries engage in some form of national surveillance of molecular HIV data. In Australia, despite the absence of ongoing national surveillance, a number of stakeholders have examined the prevalence of different subtypes and transmitted drug resistance and changes over time, although not continuously and not in a

nationally representative manner. In response to global standards and changes in treatment and prevention strategies, the Communicable Diseases Network Australia National Blood Borne Virus and Sexually Transmissible Infections Surveillance Subcommittee endorsed an assessment of the feasibility of national surveillance, in order to routinely collected and report subtype and transmitted drug resistance data as part of national HIV case reporting.

2. National HIV surveillance

AIDS was made a nationally notifiable disease in Australia in 1982. Since 1989, new diagnoses of HIV have also been notifiable in all Australian states and territories, with retrospective collection of cases from the early 1980s. (71, 72) From 2013 onwards, cases of newly diagnosed AIDS were no longer recorded separately and from October 2016, only newly diagnosed HIV remained notifiable. (73) The Kirby Institute at the University of New South Wales coordinates national surveillance of HIV through the National HIV Register. The National HIV Register is completely separate from the National Notifiable Diseases Surveillance System that was introduced in 1990 and coordinates national surveillance for most other nationally notifiable diseases. The purpose of the national HIV surveillance system is described as follows:

> "To monitor the extent and characteristics of new diagnoses of HIV in order to inform governments and communities about (a) trends in HIV transmission (b) behavioural, geographic and demographic factors associated with HIV transmission (c) the numbers and demographic characteristics of people living with HIV (d) the morbidity and mortality due to HIV infection (e) the impact of public health and clinical interventions on the occurrence of HIV." (73)

The operation of the national HIV surveillance system is described in the Kirby Institute's Standard Operating Procedures for National HIV/AIDS Case Reporting. (73) Cases are reported to the Kirby Institute by all Australian jurisdictions, which mandate the reporting of new HIV infections by doctors and laboratories under individual public health legislation. Notifications provided to the Kirby Institute must meet the national surveillance case definitions, agreed by Communicable Diseases Network Australia (CDNA). The current case definitions

have remained unchanged since 2004[2] and differentiate between the three mutually exclusive categories of newly acquired HIV infection, unspecified HIV infection, and HIV infection in individuals less than 18 months of age. (74-76) CDNA requires both confirmed and probable cases to be notified to jurisdictional health departments, and both are sent to the Kirby Institute. However, the determination of subtype and detection of resistance mutations requires the detection and sequencing of viral DNA or RNA, which means that cases would normally meet the confirmed case definitions shown in Table 1 below. The categorisation of a case as newly acquired HIV infection requires evidence of the infection having occurred within the previous 12 months. (74-76) For surveillance purposes, newly acquired infections can serve as a measure of changes in the epidemiology of HIV in the context of current prevention and treatment approaches.

Table 1: National confirmed case definitions for HIV

HIV category	**Confirmed case definition**
Newly acquired	Requires laboratory definitive evidence. <u>Laboratory definitive evidence:</u> 1. Repeatedly reactive result on a screening test for HIV antibody followed by a positive result on a western blot AND laboratory evidence of a negative or indeterminate HIV antibody result in the 12 months prior to blood sample collection OR 2. A group IV indeterminate western blot AND detection of HIV by at least one of the following virologic assays (nucleic acid testing for proviral DNA; HIV p24 antigen, with neutralisation; virus isolation). A group IV indeterminate western blot is defined by the presence of a glycoprotein band (gp41, gp120 or gp160) and one or two other HIV specific bands.
Unspecified	Requires laboratory definitive evidence only AND that the case does not meet any of the criteria for a newly acquired case. <u>Laboratory definitive evidence:</u>

[2]At the time of writing, revised HIV case definitions were under consideration.

HIV category	Confirmed case definition
	1. Repeatedly reactive result on a screening test for HIV antibody followed by a positive result on a western blot. A positive result on a western blot is defined by the presence of a glycoprotein band (gp41, gp120 or gp160) and at least three other HIV-specific bands OR 2. Detection of HIV by at least two virologic assays (nucleic acid testing for proviral DNA; HIV p24 antigen, with neutralisation; virus isolation) performed on at least two separate blood samples.
Child aged less than 18 months at the time of blood sample collection	Requires laboratory definitive evidence. <u>Laboratory definitive evidence:</u> Detection of HIV by at least two virologic assays (nucleic acid testing for proviral DNA; HIV p24 antigen, with neutralisation; virus isolation) on at least two separate blood samples (excluding cord blood).

The reporting of HIV cases to jurisdictional health departments requires a range of sociodemographic, clinical, and laboratory data. HIV remains the only nationally notifiable disease in Australia for which name codes derived from the first two letters of the last name and the first two letters of the first name are used. For each notification of newly diagnosed HIV received by the jurisdictions, data variables listed in the surveillance protocol (73) are then forwarded to the Kirby Institute for inclusion in the National HIV Register. Data transfer to the Kirby Institute is primarily done using password protected Excel files sent via e-mail on a quarterly basis. One large jurisdiction has set up a secure online portal to transfer its data and one jurisdiction with very low case numbers sends completed notification forms directly to the Kirby Institute for data entry. For jurisdictions reporting quarterly, the Standard Operation Procedures state an expected turnaround time of four weeks from the end of each quarter. (73) The introduction of an electronic interface to simplify the transfer of data from the jurisdictions to the Kirby Institute was under development at the time of writing.

Prior to entry into the National HIV Registry, Kirby Institute staff review each notification to determine possible duplicates where a case had been previously notified by another jurisdiction. In addition, cases are identified that do not meet the criteria for inclusion in the register based on a person's duration of stay in Australia prior to diagnosis and intention to remain in the notifying Australian jurisdiction. (73) Prior to 2014, national reporting of new diagnoses of HIV in Australia included cases with a known previous overseas diagnosis. Reporting now focuses on cases first diagnosed in Australia, but also describes separately the number of cases with a known previous overseas diagnosis.

The analysis of HIV notification data and dissemination of results follow an annual reporting cycle. At the national level, surveillance data are reported in the *Annual Surveillance Report on HIV, viral hepatitis and sexually transmissible infections in Australia*, the *Annual Surveillance Report on bloodborne viral and sexually transmissible infections in Aboriginal and Torres Strait Islander people*, and the *National Blood-borne Virus and Sexually Transmissible Infections Surveillance and Monitoring Report*. HIV Register data are also made available publicly as de-identified, reduced datasets that are updated annually. Requests for access to more detailed data, primarily for research purposes, require approval by the Kirby Institute and CDNA. (73)

3. Aims and objectives of national surveillance of HIV subtype and transmitted drug resistance

A working group consisting of members of the CDNA National Blood Borne Virus and Sexually Transmissible Infections Surveillance Subcommittee developed draft objectives for national surveillance of HIV subtype and transmitted drug resistance. These objectives were then sent to the full committee for review and input. As a result of this process, the aims of national surveillance of HIV subtype and drug resistance have been defined as the systematic identification, recording, and monitoring of subtype and transmitted HIV drug resistance for all new diagnoses of HIV infection notified in Australia. Specific objectives are to:

a) Provide an understanding of subtype distribution among new notifications of HIV infection and monitor changes in the distribution of subtypes over time.

b) Provide an understanding of the epidemiology of drug resistance among new notifications of HIV infection, monitor trends, and detect prevalence levels of transmitted drug resistance that require public health intervention.

c) Inform the development and assessment of public health and clinical interventions in the context of treatment as prevention and increasing uptake of PrEP.

These specific aims and objectives for surveillance of subtype and drug resistance coexist with the overarching aims of national HIV surveillance, broadening the current focus on behavioural, geographic and demographic factors associated with HIV infection (73) to include viral characteristics at the time of diagnosis.

4. Methods

The United States Centers for Disease Control and Prevention (US CDC) guidelines for the assessment of disease surveillance systems (1), described in more detail in chapter 4 of this thesis, were used to describe and assess the attributes of the proposed surveillance system components. Considerations for the implementation phase were put forward where appropriate.

The assessment of the system attributes was based on information collected during stakeholder consultations with two to three representatives from each jurisdiction, usually a surveillance officer and an epidemiologist. These consultations were informal and the key purpose was to explain the rationale and benefit of the proposed system and steps required for implementation. Additional information was gathered from South Australia (SA) as the only jurisdiction that routinely collected transmitted drug resistance information.

In addition, a descriptive analysis of subtype and transmitted drug resistance data from SA and New South Wales (NSW) was performed. The data were provided by the Communicable Disease Control Branch at SA Health and the NSW Prevention Partnership project, a research partnership including NSW Health, for the purpose of the 2017 Annual Surveillance Report and are used here with permission. Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) and STATA IC v14.2 (StataCorp, College Station, Texas) were used for all data analyses. Ethics approval was provided by the Australian National University's Human Research Ethics Committee (protocol #2017/698).

5. Outline of the proposed surveillance system components

As outlined in section 1.4, there are several options to collect molecular HIV information. The proposal developed by the Kirby Institute in collaboration with jurisdictions is based on full integration of subtype and drug resistance data into existing national case-reporting. This integrated approach has two main advantages over a stand-alone system for surveillance of molecular data. First, it allows subtype and resistance data to be combined with epidemiological information at the individual level to monitor trends by key characteristics such as HIV risk exposure or likely place of acquisition. It also ensures that the date of first diagnosis is known to determine that resistance testing was done close to the time of diagnosis, in order to reflect transmitted drug resistance rather than acquired drug resistance. Second, recording of information derived from genotyping in the National HIV Registry ensures that subtype designation and resistance mutations are captured in a standardised form, while the full genotype remains with the laboratories.

Despite the proposed integration of subtype and resistance surveillance into the national HIV surveillance system, the new system components require the development of separate procedures for data collection and transfer at the jurisdictional level and changes to current data management systems and reporting templates at both jurisdictional and national levels. The implementation process will involve laboratories, jurisdictional surveillance officers and staff in charge of data entry and maintenance of jurisdictional HIV notification databases, and staff at the National HIV Registry. Any changes to national surveillance procedures must be agreed by the CDNA National Blood Borne Virus and Sexually Transmissible Infections Surveillance Subcommittee and documented in the national HIV Surveillance Standard Operating Procedures. (73) The requirements for changes to jurisdictional HIV surveillance systems vary according to the respective legal framework and current rules and procedures in place in each state and territory. Figure 1 below provides an overview of the proposed workflow of subtype and resistance surveillance.

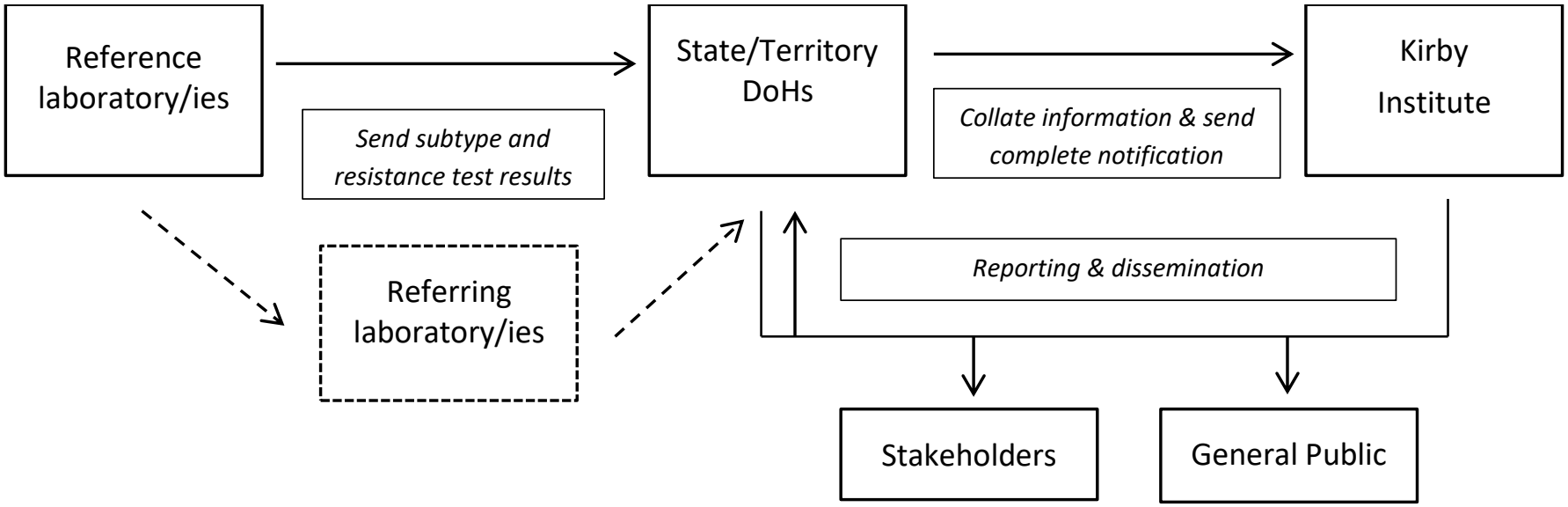

Figure 1: Proposed workflow of Australian national HIV subtype and transmitted drug resistance surveillance, 2017

Under the current proposal, reference laboratories would routinely send subtype and resistance information to jurisdictional departments of health. Australian reference laboratories use tools associated with the Stanford University HIV Drug Resistance Database to match nucleotide sequences isolated from patient specimens to known drug resistance mutations. Based on feedback from South Australia, where routine surveillance for resistance has already been implemented, it appears that the HIVdb Program (77), the service's Genotypic Resistance Interpretation Algorithm, is used by the South Australian HIV reference laboratory SA Pathology. The HIVdb Program is based on an expert list of mutations that are known to confer resistance to 22 antiretroviral drugs currently approved in the US for treatment of HIV, including three integrase strand transfer inhibitors. (78) In Australia, testing for integrase resistance mutations is currently performed only when specifically requested and not considered part of the standard of care. (15)

South Australia has been receiving laboratory results that are provided to the ordering doctor with the primary goal of informing the initial antiretroviral regimen. These results report major mutations alongside a clinical interpretation, but do not list SDRMs. While there is overlap between the two lists, not all SDRMs are also major mutations.[3] As SDRMs are provided with a different output option within the same program, it will be necessary to determine in collaboration with laboratories and jurisdictional surveillance officers whether SDRM output can be provided routinely to jurisdictional health departments.

In South Australia, SA Pathology sends results via an automated process with complete patient demographic information, including full first and last name. A similar process would enable all jurisdictional health departments to match the additional laboratory information to existing HIV notifications. State and territory health departments would then send the notification with to the Kirby Institute for inclusion in the National HIV Registry in line with the standard operating procedures described above, including the use of name codes instead of full names. It is proposed that subtype and resistance information are integrated into the reporting of notifications which is currently being done on a quarterly basis for

[3]SDRMs are determined based on their inclusion in up to five expert lists of drug resistance mutations, which include the HIVdb Program list and also four additional lists.

most jurisdictions. The dissemination of subtype and resistance data is expected to be part of the Kirby Institute's Annual Surveillance Report. In addition, individual states and territories may opt to include subtype and resistance data for their jurisdictions in a format of their choice in their respective surveillance reports.

Additional data fields will be required in both jurisdictional databases and the National HIV Registry to record subtype and resistance information. As jurisdictions use different data management systems and receive different notification volumes, individual jurisdictions may choose to record these data in any format they see fit as long as reporting is nationally consistent. The following information needs to be recorded at the jurisdictional level:

a) Date of collection of specimen used for resistance testing, or if not available the date of the resistance test. This information is required to determine if the resistance test was conducted within 12 months of the date of diagnosis.
b) Fields to record mutations by drug class or nucleotide sequence based on the Stanford HIVdb Program output.
c) Field to record subtype

The data specifications in Table 2 below provide an example of how data may be recorded at both jurisdictional level and in the National HIV Registry. The data fields for subtype information shown below are already included in the National HIV Registry. The laboratory number and specimen collection date are not required for national reporting and would therefore not be provided to the Kirby Institute for entry into the National HIV Registry.

Table 2: Proposed dataset specifications for HIV subtype and transmitted resistance information, 2017

Data field	Data entry	Description
Laboratory number	Sequence of alphanumeric characters	Laboratory number allocated to the specimen used for resistance testing.
Date of specimen collection	DD/MM/YYYY	Date when specimen used for resistance testing was collected.

Data field	Data entry	Description
Subtype	1 = Subtype A 2 = Subtype B 3 = Subtype C 4 = Subtype D 5 = Subtype F 6 = Subtype G 7 = Subtype H 8 = Subtype J 9 = Subtype K 10 = CRF01 AE 11 = CRF02 AG 12 = CRF03 AB 13 = Other CRF 14 = Other recombinations 0 = Not reported	Reports subtype of HIV.
SDRMs by sequence		
Protease (PR) SDRMs present	0 = Not reported 1 = yes 2 = no	Indication whether any Protease SDRM was reported in the Stanford HIVdb Program output.
Protease (PR) SDRMs	Sequence(s) of alphanumeric characters	Protease SDMRs as reported in the Stanford HIVdb Program output. Multiple mutations may be present.
Reverse Transcriptase (RT) SDRMs present	0 = Not reported 1 = yes 2 = no	Indication whether any Reverse Transcriptase SDRM was reported in the Stanford HIVdb Program output.
Reverse Transcriptase (RT) SDRMs	Sequence(s) of alphanumeric characters	Reverse Transcriptase SDMRs as reported in the Stanford HIVdb

Data field	Data entry	Description
		Program output. Multiple mutations may be present.
Integrase (IN) mutations present *(optional)*	0 = Not reported 1 = yes 2 = no	Indication whether any Integrase mutation was reported in the Stanford HIVdb Program output.
Integrase (IN) mutations *(optional)*	Sequence of alphanumeric characters	Integrase mutations as reported in the Stanford HIVdb Program output. Multiple mutations may be present.

The suggested dataset specifications are intended to minimise the additional workload required of laboratories and jurisdictional health departments to provide these data. As the Stanford HIV Drug Resistance Database's HIVdb Program reports Protease and Reverse Transcriptase SDRMs in its HTML and Excel results for the sequence input option, it is currently suggested that the data fields mirror this output. However, to differentiate further between drug classes, the Reverse Transcriptase mutations need to be assigned to resistance against Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI). The proposal under consideration by the jurisdictions at the time of writing suggests that the Kirby Institute will routinely match the reported SDRMs to the relevant drug class according to the most recent WHO-endorsed list. However, depending on state and territories' planned use of resistance data, it may be more practical for this step to occur at the jurisdictional level, with the Kirby Institute receiving mutations by drug class rather than gene region. Final dataset specifications at both levels would need to reflect this decision. An additional consideration with regard to the way resistance data are recorded is the WHO recommendation to revise the SDRM list to include Integrase resistance mutations of public health importance. (50) Major Integrase mutations are already reported in the Stanford HIVdb Program output and it is suggested that these will be recorded where available.

A template for national reporting of subtype and resistance data was trialled in the 2017 Annual Surveillance Report using 2015 subtype and resistance data from New South Wales and South Australia. (3) These data had been integrated with jurisdictional HIV notification databases through routine case-based surveillance in South Australia and through a data linkage project in New South Wales. In these two states in 2015, 11% of new HIV diagnoses which had undergone drug resistance testing had any surveillance drug resistance mutation, with the percentage slightly higher for MSM compared to all notifications (Table 3). For non-nucleoside reverse transcriptase inhibitors, prevalence was 4% in the two states. This is below the WHO threshold of 10%.

Table 3: Proportion of new HIV diagnoses with surveillance drug resistance mutations (SDRMs) by drug class, NSW and SA, 2015, overall and in the male-to-male exposure category, as presented in the 2017 Annual Surveillance Report

HIV exposure category	Individuals tested (n)	SDRMs by drug class n (%)			
		Protease inhibitors	Nucleoside Reverse Transcriptase inhibitors	Non-nucleoside Reverse Transcriptase inhibitors	Any SDRM
Male-to-male sex	179	5 (2.8%)	12 (6.7%)	6 (3.4%)	21 (11.7 %)
Total	235	5 (2.1%)	13 (5.5%)	9 (3.8%)	25 (10.5 %)

Also in 2015, new diagnoses in these two states showed distinct subtype distributions based on reported risk exposure. Among males with male-to-male sex as their exposure, just over two thirds of new HIV diagnoses were characterised as subtype B, whereas almost 80% of heterosexually acquired

infections were non-B subtypes. For both MSM and individuals with heterosexual exposure risk, subtype B prevalence varied by place of birth but the difference was most pronounced in MSM. A higher proportion of new HIV diagnoses in Australian-born MSM (85%) were characterised as subtype B compared to 45% among non-Australian-born MSM. By contrast, among people who reported heterosexual sex as their exposure risk, 27% of diagnoses in Australian-born people were characterised as subtype B, compared to 19% in non-Australian-born people. (3)

Individual states and territories may also choose to report on subtype and transmitted drug resistance for their jurisdiction in a format of their choice. Future Annual Surveillance Reports will include data from all states and territories and therefore draw on a larger number of notifications. As a result, further breakdowns such as additional exposure categories, additional subtypes, or place of acquisition may be reported. All data will be presented in tabular, aggregated form and any combination of categories that contain a small number of individuals will be presented as part of a larger grouping. The balance between the need for detailed public health information and concern among affected communities about stigma and legal or immigration implications is further discussed in section 6.4 as part of an assessment of the likely acceptability of the system to different groups of stakeholders.

6. Attributes of the proposed surveillance system components

6.1. Simplicity

Compared to stand-alone systems for molecular surveillance, the proposed approach benefits from the integration into existing national case reporting. Although introducing entirely new system components with specific requirements for data collection, transfer, and management, subtype and resistance surveillance will be consistent with existing case definitions. As subtype and drug resistance surveillance can apply only to cases that have already met one of the CDNA confirmed surveillance case definitions for HIV, no separate case definition is required other than restricting resistance results to the first test within 12 months of diagnosis.

The new surveillance components will be implemented within an established framework for data transfer from jurisdictions to the Kirby Institute and analysis

and reporting at the national level. Despite the existing surveillance infrastructure, the introduction of subtype and resistance surveillance adds to the complexity of the national HIV surveillance system, particularly at the jurisdictional level. Simplicity in different jurisdictions will depend on the degree to which laboratories are able to automatically extract and notify SDRM information to their health departments. As noted previously, HIV subtype and drug resistance are not available at the same time as the HIV diagnosis, so additional data transfer from laboratories is necessary. It is not yet clear yet if laboratories are generally reporting major/other mutations along with the clinical interpretation rather than SDRMs which are listed in a different output option of the same program. Depending on the additional workload associated with reporting SDRMs, it may be worth considering changes to the suggested dataset specifications to enhance simplicity at the data collection level, with only minor loss of information. Similarly, some laboratories report subtype for all three gene regions that are routinely sequenced. Therefore, the dataset specifications may need to be amended to either allow recording of subtype by gene region or to specify which subtype to record to ensure consistent reporting (e.g. only the protease subtype, and possible substitutes where protease was not sequenced).

Another determinant of simplicity is the ability of jurisdictional databases to accommodate subtype and resistance information in a standardised format (as opposed to requiring separate data management solutions associated with more complexity and higher workloads). An assessment of the number of stakeholders involved in data generation, transfer, and collation in each jurisdiction will also be an important consideration in the roll-out of the system. For instance, New South Wales requires coordination with three laboratories currently performing resistance testing. Tasmania receives reference laboratory data from interstate through the local public health laboratory. The simplicity of the process, including data transfer from laboratories, recording in jurisdictional databases, and transfer to the Kirby Institute, may change over time as several jurisdictions were in the process of replacing or updating their surveillance systems at the time of writing and other jurisdictions were exploring the introduction of a Commonwealth-led national interoperable communicable disease surveillance and outbreak management system. The introduction of an electronic interface for data transfer to the Kirby Institute is expected to increase the overall simplicity of the HIV

surveillance system, but may not impact on complexities experienced by certain jurisdictions in relation to obtaining and managing subtype and resistance data.

Once data have been collated, the calculation of prevalence of resistance and subtype categories for national reporting should be simple. The feasibility of reporting resistance and subtype data was demonstrated in the 2017 Annual Surveillance report and options for more detailed reporting in the future are related to considerations around acceptability (section 6.4).

Box 1: Key considerations for simplicity

1. The feasibility of reporting SDRMs rather than major mutations should be clarified with reference laboratories and current dataset specifications be reviewed, if necessary.
2. Integration of subtype and resistance information into existing HIV databases and standardisation of data fields to minimise data entry errors (e.g. look-up of SDRMs) would facilitate simplicity and enhance the utility of the data at jurisdictional health departments.

6.2. Flexibility

System flexibility cannot be assessed at the design stage as the ability to accommodate revised data requirements will most likely become evident only after an initial period of operation. This will include the addition of Integrase mutations to the WHO-endorsed list of SDRMs and potentially the identification of additional mutations related to new and established antiretroviral agents which would require additional data fields in national and jurisdictional databases and a revised reporting template at the national level. Where tests are not done at the same time (integrase resistance testing is currently a separate test), the addition of new mutations of public health importance to the surveillance system may require additional notifications by laboratories.

Additional flexibility may be required, particularly with regard to data analysis and reporting, to add information that enhances the public health relevance of the data presented. For instance, consultations for the 2017 Annual Surveillance Report indicated that stakeholders were interested in the prevalence of mutations known to confer resistance to emtricitabine and tenofovir specifically given the

rapid increase in PrEP uptake. As a result, the antiretroviral agent may need to be reported routinely in addition to the drug class for selected mutations. The flexibility of the overall HIV surveillance system to accommodate the introduction of resistance and subtype is likely to vary substantially between jurisdictions. Aspects such as systems in place for data transfer and current and future data management capabilities are discussed in more detail under other attributes.

Box 2: Key considerations for flexibility

1. Data management changes to implement the new surveillance components should be made in such a way that future changes, particularly of the SDRM list, can be accommodated.
2. Reporting templates, mainly for the Annual Surveillance Report and for jurisdictional reports where applicable, should to remain receptive to stakeholder preferences.

6.3. Data quality

Similar to system flexibility, data quality is difficult to assess at the design stage before any routine data can be reviewed. The following points mainly relate to ensuring that data quality aspects are considered in the implementation phase. Data quality is related to acceptability and simplicity of the system, and can refer both to the completeness of data fields and the quality of the data provided, i.e. accuracy and validity. Data quality will depend on the extent to which the final dataset specifications reflect current laboratory practice and the complexity systematically recording these data in jurisdictional surveillance databases. It is expected that data quality will vary across jurisdictions during the early implementation phase.

The completeness of data fields related to subtype and drug resistance would be the primary indicator of data quality at the national level. Indicators of completeness could include the following: the number and percentage of all notifications with (a) subtype information; (b) any resistance information; (c) complete resistance information (i.e. data for all drug classes) and (d) complete resistance information and additional Integrase resistance information. If reporting of specific mutations is considered to be of public health importance, the number and percentage of notifications with resistance information by drug

class that also report one or more exact mutations should be captured. Data quality standards for HIV surveillance variables have been put forward by the US CDC, ranging from 50% completeness for CD4+ counts to 85% completeness for risk factor ascertainment. (79) Given that resistance testing prior to treatment initiation is part of the standard of care and the cost for genotypic resistance testing is fully met under the Medicare Benefits Schedule (80), a higher level of expected completeness should apply to both subtype and resistance variables.

While the national data can be interrogated for nonsensical results, the responsibility for and assessment of data accuracy is perhaps better done at the jurisdictional level as part of internal quality control checks. Jurisdictional surveillance officers will have access to the original laboratory reports and can draw on established working relationships with their respective reference laboratories to query results. With the planned introduction of an electronic interface for data transfer to the Kirby Institute, there will be functionalities to flag potential errors prior to transfer. For subtype and drug resistance information, this could include type errors (i.e. integer or string data) or validity errors (e.g. mutations not on the SDRM list or another consensus list of mutations to be reported).

Box 3: Key considerations for data quality

1. At the national level, routinely assess and communicate data completeness for each jurisdiction.
2. At the jurisdictional level, establish routine quality assurance checks to assess data completeness and data quality, and liaise with laboratories and HIV clinicians where expected standards are not met.

6.4. Acceptability

There are two key groups of external and internal stakeholders whose acceptance of the surveillance system is crucial to its operation and to maintaining the principles underpinning the wider HIV response. The first group are laboratories and jurisdictional health departments who are required to actively participate in surveillance activities. The acceptability of the system to this group will be evidenced by each jurisdiction's willingness to participate and the quality

of the data contributed by the individual jurisdiction. At the time of writing, all jurisdictions had expressed a willingness to work towards the implementation of national surveillance.

The second group are affected communities and their peak organisations. HIV remains an infection with a high potential of stigmatisation of communities and individuals in social, workplace, and healthcare settings, and concerns related to sexual identity and immigration are particularly important to the most at-risk-populations. (12, 81, 82) Consultations with peak organisations indicated that while they were comfortable with resistance surveillance, there were some reservations regarding the systematic collection of subtype information. The legal stigma associated with HIV infection and HIV transmission was of particular concern to these stakeholders, specifically the potential for surveillance data to be subpoenaed in legal procedures involving alleged transmission events. (12, 83, 84) These concerns centred on a perception that rare subtypes might be used as evidence of transmission between two persons. In response, the Kirby Institute developed a plain language Frequently Asked Questions document, included in appendix 8.3, to explain that subtype as a very crude measure of genetic relatedness is unsuitable to determine the occurrence of transmission events. Primarily in recognition of community concerns, the proposed surveillance components do not suggest that jurisdictions obtain and store full nucleotide sequences that are generated as part of subtype determination and resistance testing. Unlike subtype, sequence data are suitable for phylogenetic analyses that have previously been used in Australian criminal trials to provide evidence in support of a transmission event. (84) Each Annual Surveillance Report is reviewed by an advisory committee prior to publication. The committee includes peak organisations representing communities affected by HIV and other bloodborne viruses (73) and the consultation process is designed to ensure that affected communities are comfortable with the presentation and framing of epidemiological data, including subtype and drug resistance information.

While community concerns were related primarily to the recording in public health databases of data derived from genotyping, statistical disclosure of the identity of individuals or communities in public reporting is a concern for both affected communities and public health authorities. (85) Even though drug resistance and subtype are biological makers of a virus rather than sociodemographic

characteristics of a person, unintended individual disclosure is possible if aggregated small numbers are reported publicly. In addition, further breakdowns of these variables by epidemiological characteristics such as risk exposure, region of birth, or place of acquisition add to the risk of statistical disclosure. Small numbers also raise statistical issues with regard to interpretability, especially where percentages are presented and small absolute year-on-year-changes may give the impression of large relative changes.

HIV infection is a rare event, with just over 1,000 notifications annually, and infection with a virus that has resistance to any drug class is even rarer. Table 4, provided in the confidential appendix to this chapter (appendix 8.3), demonstrates that count data from only two states is unsuitable for public reporting when further broken down by drug class and HIV exposure risk, with several of the cross-tabulated cells containing less than three contributors. The reporting approach in the 2016 Annual Surveillance Report (see section 5) reflects one possible solution to small numbers, i.e. the restructuring of tables by combining or omitting variable categories, in this case by reporting counts only for the largest category of male-to-male sex and overall. Suppressing counts with small numbers in accordance with common threshold values such as any cells with less than three, five, or ten contributors (85) is another possible approach, particularly where row counts vary considerably between combinations of subcategories and the information is considered to have epidemiological utility.

The prevalence of subtypes by likely place of HIV acquisition in South Australia and New South Wales, shown in Table 5 in the confidential appendix, is an example of where information about the most frequently observed non-B subtypes and circulating recombinants forms and their geographical associations has public health value. However, counts may not be appropriate to disclose for all combinations of subcategories. In the future, reporting from all states and territories will increase the population under surveillance. This is expected to enable more detailed descriptions of resistance and subtype distributions in public reporting, thereby adding to the epidemiological utility of public reporting

while remaining mindful of identity disclosure and statistical validity concerns associated with small numbers.

Box 4: Key considerations for acceptability

1. At both national and jurisdictional levels, continue ongoing engagement with peak organisations and other community stakeholder to ensure acceptability of molecular surveillance.
2. With regard to national reporting, consider specifying rules to prevent statistical identity disclosure and concerns regarding statistical validity in the Standard Operating Procedures for National HIV/AIDS Case Reporting.

6.5. Sensitivity

Sensitivity is an attribute that is difficult to assess as there is no gold standard providing alternative, 'true' estimates of subtype distribution and resistance. Subtype determination and resistance testing will only be done for diagnosed HIV infections, so sensitivity will be subject to the same limitations as national case reporting overall due to incomplete and differential uptake of HIV testing. The current Australian HIV diagnosis and care cascade estimates that 11% of people living with HIV in Australia were undiagnosed in 2016. (2) In addition to undiagnosed cases with resistance, a percentage of notifications with missing resistance information may also have resistance mutations. For notifications with complete information, the sensitivity of current genotypic assays to detect resistance mutations in treatment-naïve individuals would need to be determined in collaboration with laboratories, depending on whether commercially available tests with published sensitivity and specificity are used or individual in-house assays. These considerations relate to the availability of specimens from all HIV cases for genotyping testing and the ability of genotypic testing to identify and report pre-specified mutations. A different conceptualisation of system sensitivity with regard to resistance might include the extent to which the SDRM list captures the most important mutations causing resistance that is relevant in the Australian context.

The ability of the system to detect outbreaks or thresholds that trigger public health action is a second consideration in the context of surveillance system sensitivity. (1) To detect clustering of SDRMs or unusual subtypes in a manner that is sufficiently timely and specific to enable targeted public health intervention, data would need to be analysed at regular intervals at a small geographical level and using fine demographic categories. The individual jurisdictions are the primary holders of operational public health powers, with the legal authority to collect surveillance data and the human resources to conduct regular epidemiological reviews and engage in public health follow-up. As a result, the responsibility and ability to detect rapid, potentially geographically limited changes in resistance and/or subtype patterns appears to be located primarily at the jurisdictional level. The Kirby Institute may have a role in detecting and monitoring multi-jurisdictional outbreaks. This view is reflected in the current national surveillance standard operating procedures which emphasise trends in infections and risk factor patterns, and the impact of public health and clinical interventions which necessarily require a longer term assessment period. (73) Individual jurisdictions may also be interested in the collection of full nucleotide sequences from laboratories to conduct molecular genotype surveillance similar to selected public health authorities overseas. The collection of sequencing data is not part of national surveillance, and states and territories with an interest in enhanced molecular surveillance would need to balance public health utility with community concerns about this topic.

The ability of the system, at the jurisdictional or at the national level, to identify resistance prevalence of concern would require the definition of critical thresholds for all drug classes, adapted to the Australian context. The current WHO threshold of 10% pre-treatment non-nucleoside reverse transcriptase inhibitor resistance is one such threshold that may be considered in the analysis and reporting of resistance information. However, Australia and other resource rich countries recommend the use of two nucleoside reverse transcriptase inhibitors in combination with an integrase strand transfer inhibitor for most people newly diagnosed with HIV. (15) As a result, the WHO threshold is of relatively low relevance to current treatment patterns and any resistance patterns that might prompt a review of empirical treatment guidelines. In addition, the planned introduction of a PrEP exposure at the time of diagnosis variable to national HIV surveillance will enable monitoring of the annual number of notifications having

acquired HIV while on PrEP and comparisons of resistance mutations occurring in notifications with and without PrEP exposure.

Box 5: Key considerations for sensitivity

1. Among all stakeholders, clarify to what extent the national HIV surveillance system is expected to play a role in outbreak detection, and what kind of analyses should be undertaken to monitor changes in particular populations or in the prevalence of particular mutations (e.g. mutations relevant to PrEP).
2. In the long term, establish resistance prevalence thresholds for public health action that are relevant to the Australian context.

6.6. Positive predictive value

Positive predictive value in relation to drug resistance could be considered the proportion of cases recorded as having SDRMs in the surveillance system that actually have transmitted drug resistance. Positive predictive value is most relevant to the assessment of systems where the health event under surveillance requires confirmation and surveillance case definitions have potentially low specificity. (1) As subtype and drug resistance mutations are reported only for confirmed cases of HIV, positive predictive value is not a suitable indicator for the assessment of these surveillance components at this point in time. Similar to sensitivity considerations, positive predictive value might become an important measure of usefulness in the future. This would be the case if there was evidence to suggest that the mutations on the SDRM list are a poor predictor of actual phenotypic resistance to the most frequently used antiretroviral agents in Australia, and surveillance of SDRMs therefore had limited public health and clinical relevance.

6.7. Representativeness

If all jurisdictions agree to participate in system (also see section 6.1), resistance and subtype data can be expected to be representative of the notifying jurisdictions. However, there may be initial differences in completeness between states and territories. Differences in completeness could be assessed by

calculating the percentage of notifications with subtype information and complete and partially complete resistance information (see indicators in section 6.3) in each jurisdiction by quarter to assess time trends. If a lack of genotypic resistance test orders by HIV clinicians does appear to contribute to missing data in one or more jurisdictions, the health departments in these jurisdictions may need to communicate to their providers that drug resistance testing at diagnosis is part of the standard of care.

6.8. Timeliness

There are several potential indicators of timeliness, some of which are relevant primarily in the context of possible expectations that subtype and resistance data enable outbreak or cluster detection (see section 6.5) at the jurisdictional level. For these states and territories, the time from specimen collection date to the date of notification to the jurisdiction is important and is expected to depend on arrangements worked out between laboratories and jurisdictional health departments. For national surveillance data, indicators of timeliness are largely determined by agreed procedures such as the quarterly reporting of notifications to the Kirby Institute, and a fixed recurring data dissemination cycle with the Annual Report.

Box 6: Key consideration for timeliness

At the national level, monitor jurisdictions' ability to report subtype and resistance data within four weeks from the end of each quarter and seek feedback on barriers where reporting is consistently delayed and/or differs from the patterns observed for other data fields.

6.9. Stability

System stability may be assessed from an operational and a political perspective. In regards to the latter, the degree of stability could depend on whether laboratory reporting to health departments is considered a legal obligation or is otherwise part of a formal agreement between reference laboratory and health department. In regards to operational stability, the processes put in place at the jurisdictional level to receive, record, and transfer laboratory data are likely to vary during the

first stage of implementation and may continue to evolve over the lifetime of the system. Genotypic testing for HIV antiretroviral resistance is included on the Medicare Benefits Schedule (80), therefore laboratory data for analysis and reporting is expected to be available indefinitely as long as data collection from laboratories remains operational. Appropriate resourcing to guarantee the continued operation of the surveillance system at the level of health departments and the Kirby Institute are presumed given the continued public health relevance of HIV in Australia and national and international standard and target setting. In combination, these two factors indicate a high degree of sustainability of both the system overall and the additional enhanced surveillance components.

7. Discussion and conclusion

This chapter has outlined proposed procedures, data specifications, and reporting options for national surveillance of HIV subtype and transmitted drug resistance. Routine surveillance would provide nationally representative prevalence estimates of subtype and transmitted drug resistance that were previously available only periodically from research studies and selected Australian jurisdictions. With regard to transmitted drug resistance in particular, the availability of these data will enable Australia to meet international standards for HIV surveillance. The integration of subtype and resistance data with national case reporting will enable better monitoring of the impact of treatment and prevention programs. Therefore, the proposed surveillance components are expected to meet several of the criteria put forward by the CDC to gauge the overall usefulness of public health surveillance (1):

a) Surveillance of transmitted drug resistance meets the criterion of detecting adverse health events.
b) Surveillance of subtype and transmitted drug resistance, in combination with sociodemographic variables that are already routinely collected, contribute to the identification of factors associated with HIV morbidity.
c) Both surveillance components have the potential to detect changes in disease patterns, through changes in the prevalence of transmitted resistance or the distribution of subtype, overall and within sub-populations.
d) Trends in resistance in particular can be used as an indicator of the effectiveness of treatment scale up and retention in care, alongside established indicators such as the HIV diagnosis and care cascade. (3)

Changes in subtype distribution in combination with other epidemiological data may indicate gaps in prevention and control programs.

e) In the long term, these surveillance data may lead to changes in policy and practice, for instance by providing evidence for changes in treatment guidelines or focus on prevention and control programs in sub-populations experiencing increases in disease burden. Biomedical, clinical, and operational research may also be stimulated and informed by findings from Australian and international surveillance data. This includes potential differences in resistance patterns between sub-populations with different demographic or biological markers or a rise in the prevalence of mutations conferring resistance to current PrEP formulations.

The overall level of usefulness of a surveillance system is also determined by its performance with regard to each of the nine attributes discussed above. The suggested considerations and recommendations serve to inform the implementation stage. It is anticipated that surveillance data will be representative of new HIV diagnoses across jurisdictions, as all jurisdictions had indicated their willingness to participate at the time of writing. However, with eight jurisdictional health departments collecting subtype and resistance data from different reference laboratories according to their own preferences and the capabilities of their respective data management systems, the simplicity and flexibility of the system is likely to vary considerably at the jurisdictional level, at least during the initial period of operation. Subtype determination and resistance testing are already routinely performed in Australian reference laboratories, and resistance testing is a Medicare-rebated pathology service that is part of the Australian standard of care. Therefore, it is expected that data completeness and quality will be high overall and across sub-populations once the early phase of the implementation process has concluded. The ongoing work to more closely align the dataset specifications with current laboratory practice will be crucial to ensure high acceptability by laboratories and jurisdictional health departments and high data quality from early implementation stages onwards.

Stated core functions of national HIV surveillance are to report on trends in disease patterns and disease-associated characteristics of notified cases and to assess the impact of public health and clinical interventions. The specific objectives of the subtype and drug resistance components are to provide an

understanding of subtype distribution and the epidemiology of transmitted drug resistance among new notifications of HIV infection. The ability of the system to detect a maximally high proportion of cases with resistant mutations is therefore important. This is largely a function of the overall sensitivity of the national HIV surveillance system, which is likely to improve as Australia works towards meeting the UNAIDS 90-90-90 and 95-95-95 goals. A key purpose of resistance surveillance is to identify prevalence levels of concern that would require a programmatic or policy response. This would require the definition of critical thresholds adapted to the Australian context for all drug classes and potentially also for specific antiretroviral agents such as tenofovir and emtricitabine due to their use in PrEP. Apart from the WHO threshold for Non-Nucleoside Reverse Transcriptase inhibitors, which is of limited relevance to current treatment regimens in Australia, there are currently no agreed surveillance signals such as thresholds for commonly used drugs in Australia to prompt public health action.

Potential differences in view regarding the public health utility of data derived from genotyping and the perceived risk to affected communities may influence the acceptability of the system to different stakeholders. It is not currently suggested that jurisdictions obtain and store full nucleotide sequence data that would enable phylogenetic analyses, which makes the system acceptable to all parties. At the national level, established community consultation mechanisms give community representatives the opportunity to review suggested reporting formats and the data presented each year in the Annual Surveillance Report. In the short term, it may be useful to consider the development of standards for public reporting of HIV data derived from genotyping that jurisdictions can be encouraged to apply in their own public reporting. Independently from national surveillance, jurisdictional health departments can analyse the surveillance data they collect to support the rapid detection of clusters of rare subtypes or drug resistant mutations. However, jurisdictions may eventually also like to have the ability to analyse newly diagnosed HIV for phylogenetic clustering to improve outbreak detection and enable targeted public health follow-up. The introduction of limited molecular surveillance is thus unlikely to end the discussions about the trade-offs between epidemiological utility of more detailed genotypic data and concerns around legal stigma and the privacy of individuals and communities.

Another challenge for the operation of the system in the long term, and specifically for drug resistance surveillance, is expected to be associated with continued system flexibility. The introduction of routine surveillance of subtype and drug resistance comes at a time where several jurisdictions and the Kirby Institute are in the process of upgrading or replacing their data management systems. These changes likely represent a window of opportunity facilitating the addition of new data fields in some jurisdictions. However, these new systems also need to remain flexible after the initial implementation phase to accommodate new mutations of public health importance as new antiretroviral agents are introduced and formulations approved for biomedical prevention may be broadened.

In summary, the major strengths of the proposed surveillance system are high public health relevance in a context of ambitious national and international target setting, a high level of acceptability to all stakeholders in part due to responsiveness to community concerns about molecular surveillance, and the integration of laboratory data with epidemiological data collected through established national case reporting. Potential improvements to the system as it is currently proposed will need to be explored further during the pre-implementation phase and are likely to relate primarily to data collection and data management at the jurisdictional level. A formal evaluation after a period of operation is needed to assess the ability of the system to meet its objectives. During the implementation phase, agreement should be sought regarding thresholds of resistance prevalence that would be considered a surveillance signal requiring public health action. In the long term, challenges may relate to balancing the public health utility of subtype and resistance surveillance with community concerns about the collection and public reporting of data derived from genotyping and the need for continued system flexibility at all levels.

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6. Investigation of an increase in *Salmonella* Typhimurium phage type 44 notifications during a parallel point source outbreak

Preface

This chapter documents the work conducted to meet the MAE core requirement of conducting an outbreak investigation. This MAE component was completed externally at the Communicable Disease Control Branch, South Australia Department for Health and Wellbeing (SA Health), during a six week period in March and April 2018. During this time, I co-led a descriptive epidemiological investigation into a *Salmonella* Typhimurium phage type 44 (STm 44) cluster. The investigation took place amongst the background of a point source outbreak of the same type of *Salmonella* (referred to in the following as the Café X outbreak), which was managed in a separate outbreak investigation. The focus of this cluster investigation was on a concurrent increase in notifications that were not linked to the original point source. In addition, during my time at SA Health I participated in a number of other public health activities which were briefly summarised in Chapter 1 under “Additional workplace activities”.

Student role

This work took place within the Disease Surveillance and Investigation Section (DSIS) which is managed by Emma Denehy. Supervision was shared among several senior DSIS staff members, including Rebecca Beazley, Emma Denehy, and OzFoodNet epidemiologist Emily Fearnley. Emma Collins, Jodie Halliday, Isabella Johnson, and Sharon Stendt also collected and documented interview data related to the STm 44 cluster investigation. My role encompassed the following components, which align with the traditional ten steps of an outbreak investigation (1) to the extent that each step was appropriate for this investigation:

1. Determine the existence of an outbreak: analysis of notification data to establish a marked increase in notifications of STm 44 from the five year average for the first quarter of the year; development of the cluster case definition to capture cases not linked to the concurrent point source outbreak and to determine that the number of STm 44 notifications remained above the expected number after accounting for cases attributable to the known outbreak.

2. Confirm the diagnosis: laboratory notifications were received for all cases; medical notifications were actively sought where not already provided for *Salmonella* notifications once serotyped and phage-typed as STm 44.

3. Define and count cases: monitoring of data in the Notifiable Infectious Disease Surveillance (NIDS) database at SA Health and identification of cases for interview. Cases were determined to meet one of the two case definitions (point source outbreak or cluster). Cases meeting the cluster case definition were linked on NIDS and line listings were extracted regularly for descriptive data analyses.

4. Orient data with regard to time, place and person: creation of an epidemic curve, descriptive analyses of cases by age and sex and geographical distribution.

5. Determine who is at risk: in addition to the analyses of demographic data and location of cases performed under step 4 to determine if particular population groups are disproportionately affected, all notifications were monitored for cases living in residential facilities and any clustering by educational institution or workplace.

6. Develop and test hypotheses: interviews with cases of STm 44 using the National OzFoodNet *Salmonella* Hypothesis Generating Questionnaire (2015) were conducted; documentation of case interview data in the NIDS database and in a separate food frequency spreadsheet; descriptive analysis of exposures. No specific hypothesis was developed.

7. Plan more systematic study: No hypothesis-confirming analytical studies were conducted as the initial investigation did not yield a testable hypothesis with regard to a potential common source of infection.

8. Compare hypotheses with facts: comparison of the results from the food frequency analyses to known high risk foods for *Salmonella* infection and specific sources of *Salmonella* Typhimurium identified in the literature.

9. Prepare a written report: throughout the investigation, findings were communicated on a regular basis to all stakeholders required to provide assessments and consider follow-up action. This included ongoing liaison

with officers from Food Standards Surveillance Section at SA Health as part of the outbreak response. Formal documentation of the investigation consisted of the preparation of the initial risk assessment document, which was presented and discussed at an outbreak team meeting that I led, and the preparation and circulation of two situation reports for the investigation to stakeholders at SA Health.

10. Execute control and prevention activities: control measures could not be implemented as a common source of infection was not identified. However, disease prevention aspects are routinely included in case interviews through the provision of information on *Salmonella* infection, risk factors, and the possibility of bacterial shedding after symptoms cease.

Additional work conducted by the outbreak team after my involvement included a second risk assessment held on 3 May 2018. At this meeting, a decision was made to close the investigation if notifications declined substantially in the reporting week 29 April to 5 May 2018. The investigation was formally closed on 16 May 2018.

Lessons learned

This cluster investigation did not identify any testable hypotheses regarding a source of infection and did therefore not progress to an analytical study. This outcome in itself was a valuable lesson-learned as classroom-based introductions to outbreak investigations rarely drive home the point that more often than not, the source of infection will not be identified. Nevertheless, the investigation allowed me to become familiar with the process of managing notifications and conducting public health investigations into foodborne diseases at the Communicable Disease Control Branch, SA Health. The interpersonal element of conducting case interviews and collecting primary data was a welcome change from previous work with secondary data only and people's diverse range of responses to being contacted by the health department required a lot more plain language explanation of my work than I was previously accustomed to give. I also developed a greater appreciation of the importance of laboratory evidence to help define case definitions, in this case, further characterisation of common *Salmonella* serotypes using phage typing and Multiple Locus Variable Number of Tandem Repeats Analysis. More generally,

participating in the day-to-day operations of a public health unit highlighted the fact that most outbreak investigations take place among competing priorities and put additional pressure on limited resources such as staff time.

Public health impact

This investigation did not identify any links between cases. As a result, limited public health action could be taken. Nevertheless, the investigation and documentation of this cluster contribute to evidence indicating that there is a burden of disease of *Salmonella* Typhimurium arising from both point source outbreaks and intermittent exposures in the community. In addition, case interviews provided an opportunity to deliver targeted public health information that may prevent secondary cases among contacts or repeat infections with foodborne pathogens. In particular, cases or their caregivers are educated about risk factors for *Salmonella* infection and the modes of transmission, including the possibility of prolonged shedding after symptoms cease. Given that eggs prepared at home were one of the most commonly consumed foods among cases, safe egg handling was stressed in interviews and as part of general food safety messaging undertaken by the Food Standards Surveillance team at SA Health.

Abstract

Background: In February 2018, the South Australian Communicable Disease Control Branch (CDCB) investigated a point source outbreak of *Salmonella* Typhimurium phage type 44. As part of this investigation, a sustained increase in *Salmonella* Typhimurium phage type 44 notifications not linked to the known point source was observed, with notifications at eleven times the expected number for the first quarter 2018 and at seven times the expected number after accounting for the outbreak-associated cases, compared to the five year historical mean (2013-2017).

Methods: A cluster case definition was established and a descriptive case series was undertaken with the aim to (1) confirm the existence of a cluster separate from the parallel point source outbreak, (2) characterise the cluster in terms of person, place and time, and (3) identify a probable source of infection. All cases of *Salmonella* Typhimurium phage type 44 notified to the CDCB between 22 February and 3 May 2018 were attempted to be contacted to collect information on demographics, symptoms, and food and environmental exposures using the South Australian adaptation of the National OzFoodNet *Salmonella* Hypothesis Generating Questionnaire (2015). Descriptive analyses of case characteristics and exposures were undertaken.

Results: A total of 60 cases met the cluster case definition. Cases had a median age of 31 years (range 0-91) and 55% (n=33) were females. Twenty-one cases (35%) were hospitalised and one case died due to complications of *Salmonella* infection. Cases resided in 25 different Local Government Areas. The most common food items consumed by the 48 cases interviewed (80% response rate) were eggs prepared at home (60%, n=29), bread (50%, n=24), and milk (46%, n=22). Eggs were the only item considered to be a high-risk food for salmonellosis; however only one egg brand and place of purchase combination were named more than once (n=2). As a result, the investigation was not able to determine a testable hypothesis regarding a common source of infection.

Conclusion: Although often associated with point source outbreaks, *Salmonella* Typhimurium page type 44 is also an important cause of foodborne illness in the community. The investigation also highlights the diffculty in ascertaining detailed food exposures where the infection was likely acquired in the home.

1. Introduction

Salmonellosis is a gastrointestinal disease caused by *Salmonella* bacteria. There are more than 2,500 serotypes of *Salmonella*. (2) Transmission is frequently foodborne, but can also result from contact with animals that are natural reservoirs of *Salmonella* and from exposure to contaminated non-food animal products. Eggs and egg-containing food items in particular are frequently identified as sources of human *Salmonella* infection. (3-7) Person-to-person transmission via the faecal-oral route can occur. The incubation period ranges from 6 to 72 hours, with illness onset within 12 to 36 hours from exposure common. Rarely, the incubation period can extend to up to 16 days. (2)

Symptoms include diarrhoea, abdominal pain, fever, and nausea. Bloody diarrhoea and vomiting may also occur. While mortality from salmonellosis is generally low, death can occur in very young and very old persons and in otherwise immunocompromised people. (2) The infectious period starts with symptom onset and cases may continue to shed bacteria in their faeces for several weeks after symptoms cease, and in very rare cases for up to one year. Clinical severity, common sources of infection, and infectious periods vary by *Salmonella* serotype. (2)

A mandatory dual notification system applies to all notifiable diseases under section 64 of the *South Australian Public Health Act 2011*. This means that both medical practitioners and pathology services must notify the Communicable Disease Control Branch (CDCB) at SA Health within three days of suspecting or confirming a diagnosis of a notifiable condition. At the time of writing, there were 72 notifiable conditions as defined in the South Australian Public Health (Notifiable and Controlled Notifiable Conditions) Regulations 2012, including salmonellosis which is a notifiable disease in South Australia and nationally. In South Australia, clinical *Salmonella* isolates are routinely serotyped. Certain common serovars are then phage-typed using the Kauffman-White scheme, and isolates of the most common serovar *Salmonella* Typhimurium also undergo further characterisation using the molecular technique of Multiple Locus Variable Number of Tandem Repeats Analysis (MLVA).

In 2017, the National Notifiable Diseases Surveillance System (NNDSS) recorded 16,431 notifications of salmonellosis nationally, making *Salmonella*

infection the second most commonly notified gastrointestinal disease after campylobacteriosis in all states and territories. (8) At 84.6 notifications per 100,000 population, the salmonellosis notification rate in South Australia was higher than the national average of 66.8 notifications in 2017 (Figure 1). (2)

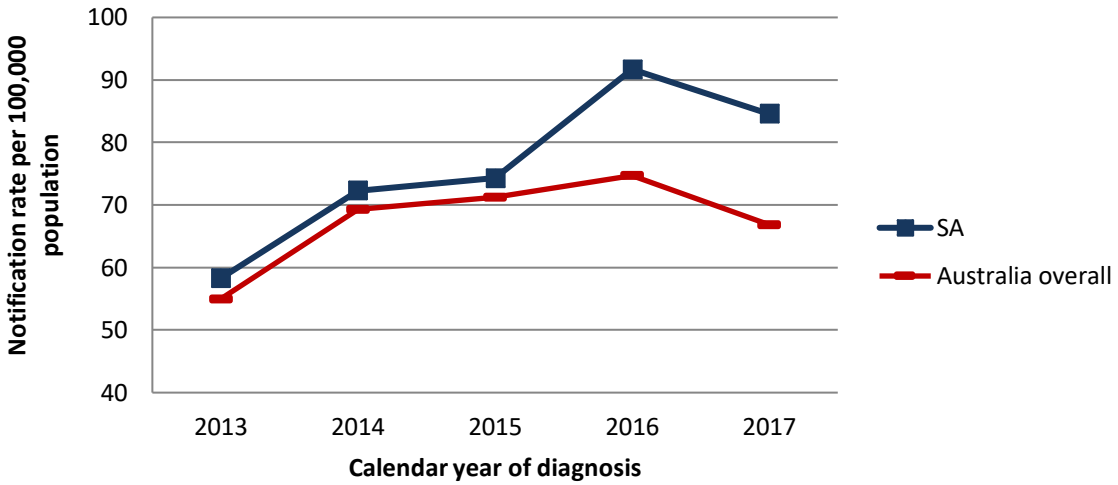

Figure 1: Salmonellosis notification rate by calendar year of diagnosis, South Australia and Australia overall, 2013-2017 (NNDSS)

In 2016, the most recent full calendar year for which data was publicly available at the time of writing, 33% (n=6,017) of all salmonellosis notifications nationally were serotyped as *Salmonella* Typhimurium (9). At 42% (n=654), South Australia had the second highest percentage of *Salmonella* Typhimurium notifications after Victoria, and is on par with Western Australia (Figure 2). (9)

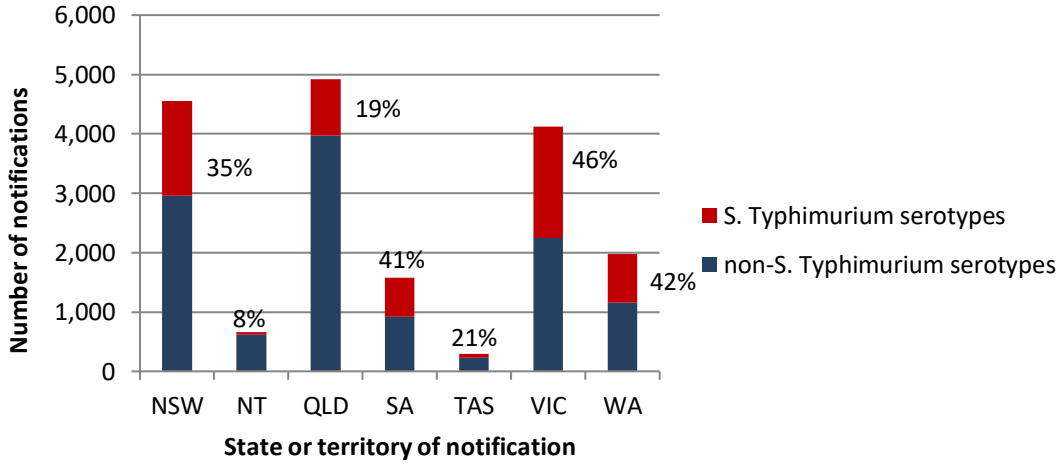

Figure 2: Number and percentage of *Salmonella* Typhimurium notifications by state and territory, Australia, 2016 (NNDSS)

Generally over the time period 2000-2013, there was a steeper increase in the notification rate of *Salmonella* Typhimurium in Australia compared to non-Typhimurium serogroups. (10) The same data indicate that *Salmonella* Typhimurium notification rates were slightly lower in males and peaked in an older age group than non-Typhimurium *Salmonella* infections, i.e. in 1 year olds rather than <1 year olds. (10)

2. Investigation trigger and objectives

On 26 February 2018, the CDCB received a report of suspected food poisoning linked to a catered event and an outbreak investigation was commenced on the same day. This became a point source outbreak of *Salmonella* Typhimurium phage type 44 (STm 44), MLVA pattern 03-10-08-09-523. Café X was identified as the point source and the outbreak was attributed to poor food handling practices involving eggs, with raw egg mayonnaise identified as the likely vehicle. As part of the investigation, a general increase in notifications of STm 44 cases with the same or very similar MLVA patterns was observed. National data for MLVA 03-10-08-09-523 demonstrated that the increase was confined to South Australia (data not shown). Figure 3 below shows that the number of notifications of STm 44 in South Australia from February 2018 onwards was considerably higher than in the previous five years. Comparing only the first quarter of the year, 75 notifications were received in the period January-March 2018 compared to the five year average of 6.8 notifications in 2013-2017. This represents an 11-fold increase over expected notifications. After accounting for 28 cases notified in the first quarter that reported exposure to the Café X point source outbreak, the remaining cases (n=47) were still at a level of seven times the expected number of notifications for the first quarter of the year.

Given this sustained increase in STm 44 notifications after public health intervention had taken place at the Café X point source, an investigation was commenced on 20 March 2018 with the following three objectives:

- Confirm the existence of a cluster separate from the parallel point source outbreak;
- characterise the cluster in terms of person, place and time;
- identify a probable source or sources for hypothesis testing and possible public health action to prevent further illness.

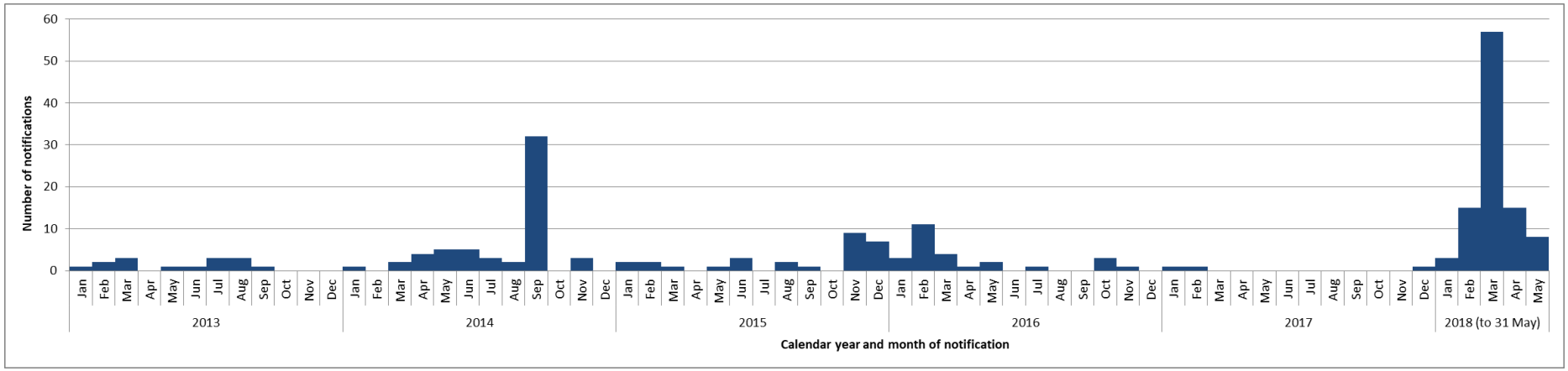

Figure 3: Notifications of *Salmonella* Typhimurium 44 by year and month of notification, 1 January 2013 to 31 May 2018, South Australia

3. Methods

3.1. Study type

A descriptive case series was undertaken to generate a hypothesis for the increase in non-outbreak STm 44 notifications.

3.2. Case definition

The following case definition was applied to define cluster cases:

Box 1: Cluster case definition

Salmonella infection meeting the national confirmed case definition for salmonellosis, typed as *Salmonella* Typhimurium phage type 44, and notified between 22 February 2018 and 3 May 2018 without reported exposure to Café X.

Cases not interviewed due to refusal or loss to follow-up were also considered as meeting the case definition. This decision was taken due to the primary concern at the beginning of the investigation being the assessment of the notified disease burden with no evidence of a link to the Café X point source outbreak. The national confirmed case definition referenced in the cluster case definition above requires laboratory definitive evidence only, defined as the isolation of a *Salmonella* species other than *Salmonella* Typhi, *Salmonella* Paratyphi A or *Salmonella* Paratyphi B. (11)

3.3. Epidemiological investigation

3.3.1. Notification data

All data from laboratory and medical notifications are recorded in the Notifiable Infectious Disease Surveillance (NIDS) database at SA Health. This includes patient demographic data (name, residential address, date of birth, Indigenous status); clinical notes where provided; notifier information; and laboratory data, including type and collection date of specimens, test type, test result, test value, and result date. In addition to serotyping and phage typing results, laboratory data reported to SA Health and recorded in NIDS also include MLVA patterns for most *Salmonella* Typhimurium isolates, as molecular typing is routinely performed for this serotype. In addition, information collected through case interviews is partially

recorded in NIDS. Date of symptom onset and symptoms are obtained by direct case interview. In the absence of a case interview, the onset date as reported by the notifying doctor is retained. If neither case nor doctor provided this information, a default date of onset is automatically calculated based on the earliest date of notification or laboratory-related dates, usually the specimen collection date.

3.3.2. Interview data

For this cluster investigation, interviews were attempted with all cases of *Salmonella* Typhimurium phage type 44 notified to the CDCB between 22 February 2018 and 3 May 2018. As per routine practice, CDCB staff contacted cases tabled for interview on several days at different times of the day, using all contact numbers provided by the notifiers. After multiple unsuccessful contact attempts, cases were declared lost to follow-up. In the absence of information included in the medical notification indicating exposure to the known point source at Café X, the determination whether a case met the cluster case definition was made after ascertainment of exposures during the case interview. For cases under the age of 16 years, the parent or other main caregiver was interviewed, or multiple caregivers where caring responsibilities were shared. For cases between 16 and 18 years of age, permission was obtained from a parent to speak with the case directly.

All interviews were conducted using the South Australian adaptation of the National OzFoodNet hypothesis generating questionnaire for *Salmonella* (2015), which includes details on date of onset of symptoms, symptoms, hospitalisation, travel history, environmental exposures, places of purchase of foods, an open ended 7-day food history and priority trawl sections on poultry and egg consumption. Food and environmental exposures reported in the questionnaire were recorded in a food frequency template in Excel. Symptom and hospitalisation information was added to case records in NIDS. All data were stored on restricted SA Health network drives.

3.3.3. Environmental and microbiological investigations

No environmental samples were taken and no microbiological investigations other than the routine characterisation of isolates were conducted. As noted in

section 1, phage typing of *Salmonella* Typhimurium isolates continues to be routinely done in South Australia. Phage typing results are generally received from the South Australian Salmonella Reference laboratory on a regular schedule multiple times a week, making it a more reliable discriminatory tool for surveillance purposes and time-sensitive public health follow-up than MLVA. MLVA results are also reported to the CDCB by the reference laboratory when available, but are not currently provided according to a regular schedule.

3.3.4. Data analysis

Case demographic, symptom, and MLVA data were extracted from NIDS and analysed descriptively, including breakdowns of demographic data by sex, age group, and Local Government Area. Australian Bureau of Statistics estimated resident populations for each Local Government Area as at 30 June 2016 were used to calculate notification rates. (12) Food frequencies were tabulated to calculate the percentage of cases reporting exposure to each item. Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) and STATA IC v14.2 (StataCorp, College Station, Texas) were used for all analyses. Ethics approval was provided by the Australian National University's Human Research Ethics Committee (protocol #2017/909).

3.3.5. Risk assessment process

Two risk assessments were conducted over the course of the investigation, following a standardised internal process: investigations of suspected food-borne clusters or outbreaks at SA Health use a rapid risk assessment approach based on the World Health Organization's Rapid Risk Assessment of Acute Public Health Events guidelines (13) to systematically share and assess information. The descriptive part of a standardised risk assessment template (provided in appendix 8.6) is initially completed in collaboration between the lead investigators from the Disease Surveillance and Investigation Section (DSIS) and the Food Standards Surveillance (FSS) team and designed to capture all relevant evidence available at the time. This information is then presented and discussed at a risk assessment meeting, involving at a minimum the lead investigators and managers of DSIS and FSS for the initial meeting. The assessment team assigns a risk level to the event and determines appropriate further investigative steps and internal and external communication strategies. Internal communication may

include the decision to draft and circulate a situation report summarising the results of the risk assessment for stakeholders that are not part of the outbreak team, but need to be informed at a more general level.

4. Results

4.1. Descriptive epidemiology

Sixty cases met the cluster case definition. Figure 4 below shows the number of STm 44 notifications by date of notification and cluster status, with the point source exposure referring to the concurrent outbreak linked to Café X. Of the 60 cluster cases, 80% (n=48) were interviewed. The remaining cases declined interview participation (n=3) or were declared lost to follow-up (n=9). The median time between date of illness onset and date of interview was 19 days in this cluster investigation, with a range of 10 to 38 days.

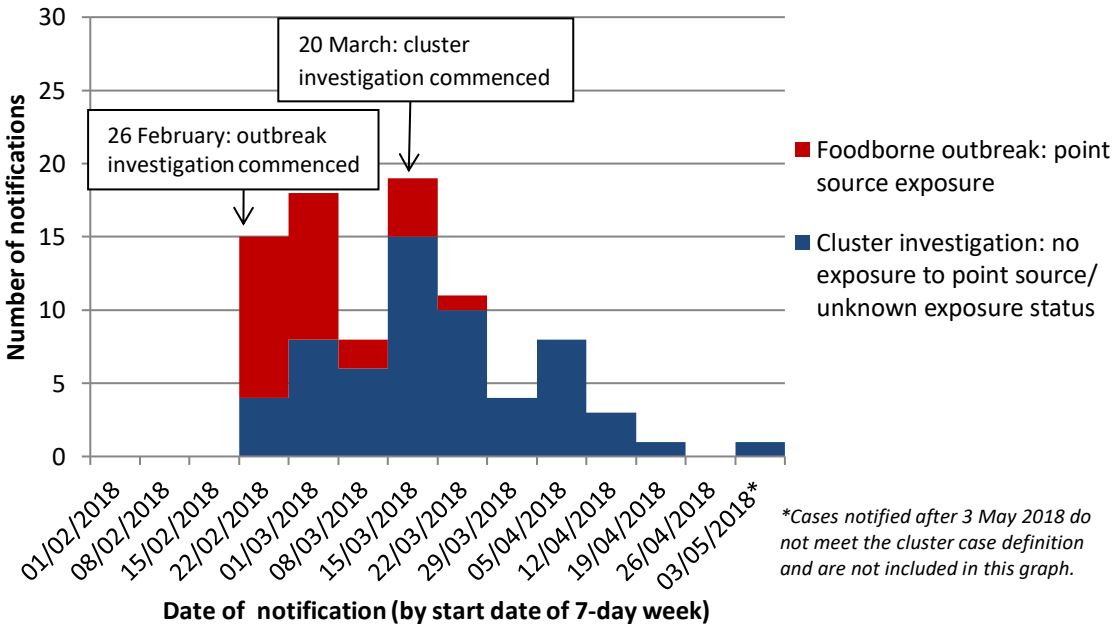

Figure 4: Epidemiological curve of STm 44 notifications by notification date and outbreak status, South Australia, 1 February-3 May 2018

MLVA patterns were available for 95% of cases (n=57) at the time of writing (May 2018). Of these, 95% of cases (n=54) had a MLVA pattern identical to the strain identified in cases linked to the Café X point source outbreak. Of the remaining 3 cases with MLVA patterns, one had a similar MLVA profile with one repeat difference on the third loci, and two others were less similar, one with a three repeat difference on the second loci and the other with a one repeat difference on the second loci and a two repeat difference on the fourth loci (Table 1).

Table 1: Summary of MLVA profiles recorded for STm 44 cluster cases, South Australia, 22 February-3 May 2018

MLVA profile	Number and proportion of all cluster cases with MLVA reported
03-10-08-09-523	54 (95%)
03-10-09-09-523	1 (1.75%)
03-11-10-09-523	1 (1.75%)
03-07-08-09-523	1 (1.75%)

Of the 60 cluster cases, 55% (n=33) were females and 45% (n=27) were males. The median age of cases was 31 years (range one to 91 years). As shown in Figure 5, case numbers were slightly higher in the 0-4 and 10-14 year age groups, representing 15% and 10% of cases respectively. Male-to-female ratios were similar across most age groups, with older adults aged 55 and over having a more pronounced female skew than younger age groups.

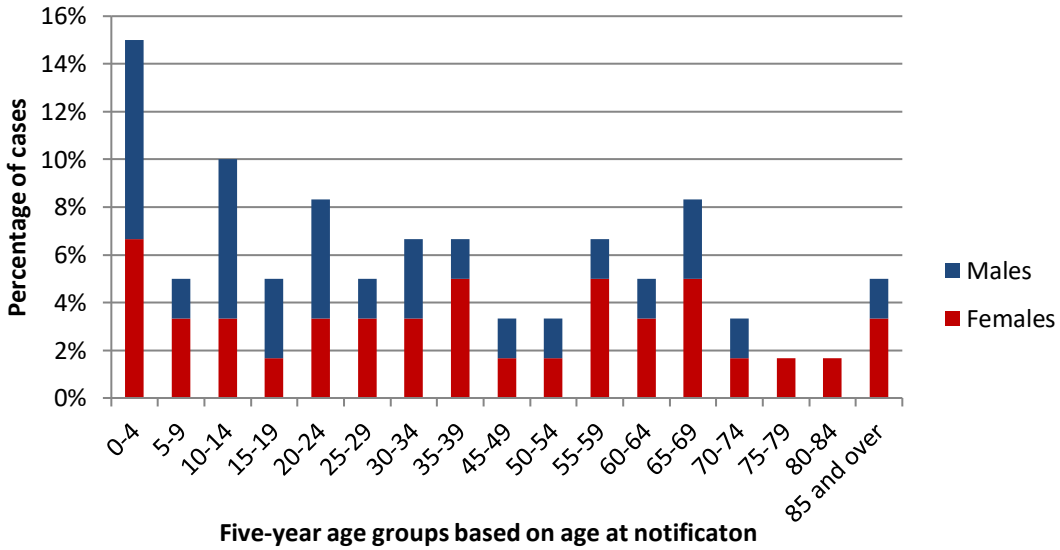

Figure 5: Distribution of STm 44 cluster cases by five-year age groups and sex, South Australia, 22 February-3 May 2018

No geographical clustering of notifications was observed. Cases were notified from 25 different Local Government Areas (LGAs), with 73% of cases residing in metropolitan Adelaide. The highest rate in LGAs with multiple notifications was

observed in the regional LGA of Victor Harbor, followed by the metropolitan LGA of Norwood-Payneham-St Peters (Table 2). Two cases were reported from the same workplace, with no others reported ill. No cases attended residential institutions such as aged care facilities, correctional facilities, or boarding schools.

Table 2: Number and rate of STm 44 cluster cases by LGA[1], South Australia, 22 February-3 May 2018

LGA[1]	Number of cases (% cases; n=60)	Rate per 100,000 population
Victor Harbor (C)	3 (5%)	19.9
Norwood Payneham St Peters (C)	7 (12%)	19.2
Prospect (C)	2 (3%)	9.5
Barossa (DC)	2 (3%)	8.2
Alexandrina (DC)	2 (3%)	7.5
Onkaparinga (C)	12 (20%)	7.1
Playford (C)	6 (10%)	6.6
Campbelltown (C)	2 (3%)	3.9
Charles Sturt (C)	3 (5%)	2.6
Marion (C)	2 (3%)	2.2
Salisbury (C)	3 (5%)	2.1
Tea Tree Gully (C)	2 (3%)	2.0
Port Adelaide Enfield (C)	2 (3%)	1.6

[1]Note: only LGAs with ≥2 cases are included.

Doctor or patient-reported dates of illness onset were known for 55 cases and ranged from 18 February 2018 to 29 April 2018. Twenty-one cases (35%) were hospitalised. One case was classified as having died due to the notifiable

disease; this patient was hospitalised and died due to a complication of *Salmonella* infection. Among the 48 cases interviewed, diarrhoea was the most common symptom reported by 98% of cases (n=47), with just under one third reporting bloody diarrhoea (n=15) (Table 3). A large majority of cases also experienced lethargy and abdominal pain and three quarters had a fever. Nausea and vomiting were reported less frequently by 65% and 56% of cases, respectively.

Table 3: Symptoms reported by STm 44 cluster cases at interview (n=48), South Australia, 22 February-3 May 2018

Symptoms	Number	Percentage of cases interviewed
Diarrhoea	47	98%
Lethargy	41	85%
Abdominal pain	40	83%
Fever	36	75%
Nausea	31	65%
Vomiting	27	56%
Headache	18	38%
Joint and muscle pain	17	35%
Bloody diarrhoea	15	31%

Of the 48 cases interviewed, the most common food items consumed included eggs eaten at home (60%, n=29), bread (50%, n=24), and milk (46%, n=22). In addition to food exposures, 63% reported contact with any pets, and 58% reported contact with dogs (Table 4). No patterns regarding foods consumed outside the home were established as cases did not report eating at common food venues. Places of purchase for eggs consumed at home varied: 16 cases (33%) recalled buying eggs from Woolworths, followed by Coles (21%, n=10) and

Foodland (19%, n=9). Eight cases remembered the brand of eggs eaten, with only one brand/store combination to be named more than once (n=2).

Table 4: Summary of high-frequency exposures reported by STm 44 cluster cases, South Australia, 22 February-3 May 2018

Item	n	% of all cases interviewed (n=48)
Food exposures		
Eggs eaten at home (trawl)	29	60%
Any eggs (open ended 7-day food history)	24	50%
Bread	24	50%
Milk	22	46%
Chicken pieces (purchased raw and cooked at home)	19	40%
Cheese (block/sliced)	16	33%
Chicken (purchased cooked; trawl)	12	25%
Chicken (open ended 7 day food history)	12	25%
Environmental exposures		
Contact with pets	30	63%
Contact with dogs	28	58%

4.2. Risk assessment and public health action

A risk assessment was completed on 9 April 2018 and concluded that there was no testable hypothesis emerging from the epidemiological data. Given that eggs consumed at home were the most common food exposure reported by cases,

and that the source of the concurrent point source outbreak was eggs (the exact brand could not be determined), the FSS team ran a social media post via the SA Health Facebook page on 29 March 2018 on safe egg handling in the home. The 50 second video featured the SA Health Food Safety Ambassador Adam Liaw, a television chef and author, and had appproximately 1,400 views by the end of May 2018. (14) The video also provided a link to an exisiting resource on the SA Health website about safe food handling at home. (15)

In addition, over the course of the investigation, two food premises were referred to the FFS team as per standard practice: food venues specifically implicated by a case as the suspected source of their infection or named by two or more cases as part of an investigation into foodborne disease are routinely referred to the section for assessment and further action where required. However, each of these two premises was a common exposure among only two or fewer of the 48 cluster cases (<4%) interviewed and therefore not suspected as a common source of infection for the wider cluster. FSS do not routinely report to DSIS on individual referrals and it is therefore not known if local environmental health officers in the relevant LGAs inspected the two premises in question.

A second risk assessment was conducted on 3 May 2018 and the decision was made to suspend interviews and close the investigation if no more than six notifications of STm 44 were received in the reporting week 29 April to 5 May 2018. The benchmark of six notifications reflects a pragmatic decision about an acceptable level of notified disease activity (just below the five-year first quarter average of STm 44 notifications) in the context of limited resources at DSIS and the absence of actionable information emerging from the investigation. At the time of assessment, one *Salmonella* notification received in the reporting week of interest had been further characterised as STm 44 and two notifications were awaiting further typing (these where later determined to be non-STm 44 infections). As a result, the investigation was formally closed on 16 May 2018 and all subsequent notifications of STm 44 were assessed according to standard protocols.

5. Discussion and conclusion

The epidemiological investigation did not identify a common source of infection such as a specific food item or food venue. While the cases were clustered in

time, there was no obvious geographical clustering and no particular population group were disproportionally affected. As a result, limited public health action could be taken. As this investigation grew out of the Café X outbreak investigation and interviews with all cases of STm 44 served to allocate cases to one of the two complementary case definitions, the cluster investigation helped delineate the extent of the concurrent point source outbreak. Following the determination that there was a higher than expected number of STm 44 notifications after accounting for the Café X outbreak, the investigation served to eliminate the possibility of an additional point source. Given the concurrent nature of the Café X outbreak and the community cluster as well as the close relatedness of a large majority of isolates based on MLVA profiles, it seems plausible that the same source of infection that caused the Café X outbreak may also have been available in the community.

The investigation into the Café X outbreak, through a combination of descriptive epidemiological evidence and the results of an environmental investigation, established raw egg mayonnaise as the most likely vehicle of infection. While there was limited evidence to link the cluster cases to eggs, eggs consumed at home were the most frequently mentioned food item in the case interviews, followed by any eggs, bread, and milk. Raw or undercooked eggs and egg products are well-established high-risk food items for *Salmonella* infection (2) that have been frequently linked specifically to *Salmonella* Typhimurium outbreaks. By contrast, there is a lack of evidence implicating bread and pasteurised milk products as sources of *Salmonella* Typhimurium.

In South Australia during the time period 2000-2010, a Bayesian source attribution model (3) estimated that 37% (95% Credible Interval: 20%-49%) of sporadic cases of salmonellosis could be attributed to eggs and another 35% (95% Credible Interval: 20%-49%) to chicken meat, while a higher percentage of outbreak cases were likely to be related to eggs (59%; 95% Credible Interval: 29%-75%). When looking at *Salmonella* Typhimurium serotype separately, the attribution rate for eggs rose to 52% (95% Credible Interval not reported) of sporadic cases. (3) A review of egg-associated *Salmonella* outbreaks that occurred in Australia between 2001 and 2011 showed that *Salmonella* Typhimurium was the causative serogroup in 90% of these outbreaks. (16) Of the *Salmonella* Typhimurium outbreaks included in the analysis, 17% were caused

by phage type 44 which was the second most common Typhimurium phage type after phage type 108/170 (32%). (16) The same analysis found egg-associated outbreaks to most frequently originate from commercial food premises and catered events, and identified food items containing raw or undercooked eggs as the predominant vehicle of infection. (16) The January to March 2015 OzFoodNet quarterly report, the latest report available at the time of writing, reported food items containing eggs (n=9) or potentially containing eggs (n=4) as the source of infection in 65% of outbreaks with STm 44 or non-phage-typed Salmonella Typhimurium as the aetiological agent. (7) In the published literature, there were three accounts of individual outbreaks of STm 44 in Australia. All identified egg-containing food items as the source of infection: a 2009 outbreak at a wedding reception in South Australia was linked to aioli containing raw egg yolk (4); poached eggs and hollandaise sauce were implicated in a 2008 outbreak at a restaurant in the Australian Capital Territory (5); and a raw-egg dessert was identified as the cause of illness in an aged-care facility in New South Wales, with an environmental investigation also having detected STm 44 on eggs sampled from the kitchen. (6) These examples underline that the consumption of raw or undercooked eggs or egg products, while not established as a source of this cluster, is a generally plausible explanation.

This investigation was an uncontrolled case series intended to generate a hypothesis with biological plausibility, rather than an analytical study to test a hypothesis. This investigation was an uncontrolled case series intended to generate a hypothesis with biological plausibility, rather than an analytical study to test a hypothesis. Theoretically, it would have been possible to compare observed consumption percentages derived from the case interviews with the Victorian food consumption database which provides a season-specific indication of the expected background consumption percentages for a large number of foods. However, these data would have had to be requested from Victoria as a courtesy and there are differences between the Victorian and the South Australian population composition.

Due to the study design, there is also no study comparison group of healthy controls. While this means that is no risk of differential bias that would lead to a distorted effect size estimates, the descriptive consumption percentages calculated for different foods are vulnerable to different forms of bias: firstly,

selection bias may result from an under-ascertainment of cases as only those that seek medical attention, have a stool specimen taken, and undergo culture testing rather than PCR-only testing are notified and identified as an notification due to STm 44. Therefore, the cases notified with STm 44 are unlikely to represent all cases that occurred in the population. In addition, 20% of cases that met the case definition declined to be interviewed or were lost to follow-up. Secondly, information bias is a major risk for all interview-based investigations. While the ascertainment of outcomes is laboratory-based and therefore robust, the ascertainment of exposures is vulnerable to interviewer and recall bias. By using a standardised questionnaire and trained interviewers, interviewer bias was minimised, although interviewers were aware that raw eggs had implicated in the parallel point source outbreak. Recall bias is the strongest limitation of this study: as the number of cases answering in the affirmative to the generic item of 'eggs eaten at home' in the trawl section of the *National OzFoodNet Salmonella Hypothesis Generating Questionnaire* was higher than the number of cases mentioning any eggs or egg-containing dishes in the detailed, open-ended food history, it is possible that the questionnaire's focus on exposures in the seven days prior to illness onset incompletely captures ingredients or foods that are prepared and/or eaten routinely. Among the cluster cases interviewed, recall of specific food exposures was particularly poor, with a majority of cases appearing to be consume a limited variety of foods, with little eating outside the home being reported. More generally, conducting interviews in a timely fashion to maximise accurate recall is a challenge for any investigation relying on subtyping and phage typing to determine whether cases meet a case definition. Given that the South Australian adaptation of the *National OzFoodNet Salmonella Hypothesis Generating Questionnaire* covers the seven days prior to illness onset and interviews were conducted 10 to 38 days after illness onset, cases in this investigation were asked to recall foods consumed up to 17 to 45 days ago. This delay is likely to contribute to underreporting of routine consumption patterns unrelated to special occasions and not documented by bank statements and calendar entries. Conversely, narrowing the number of *Salmonella* Typhimurium infections suspected to be part of an outbreak or cluster based on phage typing allows for a more judicious allocation of limited resources, in this case the staff time associated with administering and analysing the hypothesis generating questionnaires. In the future, more timely provision of MLVA results, or the

introduction of routine whole genome sequencing, has the potential to further focus investigations on cases with clinical isolates that are closely related genetically and likely share an unidentified common source of infection.

Routine food handling practices in the home are likely to be an important risk factor for sporadic cases and potential clusters in the community as *Salmonella* presence on eggs is at least an intermittent, if not regular occurrence. Uncertainty regarding the frequency and extent of *Salmonella* contamination of retail eggs was evidenced at a 2015 national workshop for egg producers and state and national regulatory authorities by egg producers agreeing that food-handling practices in commercial food outlets were insufficient to prevent *Salmonella* contamination and more preventative action may be needed at the farm-level. (17) A 2008 retail survey of chicken and eggs carried out in South Australia found 3.5% of egg samples to be contaminated with *Salmonella* on the outside of the egg, with several phage types of *Salmonella* Typhimurium detected, although not phage type 44. (18) In Australia, food handlers in commercial settings must meet the food safety skills and knowledge requirement stipulated by the Australia New Zealand Food Standards Code (19) and may be directed to complete food safety training in response to breaches. By contrast, efforts to enforce safe food handling practices do not extend to private households and general health messaging may fall short of changing behaviours. The results from a survey of Australian consumers suggest that general risk awareness about raw eggs and *Salmonella* does not translate into practice: while a large majority of respondents (84%) reported that that they did not consume raw eggs, an equally large percentage (86%) responded that they would recently have eaten food containing raw eggs. (20) Similarly, evidence from overseas studies involving observed food handling in the home indicates that in private settings, eggs were rarely cooked to safe temperatures and widespread inadequate handwashing enabled potential cross-contamination. (21)

In summary, this investigation highlights the importance of STm 44 as a cause of foodborne illness in the community, and underscores the difficulty of ascertaining a common source where infections were potentially acquired through unsafe routine food handling practices in the home.

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7. Summary of peer-to-peer teaching and learning experience

This chapter summarises the activities undertaken as part of the peer-to-peer teaching and learning components of the MAE program. The first section outlines my contribution to and participation in the lessons from the field (LFF), a series of case studies developed by MAE students to share their workplace learning or particular areas of interest with fellow students. My LFF introduced a group of the MAE 2017 cohort to causal diagrams in epidemiological research. The second section of this chapter describes the development and presentation of a teaching session for the MAE 2018 cohort in March 2018. The topic of program logic in public health programming and evaluation was chosen by a group of MAE students whose work experience includes program development and implementation. In addition to the LFF worksheet and teaching presentation, the appendix to this chapter (appendix 8.5) also includes a presentation on spatial mapping of health information which I gave as part of the 'Issues in Applied Epidemiology' course, held during the third MAE courseblock in March 2018. Collectively, these activities demonstrate my development of skills in relation to the planning and implementation of teaching activities and the communication of lessons learned in the workplace.

7.1. Lessons from the field

The LFFs are designed to present a learning experience from the MAE to the rest of the cohort in the format of a structured series of exercises. Due to the large size of the MAE 2017 cohort, several LFF groups were formed. Between November 2017 and March 2018, I participated in the following five LFFs:

- Investigation of cancer clusters: Belinda Jones (Hunter New England Local Health District), 7 November 2017
- Clinical epidemiology - Preventative screening: Cushla Coffey (Health Protection Branch, Queensland Health), 20 December 2017
- Nginda MAE waala wiitha! (Throwing the MAE into the fire!) - The implications of investigating disease with limited Indigeneity data: Charlee

Law (Communicable Disease Branch, Health Protection NSW), 14 February 2018

- Linked Data Analysis: Julia Maguire (National Centre for Immunisation Research and Surveillance), 7 March 2018
- Rapid Risk assessment for outbreak investigation: Bernadette Kenny (Communicable Disease Control Branch & Prevention and Population Health Branch, SA Health), 20 March 2018

My LFF was held on 7 March 2018, taking advantage of the opportunity to conduct two LFFs face-to-face during the third MAE courseblock. The session introduced participants to causal diagrams in epidemiological research using the DAGitty tool, a browser-based program to draw and analyse Directed Acyclic Diagrams (DAGs). The topic is loosely related to the epidemiological research project presented in chapter 2. This project was an ecological study that investigated correlates of low HPV vaccination coverage at the school level. Decisions about the inclusion of variables were based on previous research conducted primarily overseas, investigators' assumptions about potential relationships between school characteristics and the outcome, and the practical issue of data availability. A high degree of correlation between potential independent variables further complicated both the decision-making about variables to be included in the analysis and the interpretation of differences in the direction and size of effects in univariable and multivariable analysis. This project is a good example of an observational epidemiological study that might have benefitted from a more explicit analysis of hypothesised relationships and hierarchies between variables. Causal diagrams, and DAGs in particular, are one such tool that can help researchers analyse and communicate causal assumptions more clearly and identify likely non-casual relationships occurring due to bias and confounding.

The learning objectives for the LFF were to enable participants to:

- Explain different conceptualisations of causation in epidemiological research.

- Apply the principles of DAGs to help inform the planning and analysis of epidemiological studies.
- Use the DAGitty tool to draw a basic DAG of a research question.

Appendix 8.5 provides the LFF worksheet with model answers based on my original suggestions and some of the additional aspects that the group came up with. Also included in the appendix are the full results from the peer evaluation of my LLF. The group decided to conduct a simple qualitative evaluation comprising of the following three open-ended questions:

1. What did you like about this LFF?
2. What could have been improved?
3. To what extent has this LFF been useful for your work (workplace and/or academic)?

Briefly, the feedback received indicated that the LFF was well received and participants appreciated the practical examples to demonstrate the use of DAGs in conceptualising relationships between variables. The responses demonstrate that the session was of practical relevance, with all participants indicating that they had either encountered DAGs previously and not fully understood and/or could see a use for this approach in their work following the LFF. However, it was also noted that the topic is very complex and required more self-study prior to the session than other LFFs. The opportunity to conduct this LFF meeting face-to-face mitigated some of the issues associated with the complexity of the concept and the particular rules of drawing DAGs and enabled useful discussions that allowed everyone to meet the learning objectives.

7.2. Introducing the MAE 2018 cohort to logic models

All second year MAE students were required to provide input into a teaching exercise for the MAE 2018 cohort in the afternoon of 9 March 2018. The session was divided into separate teaching components prepared in small groups. I initially suggested a session on public health program management or evaluation given the increasing number of MAE students placed in institutions whose core business is not the response to acute public health

problems on which most of the classroom teaching is centred. In a group of three MAE students with an interest and work experience in health programming, we decided to focus on logic models as a core component of program planning and program monitoring and evaluation that could easily be translated into a short group exercise. Planning of the session was shared by all group members and the presentation bookending the group activity is provided in appendix 8.5. The activity asked students to apply a generic logic model template to a fictional health program, drawing on a Russian advertisement for the 2014 Winter Olympics that featured a subway ticket machine accepting 30 squats as payment. Similar to my LFF topic, this session was designed to introduce participants to a framework that encourages the integration of program planning and evaluation and requires systematic considerations of analytical strategies to measure program success at different stages. The learning objectives for the session were to enable participants to:

- Describe the components of a logic model.
- Apply a logic model to a given public health intervention.
- Explain the challenges of capturing different aspects of complex public health interventions.

Figure 1: Results from the group activity introducing logic models for public health program evaluation, Canberra, March 2018

A short evaluation was conducted based on three five-level Likert items asking respondents to rate the usefulness of the overall format of the session, the content of the session, and the presentation style. Responses were received from 28 MAE scholars, 13 students from the 2018 cohort and 15 students from the 2017 cohort. The session was deemed useful or highly useful by 82% of respondents (n=23), with 18% (n=5) remaining neutral. Similarly, approximately 80% of the group rated the content and presentation style to be useful or highly useful. We did not have a chance to further explore the views of the five participants who considered the session to be less useful. However, the diversity of backgrounds in most MAE cohorts implies that the topic may have been completely new to some, extremely basic to others, or simply be considered peripheral to applied epidemiology by a few participants. Overall, this feedback provides an indication that the large majority of participants would have met the learning objectives and considered the topic to be of relevance to their work or personal development.

Thesis access restrictions are in place for chapters 8.1, 8.2, and parts of chapter 8.3 due to public health confidentiality considerations.

8.3 Supplemental materials chapter 5

Public appendix

This appendix contains the Frequently Asked Questions document explaining the need for HIV subtype and transmitted drug resistance surveillance that is associated with chapter 5 entitled “Description of the first stage of the introduction of national surveillance for HIV subtype and transmitted drug resistance”.

Confidential appendix

The confidential part of the appendix contains two tables referenced in the main chapter that are unsuitable for public distribution:

- Table 4: New diagnoses with SDRMs by drug class and exposure category, NSW and SA, 2015, not for public distribution
- Table 5: HIV subtype distribution in new diagnoses by likely place of acquisition, NSW and SA, 2015, not for public distribution

Public health surveillance of transmitted HIV drug resistance & subtype

The Kirby Institute at the University of New South Wales has been responsible for coordinating national HIV surveillance on behalf of the Australian Government Department of Health and in cooperation with the State and Territory Governments since 1986. Public health surveillance refers to the systematic collection and analysis of health data at a population level, in this case information related to diagnoses of HIV. The knowledge gained through surveillance activities is used to guide the public health response to HIV prevention and treatment. Key data on HIV diagnoses are reported every year in the Annual Surveillance Report of HIV, viral Hepatitis and sexually transmissible infections published by the Kirby Institute.

The medical and public health response to HIV has evolved rapidly in recent years. These changes include:

1) An increased focus on providing antiretroviral treatment to people immediately after they are first diagnosed with HIV. Starting HIV treatment early has been shown to improve a person's health compared with starting treatment later[i].

2) Starting treatment for the purpose of preventing HIV as early, sustained treatment suppresses the virus to levels where it can't be detected in a person's blood[ii]. When the virus is undetectable, the likelihood of transmission to another person is reduced to zero.

3) The establishment of HIV pre-exposure prophylaxis (PrEP) as an effective prevention strategy for individuals at high risk of acquiring HIV.[iii,iv] PrEP involves HIV-negative persons taking HIV drugs and is highly effective at preventing transmission when taken as prescribed[iv] (also see section 3).

4) A national commitment to the virtual elimination of new HIV infections by 2020[v].

With these changes, the information collected as part of public health surveillance also needs to be revised periodically. This includes information on transmitted HIV drug resistance, that is resistance to drugs that are commonly used in HIV treatment, and information on the broad distribution of HIV subtypes. Here, we explain the terms HIV drug resistance and subtype and provide answers to a few frequently asked questions regarding the public health surveillance of these indicators.

1. What is transmitted HIV drug resistance?

Transmitted drug resistance means that a newly acquired virus already contains mutations that may make it less responsive to commonly used antiretroviral drugs. When this happens, the treatment given to a person living with HIV may work poorly or not at all and they need to be switched to an alternative treatment. To help doctors select the most effective antiretroviral therapy for each

person, HIV drug resistance testing is recommended for all patients prior to or shortly after starting antiretroviral therapy[vi].

2. How is drug resistance determined?

When a person is first diagnosed with HIV, their treating doctor collects a blood sample and requests the laboratory to conduct a test for drug resistance to check whether the person has a virus that contains drug resistance mutations. This involves the laboratory test 'reading' a number of gene regions responsible for viral replication which are also the key regions that antiretroviral drugs aim to disrupt. The mutations found are then checked against an international list of mutations that are known to confer resistance to individual drugs or drug types.

3. What are the benefits of collecting information on transmitted drug resistance?

Monitoring levels of drug resistance among people newly diagnosed with HIV in Australia provides an important snapshot of how well the recommended HIV treatments are working and if any changes need to be made to current treatment recommendations[vii].

This is particularly important given the recent advances in expanding access to HIV treatment for all people living with HIV and the introduction of PrEP (pre-exposure prophylaxis). PrEP involves people who are HIV negative taking HIV antiviral treatments daily drugs to protect themselves from acquiring HIV[viii]. The drugs that are taken for PrEP are the same ones that are commonly used in the treatment of people living with HIV. With an increasing number of HIV positive and HIV negative individuals being exposed to antiretroviral drugs for treatment or prevention, surveillance of drug resistance is needed to identify emerging resistance early and adjust the guidelines for treatment and PrEP accordingly.

Resistance mutations can develop when antiretroviral treatment is interrupted and a person's viral load is no longer undetectable. This allows the resistant virus to start replicating again and the resistance mutations can then be passed on with the virus. Increases in transmitted drug resistance may therefore also indicate a need for services to better support people living with HIV with adherence to their antiretroviral treatment.

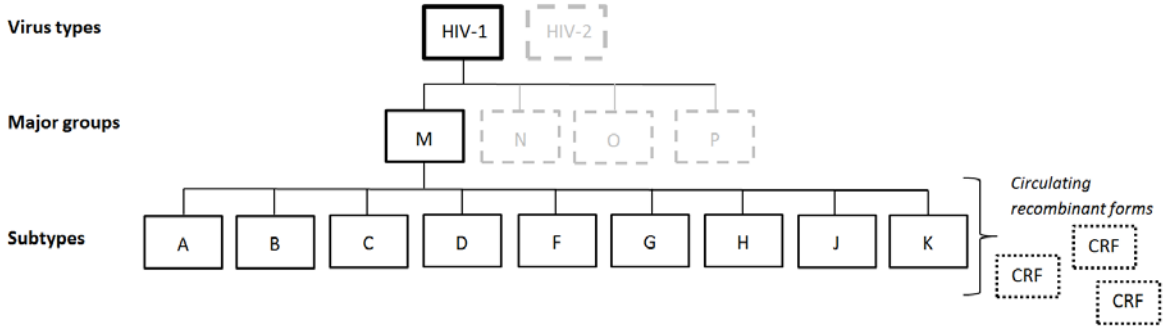
The type of information collected and how confidentiality is protected is described in section 8.

4. What is a subtype?

A subtype is a category of HIV that groups similar virus strains together. Like other infectious diseases, HIV can be further broken down into different virus types and strains that have slightly different characteristics. Figure 1 below shows the different classification levels: HIV is made up of two major virus types. HIV-1 is the most common type globally and in Australia and is usually

referred to simply as HIV. Within HIV-1, four broad groups are recognised, with the major group M being responsible for almost all HIV infections globally. The M group is further broken down into nine subtypes, also known as clades. The subtypes are denoted by one of the letters A, B, C, D, F, G, H, J, or K as shown below. When viruses belonging to different subtypes combine some of their genetic material, the resulting hybrid viruses are called 'circulating recombinant forms'. Different subtypes have distinct geographical origins. Most HIV infections in Australia, North America, and Western Europe involve subtype B, whereas subtype C is most common globally.

Figure 1: Classification of HIV



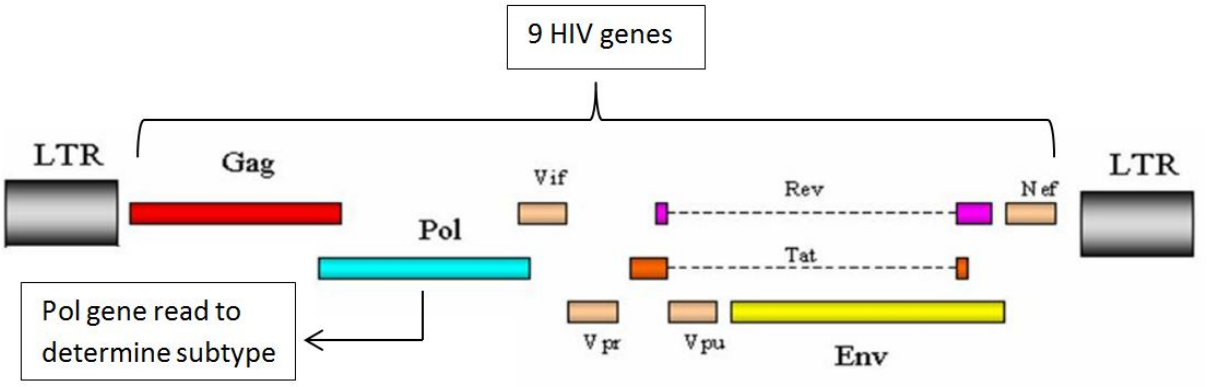
5. How is subtype determined and how is it different from genotype?

Subtype can be determined based on the same blood sample used to determine drug resistance mutations. Similar to testing for drug resistance, the process involves reading part of the virus' genes.

Figure 2 below shows that HIV is made up of nine genes. The entirety of the HIV genetic information is collectively known as the HIV genome. Each gene contains sequences of information that allow the virus to carry out particular functions, for instance the different steps needed for viral replication. The genotype refers to the exact documentation of these sequences to determine the differences that distinguish one virus from another virus. Genotypes can be determined for a particular gene or gene region, but can also involve reading of a much larger part of the HIV genome.

By contrast, the classification into subtypes requires reading of only a portion of the *polymerase* (*pol*) gene. When subtype is reported for routine public health surveillance purposes, only the letter denoting the subtype is reported. All data describing the exact make-up of the *pol* gene remain with the laboratories. Subtype information is too broad to determine relationships between the viruses that different individuals are living with. This means that even if two persons both have a rare subtype, they still belong to categories that are sufficiently broad as to not uniquely identify an individual's viral strain.

Figure 2: Genomic organisation of HIV



Adapted from: Rivera DM. Pediatric HIV Infection. Medscape. 2017. Available from: https://emedicine.medscape.com/article/965086-overview.

6. What are the benefits of collecting information on subtype?

An understanding of the distribution of HIV subtypes in Australia is important to inform HIV management guidelines. There is evidence to suggest that the way HIV progresses in the body[ix,x], how the HIV virus responds to treatment, how it develops resistance mutations[ix,xi,xii,xiii], and the accuracy of viral load tests[xiv] can all vary between different subtypes.

In addition, changes in subtype distribution may indicate shifts in the demographics of people newly diagnosed with HIV. As described in section 4, some subtypes occur more commonly in certain parts of the world. Surveillance data on subtype distribution, combined with other demographic information of people diagnosed with HIV, can help ensure that treatment and prevention strategies are tailored specifically to the needs of these populations.

7. Who has access to drug resistance and subtype information?

Once laboratory tests have been conducted, the results are reported back to the treating doctor. As part of public health surveillance, laboratories will also report subtype and resistance information to state and territory health departments. The health departments are in charge of collecting all data related to HIV notifications within their jurisdiction in accordance with the specific provisions of the public health legislation in their state or territory. They then send an agreed set of data on to the Kirby Institute which compiles a summary at the national level.

All HIV subtype and resistance data is subject to the same privacy and confidentiality legislation as any other information associated with HIV notifications. This means that only authorised staff at laboratories, health departments, and the Kirby Institute has access to these data. In addition, HIV

notifications use namecodes consisting of the first two letters of the first name and the first two letters of the last name, rather than an individual's full name, at all stages of data collection, storage, and transfer.

8. How are the data collected for public health surveillance purposes used?

The primary use of these data is a national summary of drug resistance and subtype information provided by the Kirby Institute in its annual surveillance reports. These reports may be used to inform decisions about public policy, resource allocation for treatment and prevention, or clinical practice.

9. How does public reporting protect the privacy of individuals and communities?

Under no circumstances does public reporting of any data related to public health surveillance identify individuals. All public health data are reported in aggregated from, that is all cases that fit a particular category of interest are counted and reported in summary form. In addition, all public reporting of drug resistance data is done in such a way that the potential for stigmatisation of specific population groups is minimised. Each annual surveillance report is reviewed by the Annual Surveillance Report Advisory Committee prior to publication. The committee includes members of community organisations that represent people and communities affected by HIV.

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[v] COAG Health Council. AIDS 2014 Legacy Statement. 2014. Available from: www.health.gov.au/internet/ministers/publishing.nsf/Content/6DA3F43553CD3D4DCA257D1B0023553A/$File/LEGACY_SPEECH_2014_A5_WEB.pdf.

[vi] Australasian Society for HIV Medicine (ASHM). Drug-Resistance Testing. Antiretroviral Guidelines - US. DHHS Guidelines with Australian commentary. Available from: http://arv.ashm.org.au/arv-guidelines/laboratory-testing/drug-resistance-testing.

[vii] Australasian Society for HIV Medicine (ASHM). What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient. Antiretroviral Guidelines - US. DHHS Guidelines with Australian commentary. Available from: http://arv.ashm.org.au/arv-guidelines/what-to-start.

[viii] Australian Federation of AIDS Organisations (*AFAO*). HIV Prevention-PrEP. Available from: https://www.afao.org.au/about-hiv/hiv-prevention/prep/.

[ix] Baeten J.M., Chohan B., Lavreys L. HIV-1 subtype D infection is associated with faster disease progression than subtype A in spite of similar plasma HIV-1 loads. Journal of infectious diseases. 2007; 195: 117-80.

[x] Bhargava M, Cajas JM, Wainberg MA, Klein MB, Pai NP. Do HIV-1 non-B subtypes differentially impact resistance mutations and clinical disease progression in treated populations? Evidence from a systematic review. Journal of the International AIDS Society. 2014;17(1).

[xi] Häggblom A, Svedhem V, Singh K, et al. Virological failure in patients with HIV-1 subtype C receiving antiretroviral therapy: an analysis of a prospective national cohort in Sweden. Lancet HIV. 2016;3(4):e166-74.

[xii] Kantor R, Smeaton L, Vardhanabhuti S et al. Pretreatment HIV drug resistance and HIV-1 subtype C are independently associated with virologic failure: results from the multinational PEARLS (ACTG A5175) clinical trial. Clinical Infectious Diseases. 2015; 60:1541-9.

[xiii] Häggblom A, Svedhem V, Singh K, Sönnerborg A, Neogi U. Brenner B, Lowe M, Moisi D, Hardy I, Gagnon S, Charest H et al. Subtype diversity associated with the development of HIV-1 resistance to integrase inhibitors. Journal of medical virology. 2011;83:751-9.

[xiv] Luft L, Gill MJ, Church D: HIV-1 viral diversity and its implications for viral load testing: review of current platforms. International Journal of Infectious Diseases. 2011; e661–e670.

8.4. Supplemental materials chapter 6

The following risk assessment template used for public health investigations at SA Health is associated with chapter 6 entitled “Investigation of an increase in *Salmonella* Typhimurium phage type 44 notifications during a parallel point source outbreak”.

Outbreak Team Meetings- Agenda and Minutes Template		
Outbreak name	Pathogen (if known) Cluster or Location	
Reference No.	NIDS Outbreak # / PHMS Event #	
Date and time of meeting		
Attendees		
Trigger		

1. **Apologies**
2. **Actions previous meeting**
3. **Rapid Risk Assessment**

Hazard assessment

What is the pathogen?
If there is no pathogen, what are the symptoms of the illness that has been reported?

How many people are affected?

What are the age groups and sex of cases?

What is the severity of the disease?
Number and % hospitalised:
Number of fatalities:

Exposure assessment

What is the most likely mode of transmission? Why?
[please consider the evidence to suggest if foodborne, person-to-person, animal-to-person etc]

What exposures have been associated with this hazard in the past?
[literature review, historical outbreaks etc]

If outbreak is a point source, how many people are known or likely to be exposed?
[is there a booking list or estimate of number of meals served?]

What are the most frequently consumed food items?
[food frequency analysis- is this normal?]

What is the probable source of the outbreak (if known)?
[consider epidemiological information, trace back results, food/environmental sampling results?]

Is there likely to be on-going exposure?
[are cases still being reported? Is product likely to still be in the marketplace? Is the restaurant still serving high risk food?]

Are cases confined to South Australia?
[Is this a possible multi-jurisdictional outbreak?]

Context assessment

Are there any factors about the event that might be associated with the environment, behaviours, social or cultural practices?
[is there any particular cuisine being consumed or cultural group affected?]

Are vulnerable populations affected?
[are cases occurring in an aged care facility, child care centre, hospital etc?]

What is the likelihood that all suspected cases will be identified?
[is the event likely to get bigger? Do we need to consider active case finding?]

Are there sufficient resources to respond?
[are their sufficient human resources and laboratory capacity available to respond?]

Are there any political sensitivities?
[media etc.]

Overall assessment

[Mark the appropriate box below]

Mark	Level of overall risk	Actions
	Low	Managed according to standard response protocols between the two primary investigators (in consultation with team managers)
	Moderate	Consider outbreak meetings and preparation of situation reports. Ensure Directors are informed.
	High	Convene outbreak meetings, prepare situation reports and inform Directors. Outbreak meetings will be held as required by the team, but with a minimum of weekly.
	Very high	Daily outbreak meetings, daily situation reports with distribution to CPHO, legal, media and communications

4. Actions

a. From rapid risk assessment

(*e.g. assigning actions to fill any gaps in evidence such as literature review about the pathogen etc.)*

b. Further investigations

i. Epidemiological

Options include: obtain medical notifications for cases with pending typing, continue hypothesis generating interviews, move to analytical epidemiological study.

ii. Microbiological

Options include: request samples, request further typing at reference laboratory

iii. Environment and food chain

Options include: traceback, sampling plan (include numbers of samples, types of samples), correspondence with Local Govt/regulators, correspondence with Food Business.

c. Control measures

5. Communications

People/organisations	Yes/No/NA	Person responsible/method
Situation Report		
Branch Directors		
CPHO/CMO		
Minister		
Media /communications unit		
Legal		
Public		
Healthcare providers		
Local Government EHOs		
National bodies (OFN/NFIRP/ CDNA/AHPPC/BFSN)		
Others (specify)		

6. Assess outbreak status

i. Monitor/ Escalate/ Stand Down

7. Next Meeting

(Date, time, location)

8.5. Supplemental materials chapter 7

The following documents are associated with chapter 7 entitled “Summary of peer-to-peer teaching and learning experience”:

Public appendix

This appendix contains the following documents:

- Worksheet with model answers for the LFF ‘Causal Diagrams in Epidemiological Research’
- Table 1: Peer evaluation of the LFF ‘Causal Diagrams in Epidemiological Research’
- Presentation on logic models for public health program evaluation given as part of part of the teaching session for the 2018 MAE cohort, 9 March 2018

Confidential appendix

The confidential part of the appendix contains a presentation on spatial mapping of health information given as part of the ‘Issues in Applied Epidemiology’ course, 8 March 2018

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

Jana Sisnowski

This LFF will take place in person at 6pm on Wednesday, 7th March 2018 at Liversidge Court. If you have trouble finding us on the day, please give me a call on 0481318214.

Please return your answers by Monday, 5 March 2018 to jsisnowski@kirby.unsw.edu.au.

1. Background

This LFF aims to explore some of the issues associated with causal inference from a non-mathematical perspective. To this end, it introduces causal diagrams and shows how a type of causal diagram approach called Directed Acyclic Graphs (DAGs) can help us to think more systematically about research design and data analysis.

Conceptually, causal inference refers to the process of drawing conclusions about causal relationships from statistical associations. Yet, statistical methods commonly used in epidemiology only provide information about associations observed in a specific dataset, i.e. variable **A** varies in a specific pattern with variable **B**. Additional information are needed to inform decision-making at the study design stage, e.g. which variables to collect and include in the statistical analysis, and to provide an interpretation of statistical results that is valid and relevant to public health practice.

2. Learning objectives

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

- Explain different conceptualisations of causation in epidemiological research.
- Apply the principles of DAGs to help inform the planning and analysis of epidemiological studies.
- Use the DAGitty tool to draw a basic DAG of a research question.

3. Pre-readings

Please have a read through the following resources which will help you answer the questions in subsequent sections of the worksheet:

1. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48. Read only p. 37-41 (up to "Stratification under a multiplicative model").
2. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. American Journal of Epidemiology. 2002;155(2):176-184.

3. Additional resources

Another great introduction to the topic is provided in the 'Modern Epidemiology' textbook which many of you have on your bookshelves. If you are interested in the mathematical translation and statistical application of some of the concepts introduced here, have a look at the paper by Pearl:

1. Glymour MM, Greenland S. Causal Diagrams. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 183-209.
2. Pearl J. Causal inference in statistics: An overview. Statistics Surveys. 2009;3:96-146.

Also, this free MOOC course may be worth a look.

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

Jana Sisnowski

Part 1: Recapping causation

Instructions: This section briefly revises the concept of causation in epidemiological research. Although the pre-readings may help you answer the questions below, these are mainly intended to reflect your own experiences with epidemiological questions across a range of disease areas.

Question 1: Based on your own experiences and the readings, what broad types of causes of disease and ill health do epidemiological studies investigate? Also take into account scenarios outside the infectious disease setting (e.g. social epidemiology, environmental epidemiology etc.).

Epidemiological studies investigate a broad range of predictors of disease and health states. This may include risk factors such as pathogens, genetics, behaviours, environmental exposures, or social determinants. Program evaluations studies may also look at interventions aimed at changing health outcomes. The outcomes of interest may be any measure of health and well-being, e.g. communicable diseases, non-communicable diseases, accidents and injuries, birth defects, summary indicators of population health such as life expectancy or healthy life years, or even patterns of health service access.

Question 2: In two sentences or less, how would you explain the difference between causation and association in epidemiological studies?

Association is a statistical measure that quantifies the correlation between two variables, i.e. the pattern in which variable *a* varies with variable *b*. Causation, or the presence of a cause-effect relationship between two variables, means that one state or event is the result of the other one occurring. The assessment of causation requires further investigation to provide evidence that an observed statistical association is not merely due to bias, confounding, or chance. Indicators drawing on multiple sources and types of information to establish causation such as the Bradford-Hill criteria are useful to assess whether statistical association is indicative of an underlying causal relationship.

Question 3: What type of epidemiological studies benefit most from the explicit, a priori explanation of assumptions and hypotheses that causal diagrams allow?

Observational studies are the study design for which DAGs are considered most useful. The reason for this is that observational studies have a limited ability to minimise confounding and bias through study design features that are cornerstones of RCTs, such as randomised allocation to the exposure of interest. Consequently, a comprehensive assessment of potentially confounding variables and explicit a priori statements about causal hypotheses help address the shortcomings of observational studies and to minimise the chance of 'data dredging' turning up statistical associations that were not investigated nor based on plausible causal hypotheses.

Conceptually, DAGs are grounded in the counterfactual or potential outcomes model of causation. The counterfactual approach asks what would have happened to a single individual had the exposure of interest not occurred, essentially going back in time to isolate the causal effect of one exposure, all other things being equal. RCTs come closest to this conceptual ideal of interchangeable exposed and unexposed populations by virtue of randomisation and investigator control of potentially confounding factors, whereas observational studies rely on control through statistical analysis.

Jana Sisnowski

Question 4: When designing an epidemiological study, how do you decide which variables to collect as exposures of interest and/or potential confounders? What sources of information would you use to make these decisions?

Ideally, any epidemiological study will include a systematic review of the literature to assess the extent of current and emerging knowledge about the causal relationships of the exposure and outcome of interest with other factors. In addition, expert opinion may be sought to further explore particular aspects of causal hypotheses and alternative conceptualisations of causal relationships that may have a bearing on study design and data analysis decisions. This a priori approach stands in contrast to common statistical approaches to confounder identification which rely on the designation of variables as confounders based on the change in observed associations when variables are added or removed.

Question 5: Why might it be beneficial to include variables in a causal diagram that cannot be observed or at least remain unmeasured in a specific study?

Variables that can't be measured and therefore can't be included in a statistical analysis may still influence the association between the main exposure of interest and the outcome. Including these variables in a DAG makes any potential unmeasured confounding or bias explicit and helps with the interpretation of results.

Part 2: Directed Acyclic Graphs (DAGs)

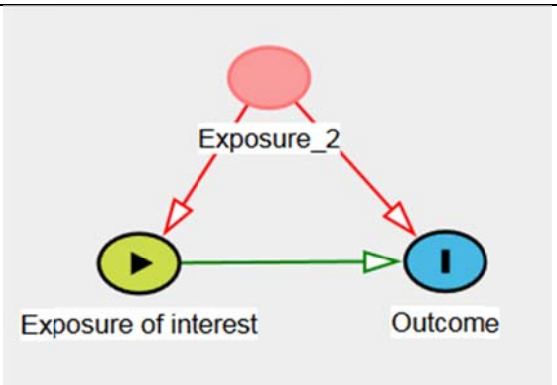
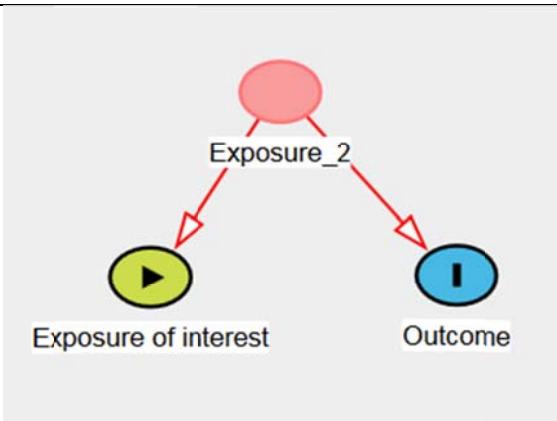
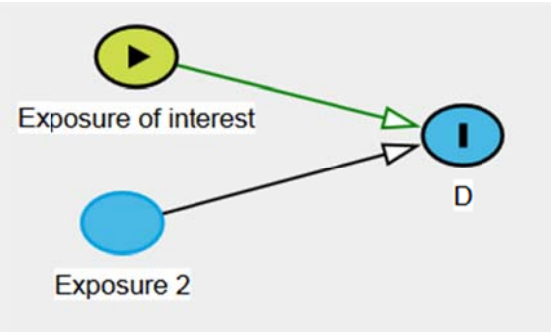
DAGs are causal diagrams that are drawn and interpreted according to set conventions. DAGs consist of the variables of interest, known as nodes, and arrows which indicate causal direction. Nodes include the outcome of interest, the exposure of interest, and any potential covariates. Paths are formed by a suite of nodes connected by arrows, regardless of which direction the arrows point into (i.e. they do not all need to point in the same direction; if they do the path is called a directed path that denotes a causal connection).

There are a few basic rules that apply to DAGs (figure numbers refer to the row numbers in the table overleaf on page 3):

- Arrows between nodes are unidirectional, i.e. each arrow can only have one head.
- As the name indicates, the graphs are acyclic. That is, nodes can't be connected back to themselves along causal paths, as this would lead to the circular logic of a variable causing itself.
- The exposure of interest is the variable for which we want to measure an unconfounded effect on the outcome.
- Confounders are causally related to both the exposure of interest and the outcome. Open backdoors paths visually represent confounding: a path that starts with an arrow pointing towards the exposure of interest and ends with an arrow pointing towards the outcome (Figures 2 & 3).
- Colliders are a concept that is unique to DAGs. A collider is a variable that is directly affected by two to other variables on a causal path. Visually, this means that there are at least two arrows going into the node (Figure 4). Colliders block a causal path. This means that any variables on the blocked path are not connected unless the collider is being taken out of the equation by being adjusted for.

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

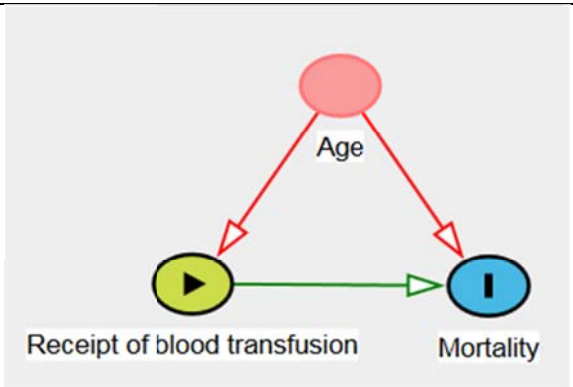
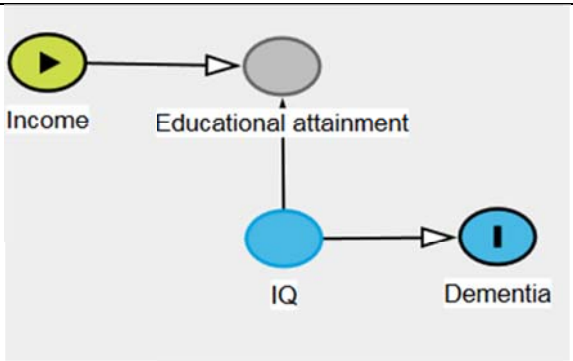
Jana Sisnowski

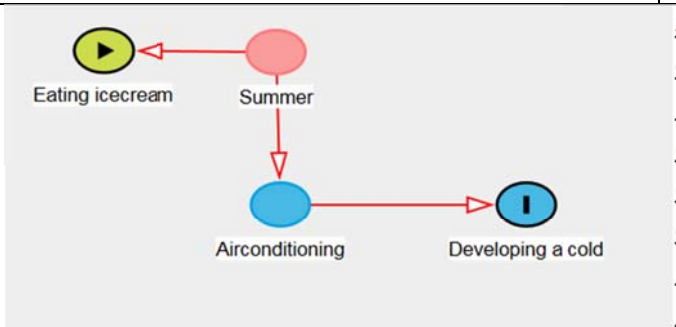
	DAG	Causal relationships shown & expected associations
1.		The exposure causes the outcome. Conversely, the lack of an arrow indicates the absence of a causal connection. The exposure is expected to be statistically associated with the outcome.
2.		Exposure 2 affects both the outcome (directly and indirectly) and the exposure of interest. The exposure of interest causes the outcome. The exposure of interest is expected to be statistically associated with the outcome. Exposure 2 is expected to be associated with the exposure of interest and the outcome. If exposure 2 was adjusted for, the observed association between the exposure of interest and the outcome would be reduced to the effect of the exposure of interest on the outcome.
3.		Exposure 2 causes both the exposure of interest and the outcome. The exposure of interest does not cause the outcome. Exposure 2 is expected to be associated with the exposure of interest and the outcome. The exposure of interest is expected to be associated with the outcome. If exposure 2 was adjusted for, the exposure of interest would not be expected to be associated with the outcome.
4.		The exposure of interest is causally related to the outcome and exposure 2 is causally related to the outcome. In this case, the outcome is a collider which blocks the potential path from the exposure of interest to exposure 2.

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

Jana Sisnowski

Task 1: Following the model above, back-translate the relationships shown in the following DAGs into causal statements and expected associations.

	DAG	Causal relationships shown	Expected associations (prior to any adjustment)
1.		Age causes mortality both directly and indirectly through the receipt of blood transfusion. The receipt of blood transfusion directly affects mortality.	Age is expected to be associated with receipt of blood transfusion and receipt of blood transfusion is expected be associated with mortality. Age is also expected to be associated with mortality, but from two sources: indirectly through its effect on receipt of blood transfusion and directly. Prior to adjustment for age, the association between receipt of blood transfusion and mortality is partially confounded by age. If age was adjusted for, the observed association between receipt of blood transfusion and mortality would be reduced to the effect of receipt of blood transfusion on mortality.
2.		Income directly affects educational attainment. IQ directly affects educational attainment and development of dementia. Income is not causally related to development of dementia.	Income is expected to be associated with educational attainment. IQ is expected to be associated with educational attainment and developing dementia. The path from income to dementia is blocked by a collider, the variable educational attainment. Income is therefore not expected to be statistically associated with development of dementia unless the model is adjusted for educational attainment which would

			open up the backdoor path from income t o dementia.
3.		Summer directly affects icecream consumption and air-conditioning usage. Summer affects the risk of developing a cold only through its effect on air-conditioning use. Air-conditioning usage directly affects the risk of developing a cold. Eating icecream is not causally related to developing a cold.	The use of air-conditioning is expected to be statistically associated with the risk of developing a cold. Summer is expected to be associated with eating ice cream and air conditioning use. Eating icecream may be statistically associated with the risk of developing a cold due to the open backdoor path between eating icecream and developing a cold. This path is not directed (the arrows in the sequence point into different directions) and it is therefore not causal. As a result, any statistical association would be due to confounding that can be eliminated by adjusting for summer and thereby blocking the path.

Question 6: In example 2, what would happen with regard to statistical associations between the exposure of interest and the outcome if you adjusted for education?

In this example, educational attainment is a collider, i.e. a variable with two arrows pointing towards its node. The collider blocks the potential path from exposure to outcome. As a result, adjusting for educational attainment would open up a non-causal path between income as the exposure of interest and dementia as the outcome. After adjustment, the statistical analysis may therefore show an association between income and developing dementia that does not fit with the causal assumptions shown in the original DAG.

Question 7: At what stages of epidemiological research might DAGs be useful?

DAGs can be useful at all stages of epidemiological research: at the conception and planning stage, DAGs can inform decisions about the hypothesis to be tested, which variables should be collected and how they should they be coded. DAGs can also facilitate discussions about alternative study design options that conceptualise causal hypotheses differently. During the statistical analysis phase, DAGS may serve to evaluate potential confounding and help make decisions about adjustments. In addition, DAGs can be a useful communication tool at any stage of a project, but particularly at the dissemination stage when study premises and assumptions need to be me made clear to external audiences.

Question 8: What are some of the aspects of causal assumptions that DAGs cannot tell us?

The following aspects of causal hypotheses are not covered by DAGs:

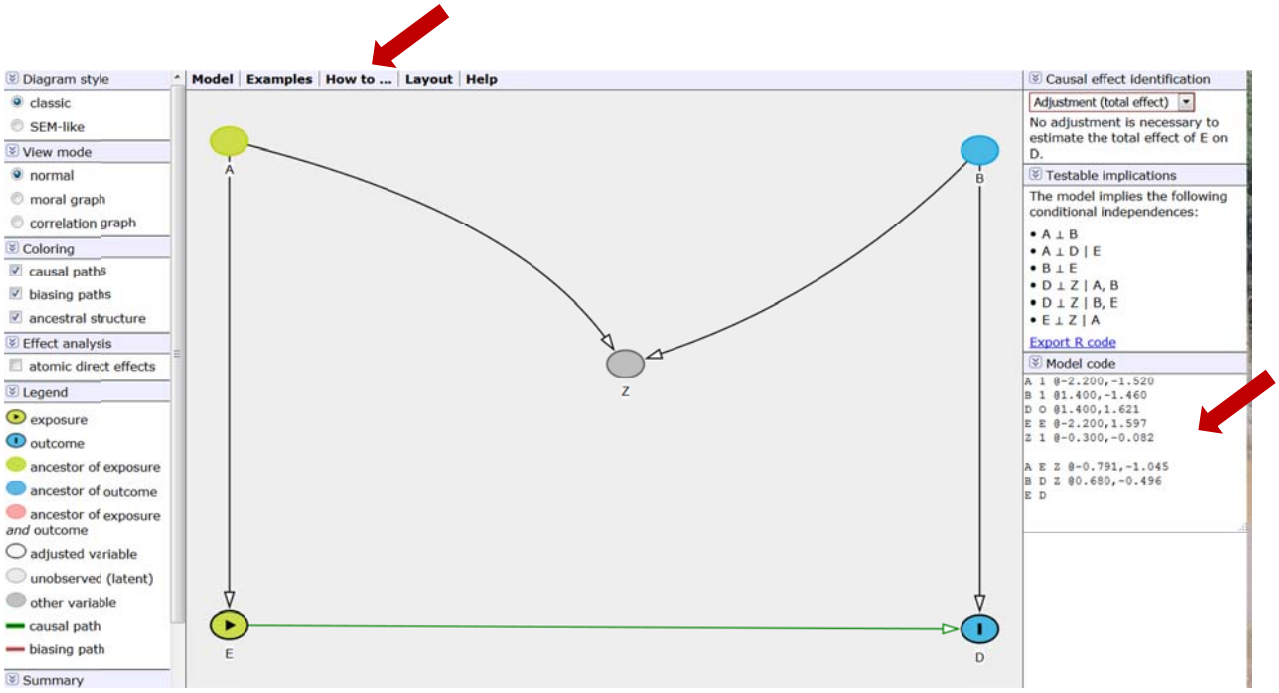
- Strength of the expected association
- Nature of the effect (disease-causing or protective)
- Sources and quality of the information used to make causal assumptions
- Any measure of time
- Any parametric assumptions
- Measurement of variables could potentially be added (e.g. BMI as a measure of obesity), but may not be included if the DAG is purely conceptual.

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

Jana Sisnowski

Part 3: DAGitty - drawing and analysing DAGs

Instructions: This section is an opportunity to try out the DAGitty program, a web-based software that allows the user to develop and export DAGs (and which is also quite useful for drawing more complex logic models). This link should open the program in your browser window. The "How to…" tab gives you all the information you need to construct a basic DAG. You can simply take a screenshot of your DAG using the screenshot function of your computer or the snipping tool (type "snipping" in the search box on the taskbar) and paste it into this document. If you want to save your DAG in an editable format, copy and paste the model code on the right hand side into a Word document and put it back into the box if you want to make any changes.



Now that you are familiar with the DAGitty tool, consider the following scenario: You are the only MAE scholar currently working in a small state where a large majority of the population lives along the coast. A recent spate in shark sightings and a series of fatal and near-fatal shark attacks has prompted a public outcry about a sudden increase in risk and effective countermeasures. Due to the recent gutting of the Department of the Environment's data section, the Department of Health has been asked for assistance and you've been volunteered to help with a preliminary investigation. Pick one main factor (''exposure'') that may be responsible for the increase in shark attacks observed and consider a study that would attempt to measure the unconfounded effect of this factor on the outcome.

MAE Lesson from the Field - Causal Diagrams in Epidemiological Research

Jana Sisnowski

Task 2: Use DAGitty to draw a basic DAG of the assumptions and hypotheses underpinning your research question/study and paste your diagram into the text box below.

No one model answer.

Question 9: Using the DAG you developed, explain if there are any variables that you would adjust for in your statistical model to measure the independent association of the main exposure of interest on the number of shark attacks observed?

No one model answer- examples may include classical confounders such as the season of the year being associated both with the likelihood of swimming in the ocean and the likelihood of a shark attack being reported. Note that ancestors of an exposure (nodes that are only connected to one other exposure are not adjusted as they are not confounding any causal relationship.

Table 1: Peer evaluation of the LFF ‘Causal Diagrams in Epidemiological Research’

	Strengths	**Weaknesses**	**Practical usefulness**
Respondent 1	• It reminded me about DAGs and the uses for them. I learnt about these years ago but never truly understood them, this was a good refresher. • Jana was able to explain each type of DAG well and relatively simply. She has a good understanding of the topic. • I was introduced to the DAGitty tool.	I think Jana chose a difficult topic to tackle in a short session. I found the lesson a bit complex however this was overcome during the actual LFF meeting/teleconference when we could discuss the concepts in greater depth.	I have not yet used DAGs in my MAE however I will definitely consider them when designing a study in the future.
Respondent 2	• Fantastic topic! • Jana facilitated discussions well • Covered key epidemiological concepts of confounding and causation • The practical examples were really good to check understanding • Using DAGitty was lots of fun and made me aware of a really useful software tool	It may be useful to provide a worked through example of a DAG with a collider as I got a little confused interpreting DAG no. 2 in part 2 task 1, but Jana explained it really well during the LFF.	This LFF was very useful as using DAGs will be very helpful in planning out projects (considering confounders) and considering what needs to be adjusted for during analysis, I will definitely be using DAGs for some of my projects.
Respondent 3	• A well organised and clearly presented LFF. • The LFF consolidated our understanding of; the types of causes of disease and ill health, the difference between	N/A	In my MAE placement [...], DAGs are often used by colleagues when discussing articles at the Epidemiology Journal Club and I feel I will have a better understanding of how the

	Strengths	Weaknesses	Practical usefulness
	causation and association in epidemiological studies and various approaches to identifying confounders. • The pre-readings were clearly referenced, and Jana also provided additional resources, including a free on-line course, to enable us to gain a more in-depth understanding of the topic. • This LFF was my first opportunity to use Directed Acyclic Graphs (DAGs) and the DAGitty software program • Whilst I found the readings to be quite a lot of information to absorb, Jana's explanations and diagrams in Section 2 of the LFF aided my understanding of the basic concepts. • I liked that we were able to apply the DAG concepts in task 1 where we interpreted DAGs and in part 3 using the DAGitty tool.		epidemiological studies can be explained in this way in the future.
Respondent 4	The LFF was the most challenging, and also the most rewarding to review and learn. The concept is completely new to me. I had no experience with DAGs prior to the LFF. I appreciate the usefulness of	The LFF required a little more time and additional sessions. In saying this, having a face-to-face session enabled useful and interesting discussions.	Following [the LFF], I have spent additional time reviewing and learning further about this area, highlighting the positive impact this LFF had on my learning and development. I applied DAGs to one

Evaluating complex public health interventions

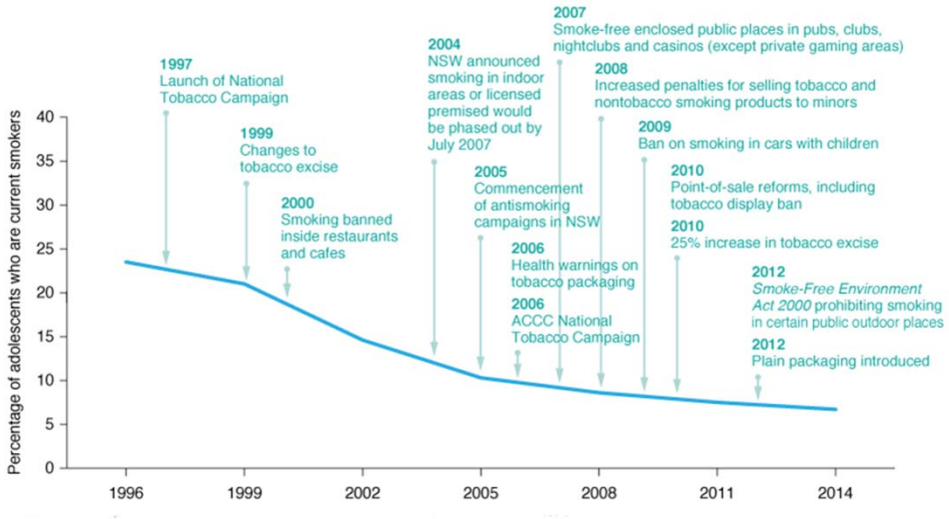
Cushla Coffey, Bobby Maher & Jana Sisnowski (MAE '17)

Learning objectives

- Describe the components of a logic model
- Apply a logic model to a given public health intervention
- Explain the challenges of capturing different aspects of complex public health interventions

2

Public health interventions creating impact…



3

Source: Dessaix et al. (2016).

… and having unintended consequences

Articles

Efficacy of infant simulator programmes to prevent teenage pregnancy: a school-based cluster randomised controlled trial in Western Australia

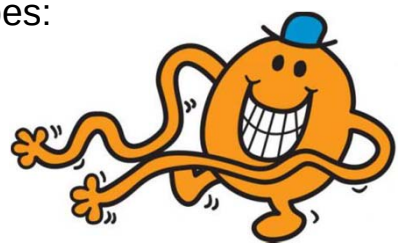
"The infant simulator-based VIP programme did not achieve its aim of reducing teenage pregnancy. Girls in the intervention group were more likely to experience a birth or an induced abortion than those in the control group before they reached 20 years of age."

4

Source: Brinkman et al. (2016).

Challenges of public health interventions

- Beholden to policy cycles
- Often not trialled first
- Choice of evaluation types:
  - Formative evaluation
  - Process evaluation
  - Outcome evaluation
  - Impact evaluation
  - (Health) economic evaluation
  - Realist evaluation



5

Logic Model

Impact

Long-term, sustained benefits

6

Logic Model

Impact

Long-term, sustained benefits

Inputs

Resources required

7

Logic Model

Impact

Long-term, sustained benefits

Inputs

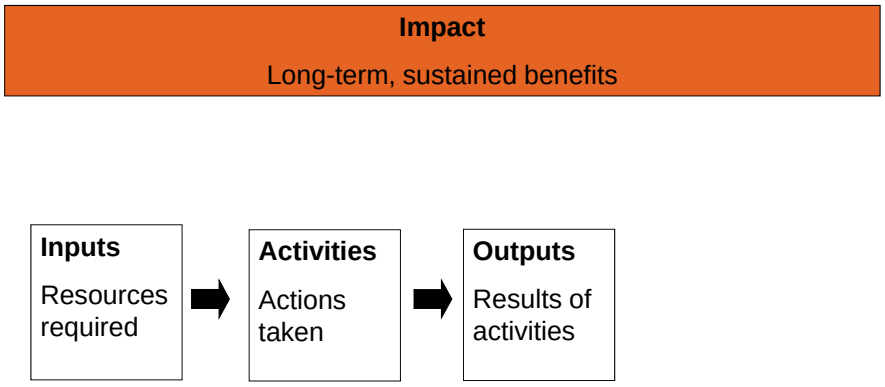
Resources required

Activities

Actions taken

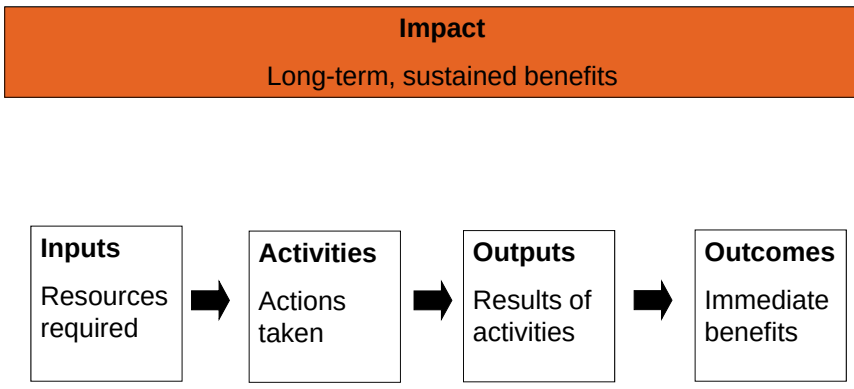
8

Logic Model



9

Logic Model



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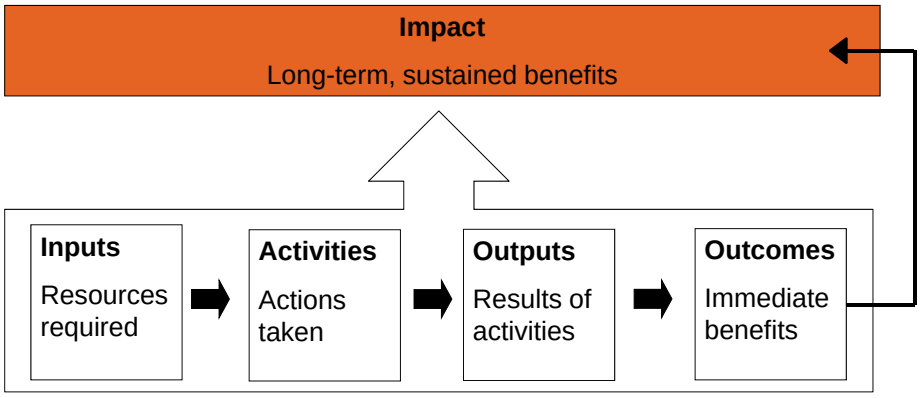
Logic Model



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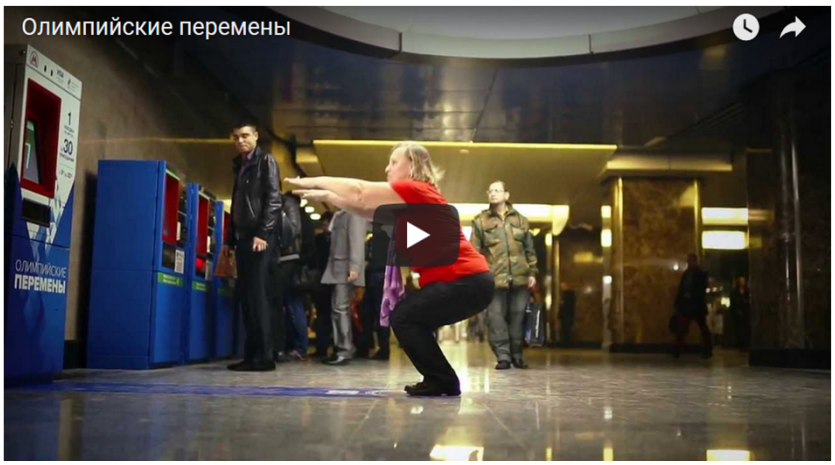
Group activity: building a logic model

In Russia, 30 squats get you a subway ticket



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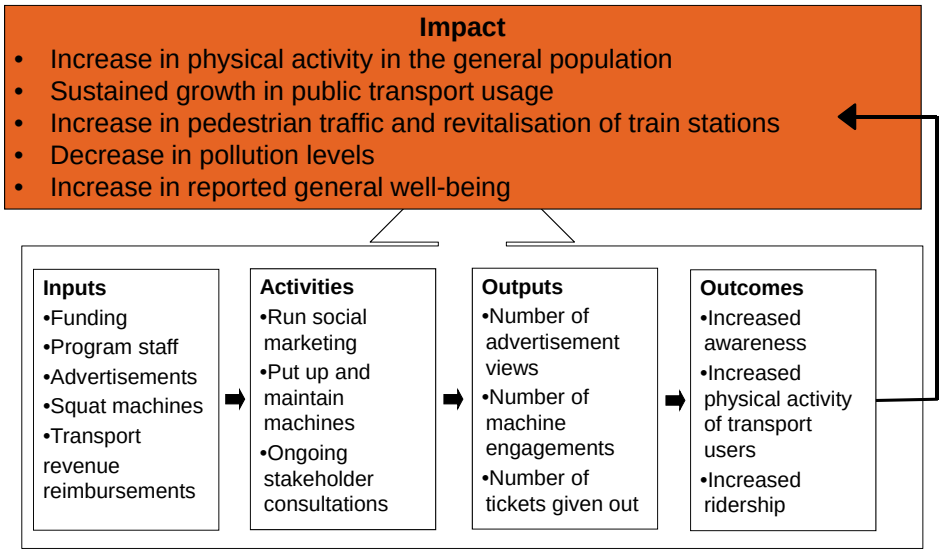
Source: https://www.wired.com/2013/11/squats-train-ticket/

Logic Model



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Additional Resources

1. US Centers for Disease Control and Prevention. (2011) Introduction to Program Evaluation for Public Health Programs: A Self-Study Guide. Available from: https://www.cdc.gov/eval/guide/
2. Bamberger, M. et. al. (2004) Shoestring Evaluation: Designing Impact Evaluations under Budget, Time and Data Constraints. American Journal of Evaluation; 25(1):5-37.
3. Johns Hopkins University. (2006) Fundamentals of Program Evaluation. Available from: http://ocw.jhsph.edu/index.cfm/go/viewCourse/course/FundamentalsProgramEvaluation/coursePage/index/

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