Surveillance and Burden of Infectious Diseases in Australia

Dr Katherine Beverley Gibney

MBBS (Hons), MPH, FRACP, FAFPHM

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Department of Epidemiology and Preventive Medicine

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Abstract

***Background*:** The epidemiology and comparative burden of communicable diseases determines which diseases warrant public health resources and intervention. Public health surveillance data are useful but are affected by variable case ascertainment. Disability Adjusted Life Years (DALYs) better define the population burden of diseases accounting for both morbidity and mortality.

***Methods*:** Infectious disease notification practices in Victoria were examined using case notification data from 2013. Data for all nationally notifiable diseases were used to evaluate the first 21 years (1991–2011) of the National Notifiable Diseases Surveillance System (NNDSS) and the epidemiology of nationally notifiable diseases. The impact of socioeconomic disadvantage and remoteness of residence on notification incidence was examined nationally, while Indigenous status was examined in three jurisdictions with completeness of Indigenous status reporting >75% (the Northern Territory, South Australia and Western Australia). Disease burden was estimated and compared for six common gastrointestinal pathogens (campylobacteriosis, salmonellosis, cryptosporidiosis, giardiasis, rotavirus, and norovirus) in Australia in 2010 using: number of cases, number of deaths, and DALYs. Post-infectious sequelae were incorporated into DALY estimates for campylobacteriosis and salmonellosis.

***Results*:** Almost half (49%) the cases notified in Victoria in 2013 were notified by laboratory report alone. Indigenous status was complete for 48% of notified cases, with higher completion of Indigenous status among doctor-notified cases, diseases with active case follow-up, and priority diseases for Indigenous status reporting. Nationally, the number of notifiable conditions increased from 37 to 65 from 1991 to 2011, with 2.4 million cases

notified to NNDSS. An increasing proportion of cases were diagnosed by PCR, while data completeness and notification timeliness improved. The 10 highest notification incidence conditions (chlamydial infection, campylobacteriosis, varicella zoster, hepatitis C, influenza, pertussis, salmonellosis, hepatitis B, gonococcal infection, and Ross River virus infection) comprised 88% of all notifications. Annual notification incidence increased 6·4% per year (12% for sexually transmissible infections and 15% for vaccine preventable diseases). Notification incidence was higher for Indigenous, remote-living and socioeconomically disadvantaged Australians; overall, these inequities lessened over the study period. An estimated 16.6 million acute gastroenteritis (AGE) cases occurred in Australia in 2010 (including undiagnosed community cases), with the most AGE cases attributed to norovirus (2,180,145), most deaths to salmonellosis (90), and most DALYs to campylobacteriosis (18,222). Inclusion of irritable bowel syndrome increased the DALY estimate for campylobacteriosis more than four-fold.

***Conclusions*:** The NNDSS expanded over its first 21 years including a greater number of notifiable conditions and notifications received. Changing testing practices and laboratory-only notifications have impacted notification practices. A nationally integrated electronic surveillance system, including electronic laboratory reporting, would further improve infectious diseases surveillance in Australia. Inadequate completeness of Indigenous status needs urgent attention, as does reducing the identified health inequities. The choice of burden of disease metric influenced the ranking of pathogens. Data on post-infectious sequelae is lacking for many gastrointestinal pathogens and their inclusion can profoundly influence DALY estimates. Routinely collected surveillance data and more detailed DALY estimates can both be used to prioritise diseases and populations for public health action and to assess the effectiveness of these interventions.

Publications during enrolment

Publications related to this thesis

Gibney KB, Cheng AC, Hall R, Leder K. Sociodemographic and geographic inequalities in notifiable communicable diseases in Australia: An analysis of 21 years of national disease surveillance data. Lancet Infect Dis 2016 [*in press*]

Gibney KB, Franklin L, Stephens N. Infectious diseases notification practices, Victoria 2013. Commun Dis Intell, 2016. 30(3) [*in press*].

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Publications arising from my collaboration with the Global Burden of Disease Study

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Thesis including published works general declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published or accepted for publication in peer reviewed journals, and one publication undergoing peer review (resubmitted following initial peer review). The core theme of the thesis is surveillance and burden of infectious diseases in Australia. The ideas, development and writing of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Epidemiology and Preventive Medicine, Monash University under the supervision of Professor Karin Leder.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2 to 6 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent (%) of students contribution
2	Infectious disease notification practices in Victoria, 2013	Accepted	Katherine Gibney – Study design, data cleaning and analysis, preparation of draft manuscript, preparation of manuscript for submission (80%) Nicola Stephens – Revision of manuscript (10%)
2	Australia's National Notifiable Diseases Surveillance System 1991–2011: Expanding, Adapting and Improving	Re-submitted following revision	Katherine Gibney – Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission (80%)
3	An overview of the epidemiology of notifiable infectious diseases in Australia, 1991–2011	Published	Katherine Gibney – Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission (80%)
4	Socio-demographic and geographic inequalities in notifiable communicable diseases in Australia: An analysis of 21-years of national disease surveillance data	Accepted	Katherine Gibney – Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission (80%)
5	Disease burden of selected gastrointestinal pathogens, Australia, 2010	Published	Katherine Gibney – Literature review; data sourcing, collation and analysis; drafting manuscript; preparation of manuscript for submission (70%)
6	Using disability-adjusted life years to set health-based targets: A novel use of an established burden of disease metric	Published	Katherine Gibney – Study concept; drafting manuscript; preparation of manuscript for submission (80%)

I have renumbered sections of submitted or in-press manuscripts in order to generate a consistent presentation within the thesis. I have not renumbered sections of published papers.

Student signature:  Date: 11th July, 2016

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature:  Date: 11th July, 2016

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Abbreviations

ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
AGE	Acute gastroenteritis
AHPPC	Australian Health Protection Principal Committee
AIDS	Acquired immunodeficiency syndrome
AMR	Anti-microbial resistance
BBVH	Blood-borne viral hepatitis
CDC	Centers for Disease Control and Prevention
CDNA	Communicable Diseases Network Australia
CEA	Cost effectiveness analysis
DALY	Disability adjusted life years
DH	Department of Health, Victoria (more recently renamed DHHS – see below)
DHHS	Department of Health & Human Services, Victoria
GBD	Global burden of disease
GBS	Guillain-Barré syndrome
GDP	Gross domestic product

GP	General practitioner
HBT	Health based target
HCC	Hepatocellular carcinoma
Hib	*Haemophilus influenzae* type B
HIV	Human immunodeficiency virus
HREC	Human research ethics committee
HUS	Haemolytic uraemic syndrome
IBS	Irritable bowel syndrome
ICER	Incremental cost effectiveness ratio
IPD	Invasive pneumococcal disease
MBS	Medicare benefits scheme
MERS	Middle Eastern respiratory syndrome
NHMRC	National Health and Medical Research Council
NIP	National immunisation programme
NNDL	National notifiable diseases list
NNDSS	National notifiable diseases surveillance system
NSW	New South Wales
NT	Northern Territory

PBAC	Pharmaceutical benefits advisory committee
PBS	Pharmaceutical benefits scheme
PCR	Polymerase chain reaction
PHESS	Public health event surveillance system
PHLN	Public Health Laboratory Network
PI-IBS	Post infectious irritable bowel syndrome
QALY	Quality adjusted life years
ReA	Reactive arthritis
SA	South Australia
SARS	Severe acute respiratory syndrome
STEC	Shiga-toxin producing *Escherichia coli*
STI	Sexually transmissible infections
UK	United Kingdom
US	United States
VPD	Vaccine preventable diseases
WA	Western Australia
WGS	Whole genome sequencing
WHO	World Health Organization

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Chapter One: Introduction, thesis rationale and thesis outline

1.1 Introduction

In high income countries (i.e. those with a high gross domestic product [GDP]) the population generally has a longer life expectancy, and a smaller proportion of all deaths are attributable to infectious diseases.[1] Australia is a developed country with many factors contributing to effective control of infectious diseases, including high living and education standards, accessible and advanced health systems, and robust public health initiatives, such as a comprehensive publicly funded vaccination program. As a result, Australia falls in the group of countries with highest GDP, longest life expectancy, and lowest fraction of deaths from infectious diseases. Despite this, communicable diseases continue to pose a health and economic threat even in Australia. Notification incidence of certain common diseases is increasing (e.g. salmonellosis and chlamydial infection), other diseases are emerging or re-emerging within Australia (e.g. syphilis and Hendra virus), while others have emerged internationally with as-yet no local transmission (e.g. Ebola, Middle Eastern respiratory syndrome [MERS], Zika, and pandemic influenza viruses – Figure 1.1).

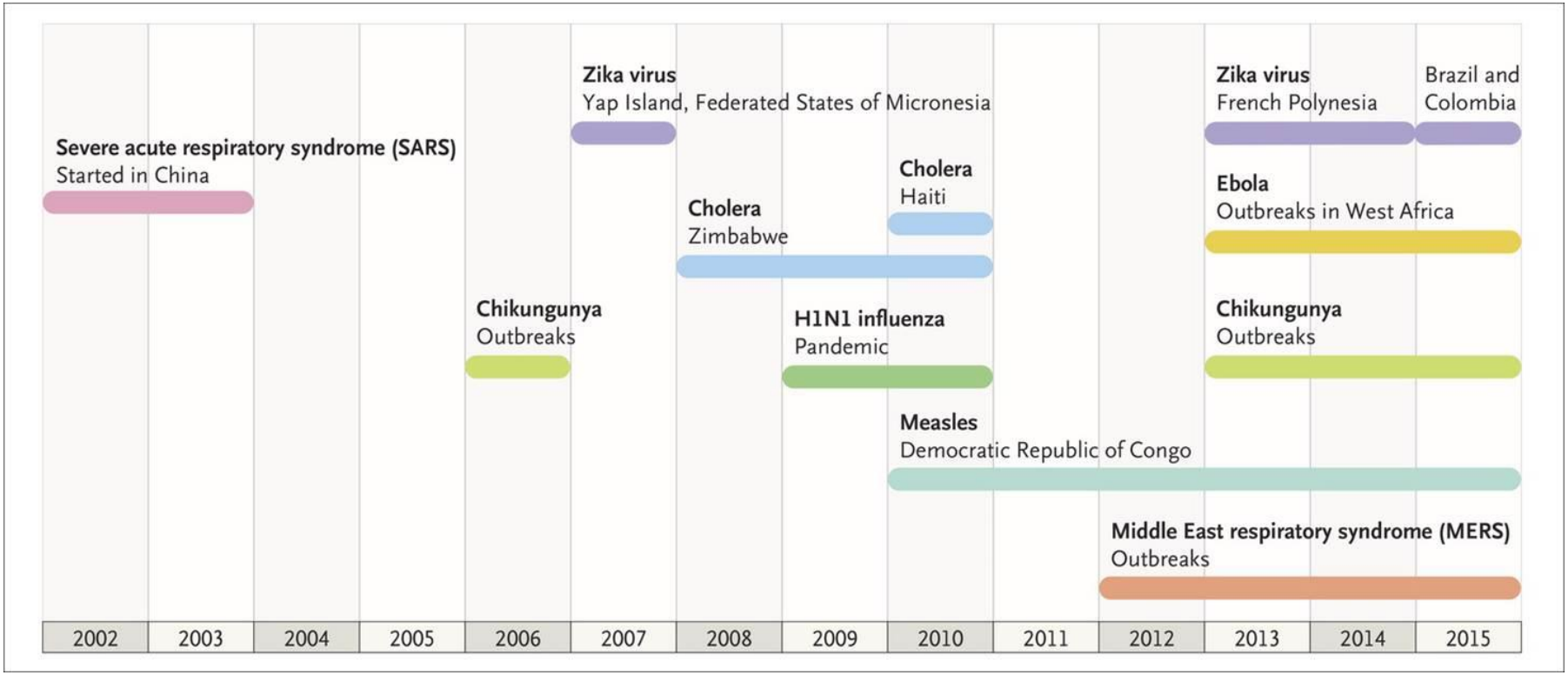

Figure 1.1: Major emerging and re-emerging infectious disease outbreaks, epidemics and pandemics, 2002–2015.

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The health, social and economic burden of infectious diseases can be extreme. It has been estimated that in the 1918–19 Spanish influenza pandemic, 40% of Australia's population were infected (two million out of a total population of five million) with 15,000 deaths.[3] In 2008 the World Bank estimated that a severe influenza pandemic could result in 71.1 million deaths and US$3 trillion in global economic losses, equivalent to 4.8% of GDP.[4] Modelling from Harvard University predicts an average annual loss to the global economy of US$63.7 billion (more than US$6 trillion per century) as a result of future pandemics, with a 10% chance that the average annual loss could exceed US$124 billion.[5] The 2014–15 Ebola virus epidemic in West Africa was perhaps the most dramatic example of the contemporary threat of emerging infectious diseases. By the end of March 2016, there had been 28,646 cases of Ebola virus disease, 11,323 deaths, and more than 10,000 survivors of Ebola virus disease in West Africa.[6] The World Bank estimates the three countries most affected by the recent Ebola epidemic – Guinea, Liberia and Sierra Leone – would lose at least US$2.2 billion in foregone economic growth in 2015 as a result of this epidemic.[7] The World Bank's *Economic Impact of Ebola* survey demonstrated that nearly half (48%) of Liberians employed before the epidemic were unemployed at the peak of the epidemic (58% in urban areas).[8] In response to this disaster, in 2015, the Commission on a Global Health Risk Framework for the Future was founded. A key area of recommendation in the Commission's report was "strengthening public health as the foundation of the health system and first line of defense".[2] A core component of this is effective infectious disease surveillance, with early action potentially preventing development of epidemics and pandemics. Infectious diseases epidemiology – including public health surveillance and burden of disease estimates – underpins effective communicable disease control throughout the world, including Australia.

1.1.1 Public health surveillance

Public health surveillance, referred to as "the cornerstone of public health",[9] has a history dating back to ancient Egyptian times.[10] In the 19th century, William Farr, the "founder of modern concepts of surveillance" developed a system to collect, analyse and widely report mortality and cause of death data in Britain.[10, 11] The International Sanitary Regulations, covering aspects of quarantine for selected diseases including plague and cholera, represent another system of surveillance developed in 19th century Europe.[12] This was mirrored in the United States (US) when an act of Congress in 1878 authorised the Public Health Service to collect morbidity reports for cholera, plague, smallpox, and yellow fever to inform quarantine measures.[13] A national public health surveillance system was introduced in the US in the mid-20th century by Alexander Langmuir to fulfil the function of the newly established CDC (Centers for Disease Control and Prevention, originally called the Communicable Disease Center) to assist the states with control of infectious diseases of national importance. He defined disease surveillance as "the continued watchfulness over the distribution and trends of incidence" of a disease.[14] He identified three components of an effective surveillance system: 1) systematic data collection; 2) consolidation and evaluation of these data; and 3) prompt dissemination of results (basic data and interpretations) to all who needed to know and to all who provided the data. The concept of public health surveillance quickly gained international acceptance and was endorsed as an essential function of public health practice by the World Health Organization (WHO) in 1968.[10, 12] A technical report of discussions at the 21st World Health Assembly in 1968 notes the following:[12]

- Effective public health surveillance involved the continuous observation of incidence of laboratory confirmed disease as well as effectiveness of control measures, vaccination coverage, distribution of vectors and their susceptibility to insecticides.

- Adequate laboratory capacity is required to support an effective surveillance system, and "all diagnostic laboratory services connected with acute communicable diseases should be available free of charge."
- Assessment and evaluation is essential to gauge the reliability of the surveillance system.
- The purposes of research and surveillance are distinct: "Research seeks new knowledge from which better control measures may develop, whereas surveillance centres on the application of existing knowledge to control."

The global benefits were demonstrated through the pivotal role of surveillance in the rapid eradication of smallpox, which reduced from 10 million cases and 2 million deaths in 1967 to zero in 1977.[15] The contemporary definition of surveillance is remarkably similar to that offered by Dr Langmuir in 1963.[14] The CDC now define public health surveillance as "the ongoing, systematic collection, analysis and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control."[9, 16] The WHO has an almost identical definition of public health surveillance as the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice.[17] Such surveillance can: serve as an early warning system for impending public health emergencies; document the impact of an intervention, or track progress towards specified goals; and monitor and clarify the epidemiology of health problems – such as their scope and magnitude, demographic and geographic distributions – to allow priorities to be set and to inform public health policy and strategies.[17, 18] Some have stressed that public health surveillance systems should, by definition, be population-based to avoid sampling errors and biases.[19]

Langmuir identified public health action resulting from intelligence gained through surveillance as a logical complement of surveillance but that disease surveillance "does not encompass direct responsibility for control activities".[14, 15] The World Health Assembly report of 1968 agreed that "the purpose of surveillance is to use all appropriate epidemiological and other methods as a guide to the control of disease".[12] More recently, some surveillance systems have explicitly incorporated response in an integrated disease surveillance and response (IDSR) strategy.[20] Since Langmuir's time, surveillance programmes have increased in number and complexity in parallel with advances in systems for data collection, analysis and communication.[15] A myriad of conditions, both communicable and non-communicable diseases, are now under surveillance worldwide.

1.1.2 The structure of communicable disease control in Australia

Australia became an independent nation in 1901 when legislation was passed in Britain allowing six Australian colonies (New South Wales, Victoria, Queensland, Western Australia, South Australia and Tasmania) to govern in their own right as part of the Commonwealth of Australia (known as Federation).[21] The two territories (the Australian Capital Territory and the Northern Territory) were created in 1911. National communicable disease control activities in Australia are organised by Australian, state and territory governments through more than 60 joint committees, networks, surveillance systems, and national centres.[22] States and territories are responsible for the collection of notification data and public health actions resulting from these data, as outlined in their respective legislation.[23] Because of differing legislation and disease threats, notification requirements and notifiable diseases lists differ between jurisdictions.[23, 24] The Australian Government initially had limited involvement in public health issues, focussing only on quarantinable diseases. However, since mid-last century the Australian Government has expanded its role to include coordination of health emergencies, biosecurity and multi-jurisdictional outbreaks. As such,

the Australian Government now shares responsibility for national communicable disease control with state and territory governments.[24]

The Australian Health Protection Principal Committee (AHPPC), chaired by the Australian Chief Medical Officer, coordinates the national approach to public health emergencies and communicable disease threats. The AHPPC includes (among others) the Chief Health Officer of each state and territory; the Communicable Diseases Network Australia (CDNA) chair; the Public Health Laboratory Network (PHLN) chair; and high-level representation from the New Zealand Ministry of Health. A legislative framework for national public health surveillance, information sharing with the WHO and countries affected by a relevant public health event, and meeting the requirements of the *International Health Regulations (2005)* is provided by the *National Health Security Act 2007*.[25] The *International Health Regulations* is an agreement between 196 countries that requires notification to WHO of four diseases – smallpox, (wild-type) poliomyelitis, human influenza caused by a new subtype, and severe acute respiratory syndrome (SARS) – as well as events which potentially constitute 'a public health emergency of international concern'.

1.1.3 National notifiable diseases surveillance in Australia

Australia's six states and two territories collect notification data from doctors and laboratories under their respective notifiable disease legislation.[23] Notifiable diseases data have been compiled nationally since 1917,[26] however a national surveillance system was not introduced until 1991. National data were published in the *Medical Journal of Australia* from 1917 to 1922; *Health* (a journal of the Commonwealth Department of Health) from 1924 to the Second World War; and the *Commonwealth Year Book* from after the Second World War to 1990. Annual compilations of notifiable diseases data were also published by the Australian Department of Health from 1917–1990, with data missing in 1941, 1943 and 1952 and the latter half of 1963.[26] Prior to 1991 there were no annual reports of national surveillance data

and there were marked inconsistencies in which conditions were notifiable in the eight jurisdictions.[27] Several conditions were reclassified according to evolution of medical understanding of the aetiology of conditions and laboratory diagnostic capabilities; for example, infectious/infective hepatitis became hepatitis A, and homologous serum jaundice/serum hepatitis became hepatitis B.

The CDNA was established in 1989 to provide national public health coordination and leadership for communicable disease prevention and control. In 1990, CDNA established the National Notifiable Diseases System (NNDSS), which began national data collection in 1991. Responsibility for NNDSS management and data monitoring lies with the Office of Health Protection in the Australian Government's Department of Health. De-identified notification data collected by the jurisdictions for conditions specified on the NNDL are submitted to NNDSS for analysis at the national level. From 1991, annual reports of the NNDSS have been published in *Communicable Disease Intelligence,* a scientific journal published by the Australian Department of Health (DH). Aggregated NNDSS data are published on the Department of Health's website and updated daily (www.health.gov.au/nndssdta), with a summary report and data table published fortnightly (www.health.gov.au/cdnareport). Australia has multiple other national surveillance systems that focus on single diseases (e.g. gonococcal infection), transmission pathways (e.g. food-borne diseases), clinical settings (e.g. general practitioners and healthcare associated infections), emerging issues (e.g. antimicrobial resistance), or population groups (e.g. children);[24, 28] not all these have the same legislative basis as NNDSS, which remains the cornerstone of Australia's national communicable disease surveillance.

1.1.4 Evaluation of national communicable disease surveillance in Australia

Evaluation is a central component of public health surveillance systems. Surveillance data can be used to evaluate the need for public health intervention and later to evaluate its

effectiveness or impact (e.g. comparing incidence of the target disease in the target population before and after an intervention). Also important is the need for periodic evaluation of the surveillance system itself, including system structure, notification processes, data quality, the type of data collected, and diseases under surveillance. In their technical discussions of surveillance in 1968, the WHO stated: "Whatever the complexity of the surveillance structure, an assessment and evaluation mechanism to gauge the reliability of the system is essential".[12]

A qualitative and quantitative review of communicable disease notifications in New South Wales in 1998 found just over half the hepatitis A, pertussis and measles cases reviewed were notified by the treating doctor, despite legislation required treating doctor notification as well as laboratory notification. Barriers to medical notification included lack of understanding of the notification process, such as what to notify and how to notify, reluctance to notify on suspicion (as directed in the legislation) for cases yet to be laboratory confirmed, concerns about privacy and undermining the doctor-patient relationship, and the lack of financial incentives to notify.[29] More recently, the 2013 NNDSS annual report indicates that ≥95% of all notifications in the Australian Capital Territory, New South Wales, the Northern Territory, Queensland and Tasmania were received from a laboratory alone (i.e. without notification from the treating doctor).[30]

During development of NNDSS, four objectives were identified and in each NNDSS annual report from 1994, additional objectives of national surveillance have been articulated (Table 1:1). [31, 32] Despite this, in an evaluation of NNDSS undertaken in 2003–2004, stakeholders identified a lack of clearly articulated aims and objectives for NNDSS as a weakness of the system. This evaluation additionally identified complexity of processes, inflexibility and lack of timeliness as areas of NNDSS that needed improvement. NNDSS strengths were acceptability, structural simplicity, and active use of the data.[31]

Table 1:1: Stated objectives for national public health surveillance in Australia

Documented in planning stages for NNDSS[31]	Documented in 2013 NNDSS annual report[30]
• Control communicable diseases	• Guide policy development and resource allocation at the national level
• Alert state and territory health authorities to communicable disease episodes which require public health action across jurisdictional borders	• Monitor the need for and impact of national disease control programs
• Coordinate national responses to disease threats	• Coordinate the response to national or multi-jurisdictional outbreaks
• Act as a clearing house for the dissemination of information	• Identify national trends
	• Describe the epidemiology of rare diseases that occur infrequently at state and territory levels
	• Meet international reporting requirements, such as providing disease statistics to the WHO
	• Support quarantine activities

Reviewing surveillance data for individual diseases can itself identify gaps in a public health surveillance system. The authors of a review of pertussis notifications to NNDSS from 1991–1997 called for the following changes to improve pertussis surveillance in Australia: 1) documentation of method of diagnosis (clinical vs. laboratory confirmed vs. epidemiologically-linked to a laboratory confirmed case); 2) documentation of method of laboratory confirmation; 3) uniform case definitions and procedures of case ascertainment by jurisdictions; 4) more complete reporting of Indigenous status; and 5) inclusion of case vaccination data.[33] By 2004, national case definitions had been developed and NNDSS fields had been added to include method of diagnosis, method of laboratory confirmation, and vaccination data.[31] These changes followed release of the first National Communicable Diseases Surveillance Strategy in 1996, which recommended improvements to NNDSS, including review of data quality, reporting timeliness, notifiable diseases list, and case definitions, along with expansion of the core data fields.[31]

More recently the AHPPC commissioned CDNA to produce the *System Overview of Communicable Disease Control in Australia 2012*, which informed the subsequent *National framework for Communicable Disease Control 2014* (the Framework).[22, 23] While the scope of the Framework is extensive, surveillance is at the forefront: Outcome 1.1 is "Better surveillance and public health laboratory testing". Incompatible data systems, different laboratory testing, and inconsistent legislation were identified in the Framework as limitations to the control of multijurisdictional outbreaks and emerging national communicable disease issues. The Framework, developed in consultation with jurisdictions and with extensive stakeholder input, identified "overwhelming support for greater national coordination for communicable disease prevention and control".

1.1.5 Limitations of surveillance data

It has long been recognised that surveillance data are incomplete and imperfect, and that in general a surveillance system is unable to provide a complete case count or precise information regarding disease incidence, prevalence, or severity.[24, 34] Surveillance gives information about patterns of disease in a community, including whether incidence is increasing or decreasing and who is most often affected. It has been acknowledged that the function of surveillance to inform public health action can be met by imperfect or incomplete data, but that it can be problematic to use surveillance data to infer disease incidence in a research setting.[34]

1.1.6 The surveillance pyramid, case ascertainment and bias

Unless a disease is severe enough to warrant health care in each occurrence and unique enough that each presentation is accurately diagnosed and notified (for example, smallpox during the global eradication campaign),[34] there will be incident cases not captured in surveillance data. The 'surveillance pyramid' is a visual depiction of the under-ascertainment of infections by a surveillance system (Figure 1.2). For certain infections, persons with

asymptomatic infections have potential to transmit the disease and are therefore relevant to public health (e.g. gastrointestinal infections in a food handler, blood-borne viral diseases or sexually transmissible infections [STIs]). For other conditions, only symptomatic infections contribute to disease transmission and disease burden. In order to appear in national surveillance data, a person with a notifiable disease must have symptoms warranting presentation to a doctor, the appropriate test ordered and specimen collected, a positive laboratory result, notification to the jurisdictional public health unit by the doctor and/or laboratory, and transmission of the notification from the jurisdiction to the NNDSS. There will be a degree of under-ascertainment at every step of the surveillance pyramid and this will be influenced by the host-pathogen interaction, duration and severity of symptoms, individual preferences of the patient/caregiver/doctor, and system factors, such as automated reporting by laboratories to health departments and by jurisdictions to NNDSS.

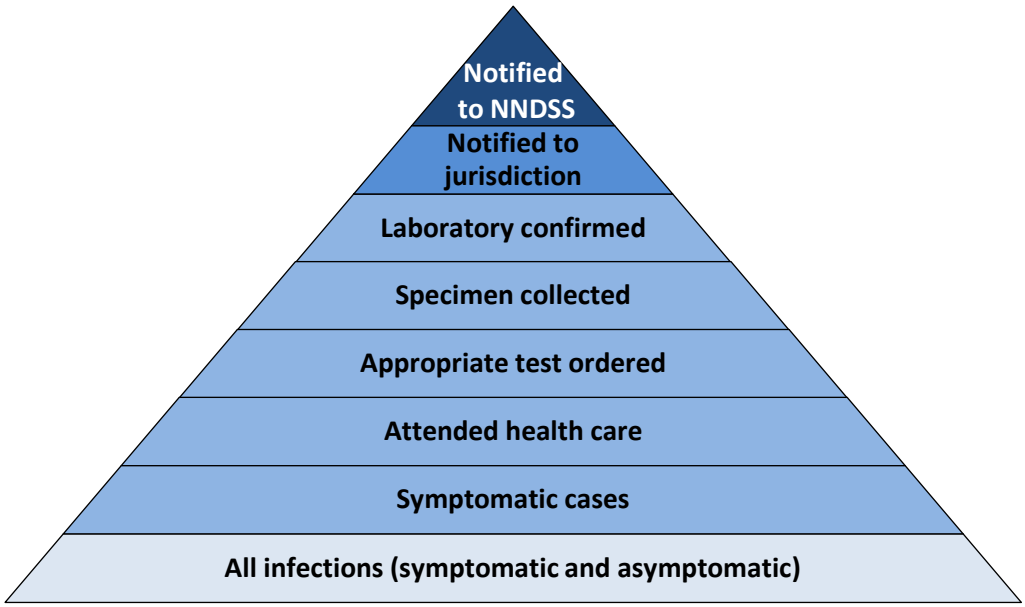


Figure 1.2: The surveillance pyramid depicting the under-representation of all infections among cases notified to NNDSS

There has been recent interest in quantifying the extent to which surveillance data underestimate the true incidence of symptomatic disease in a population, including studies in

Europe, North America, New Zealand, and Australia.[35-40] Case ascertainment is the proportion of all incident symptomatic cases captured by the surveillance system, while the multiplication factor is the factor by which the number of notified cases is multiplied to approximate true incidence of symptomatic cases in a population (the inverse of case ascertainment). There is evidence that case ascertainment varies between notifiable conditions, between countries, over time, and by age and sex, indicating potential for surveillance data to be biased. The ECDC-funded Burden of Communicable Diseases in Europe (BCoDE)-project estimated multiplication factors for salmonellosis and campylobacteriosis in European countries and reported that the most appropriate multiplication factors are often disease-, country-, age- and sex-specific.[35] Similarly, using Australian NNDSS data, differing multiplication factors have been estimated for salmonellosis (7), Shiga toxin-producing *Escherichia coli* (STEC) (8) and campylobacteriosis (10).[36] The IID2 study examined community incidence, general practitioner (GP) presentations and notification to national surveillance of intestinal infectious diseases in the United Kingdom (UK) from 2008–2009. This study confirmed that disease severity impacts the likelihood of presentation to GPs and notification. Persons with an episode of campylobacteriosis were 10 times more likely to present to a GP than those with norovirus, and those with salmonellosis were 60 times more likely to be notified than those with norovirus.[37] Compared to a similar study in England in the 1990s, the IID2 study demonstrated a ~40% rise in incidence but a ~50% fall in GP consultations for acute gastroenteritis in 2008–2009, indicating that health seeking behaviours and therefore case ascertainment changes over time. Further contributing to the changes in case ascertainment, clinicians' testing practices have changed for certain infectious diseases. For example, Australian GPs were more likely to perform a diagnostic test for pertussis among patients presenting with a compatible illness in 2010–2011 compared to 2000–2004 (OR 7.0 [95% CI

535–8.8]).[41] Finally, the completeness of notification of laboratory confirmed cases to the surveillance system contributes to the overall case ascertainment. Despite the legislative requirement for reporting laboratory confirmed cases, analysis of the first two years of invasive pneumococcal disease (IPD) surveillance in Victoria (2001–2003) demonstrated at least one-sixth of laboratory confirmed IPD disease were not notified to the state's surveillance system, with age-related differences in case ascertainment.[42]

1.1.7 Measuring disease burden

Disease burden measurements are a way of describing the impact of a disease (or group of diseases) on a population. They can be used to compare the same disease(s) between population groups, different diseases within a population, or changes over time. In addition to being an incomplete estimate of disease incidence, surveillance data do not provide reliable information on disease severity (e.g. hospitalisations and deaths attributable to notifiable diseases), symptom duration, complications resulting from chronic infection (e.g. hepatic cirrhosis, liver failure or hepatocellular carcinoma as complications of chronic hepatitis B or hepatitis C infections), or post-infectious disease sequelae (e.g. Guillain-Barré syndrome or irritable bowel syndrome following campylobacteriosis). Therefore, surveillance data are not ideal measures of disease burden within a population. Alternate simple disease burden measures include estimates of: incidence, prevalence, medical encounters, hospitalisations, and mortality. Several existing data sources can provide data for some of these measures, including mortality and hospitalisation datasets, and general practitioner electronic medical records. Problems arise with each of these approaches. For example, incidence data give no indication of disease severity or impact, while mortality data do not take into account morbidity associated with non-fatal illnesses. To address these concerns, population measures of health (or disease) incorporating mortality and morbidity into a single number were

developed. Overall, these are known as Health Adjusted Life Years (HALYs), and they include Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QALYs).

QALYs were developed in the 1960s primarily as a means of representing a health outcome in cost effectiveness analyses (CEA).[43] QALYs include both the quantity and quality of life lived, with one QALY equating to one year lived in perfect health. Imperfect health results in QALYs of less than one per year, based on the utility value of the health state ranging from 0 (dead) to 1 (perfect health). QALYs are widely used in the economic evaluation of clinical and public health interventions, including CEA of medications under consideration for listing on Australia's government-subsidised Pharmaceutical Benefits Scheme (PBS). The incremental cost-effectiveness ratio (ICER) is the incremental price per unit of health effect from a health intervention when compared with an alternative intervention. ICER can be used by policymakers to identify ways to minimise expenditure needed to achieve a pre-specified health-based target, maximise health benefits while keeping within a specified budget, and meet an explicit threshold for what is considered cost-effective.[44] Australia's Pharmaceutical Benefits Advisory Committee (PBAC) was established in 1953 to make recommendations to the Australian health minister about listing medications on the PBS. Australia was the first country to include formal mandatory economic evaluation in a national formulary. Although no explicit cost-effectiveness threshold is set by PBAC, analysis of submissions from 1993–2009 indicated the average possibility of a positive recommendation for a medication to be listed fell by 4% for each $10,000 increase in the cost per QALY gained, and the likelihood of a positive recommendation fell if the predicted annual budgetary expenditure exceeded $10 million.[45]

DALYs were developed at the WHO in the 1990s to document the global population health burden due to disability and premature mortality. While QALYs document years of healthy life, DALYs document the opposite, namely health burden in terms of years of life lost

(YLL) plus years lived with disability (YLD), whereby DALY = YLD + YLL. DALYs incorporate information on the incident number of disease cases, illness duration, disease severity (disability weight), incident number of deaths, and life expectancy at age of death. Differing health outcomes for a single disease (e.g. differing severity levels and disease sequelae) can be incorporated into DALY disease models. One DALY equates to loss of one year of "healthy" life, and the DALY metric quantifies the gap between a population's current health status and an ideal where everyone lives to advanced age, free from disease and disability.[46] On the global scale, DALYs have been widely used to compare disease burden between populations and to examine the relative impact of different diseases to set global priorities for public health interventions.

There have been several Australian Burden of Disease studies, with national DALY estimates published for the reference years of 1996, 2003 and 2011,[47-49] and fatal burden of disease estimates overall and for Aboriginal and Torres Strait Islander (Indigenous) people for 2010.[50, 51] In the recent Australian Burden of Disease Study, aggregate YLLs and DALYs are presented by disease groups (e.g. 'infection') but not by individual cause or pathogen. It was estimated that in Australia infections accounted for 2.0% of total YLLs in 2010 and 1.6% of DALYs in 2011.[49, 50] Disease burden due to complications and sequelae to some infections (e.g. cirrhosis and hepatocellular carcinoma resulting from chronic hepatitis B or C; post-infectious irritable bowel syndrome or Guillain-Barré syndrome following campylobacteriosis) were not included in the 'infection' disease group YLL or DALY estimates. This likely results in underestimation of the disease burden attributable to infections in Australia, as these complications and sequelae can contribute more to overall disease burden than the acute infection itself.[52, 53] Nationally and internationally, DALYs have been used to prioritise conditions requiring intervention and identify sections of the

community (e.g. Indigenous Australians) with disproportionate disease burden, including preventable communicable diseases.

1.2 Thesis rationale and aim

The WHO defines epidemiology as:

> The study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants.[54]

My thesis, in the field of infectious diseases epidemiology, covers much of this definition. I have used the WHO definition of epidemiology as a basis to describe my thesis aim.

***Thesis Aim*:** To study the distribution, determinants and burden of infectious diseases in Australia in order to inform the control of infectious diseases in Australia.

I will achieve this aim using descriptive studies to explore the distribution and burden of infectious diseases and analytical studies to identify disease determinants.

Periodic evaluation of public health surveillance systems is essential to ensuring their relevance to evolving public health issues affecting the population under surveillance. Analysis of the surveillance system and processes in a jurisdiction enhances our understanding and interpretation of NNDSS data. There has been no evaluation of NNDSS as a public health surveillance system for over a decade and significant changes to the system have occurred over that time. Furthermore, there has been no longitudinal evaluation of infectious disease surveillance data for all nationally notifiable diseases since the inception of NNDSS in 1991. Analysis and reporting of surveillance data is an integral component of a

surveillance system and this thesis represents a high-level view of all notification data over a 21-year period. Valuable lessons can be learned regarding the surveillance system as well as the epidemiology of notifiable diseases using an inclusive approach to the longitudinal analysis of surveillance data. Furthermore, this approach allows assessment of the socio-demographic influences on disease notification rates, with comparison between diseases and disease groups as well as analysis of temporal changes. Finally, although there have been several jurisdictional and national burden of disease studies in Australia, these do not provide granularity about burden attributable to individual pathogens and sequelae to infectious diseases. Such granularity is important if burden of disease measures, such as DALYs relating to infectious diseases, are to be used to set health based targets (HBTs) in Australia and elsewhere.

1.3 Thesis outline

This thesis is arranged in two parts as outlined below, and the contents of each chapter are subsequently detailed:

Part 1: Infectious disease surveillance in Australia

- Evaluation of a state and national public health surveillance system (Chapter 2)
- Epidemiology of nationally notifiable diseases in Australia (Chapter 3)
- Socio-demographic determinants of notifiable diseases in Australia (Chapter 4).

Part 2: Burden of selected infectious diseases in Australia

- Burden of selected gastrointestinal diseases in Australia (Chapter 5)
- Use of disability adjusted life years (DALYs) to set health based targets (Chapter 6).

Chapter 2 includes two manuscripts relating to evaluation of public health surveillance systems. The first relates to notification of infectious diseases to Victoria's Public Health Event Surveillance System (PHESS) in 2013. The second is an evaluation of the NNDSS based on notification data from 1991 to 2011. NNDSS is a compilation of notification data collected by states and territories, including Victoria. There are similarities in the findings of the two papers, in particular the importance of improving completeness of Indigenous status reporting for notified cases.

Chapter 3 includes a published article which describes the epidemiology of 65 nationally notifiable diseases in Australia using NNDSS data from 1991 to 2011. It explores some of the drivers behind the observed increase in incidence of notifiable diseases, including addition of notifiable diseases to the NNDSS, evolution of more sensitive diagnostic tests (particularly PCR), and changes in testing patterns along with true changes in disease incidence.

Chapter 4 is an analysis of socio-demographic determinants of disease notifications in Australia based on NNDSS data from 1991 to 2011, with a focus on the eight most commonly notified diseases. Persons living in remote and very remote areas and Indigenous Australians had higher overall notification incidence than other Australians – particularly for STIs – while blood-borne viral hepatitis (BBVH) had higher notification incidence among the most socio-economically disadvantaged Australians. These findings can help prioritise conditions and populations for targeted public health interventions.

Chapter 5 presents a published article that contains detailed burden of disease estimates for six important gastrointestinal pathogens in Australia – campylobacteriosis, salmonellosis, rotavirus, norovirus, cryptosporidiosis, and giardiasis – using several burden of disease measures. The ranking of pathogen burden varied according to the measure used, with norovirus having the highest incidence while campylobacteriosis had the highest DALY

burden. Post-infectious sequelae for the bacterial pathogens had a large impact on the estimated DALY burden. A lack of data regarding post-infectious sequelae for these pathogens resulted in the planning of a retrospective study of notified cases of campylobacteriosis, salmonellosis and cryptosporidiosis in Victoria. The second part of Chapter 5 details the rationale for this study and obstacles that resulted in study termination.

Chapter 6 is a published manuscript in which the benefit of using DALYs to set HBTs is discussed. The WHO recommends the use of DALYs to set HBTs for drinking water quality, and the National Health and Medical Research Council (NHMRC) is considering use of DALY estimates from Chapter 5 in revisions to the *Australian Drinking Water Guidelines*.

Chapter 7 (Discussion) highlights the key finding of this thesis, implications for the future of public health surveillance in Australia, priorities for public health intervention, and research priorities, including acquisition of Australian data on post-infectious sequelae to improve the accuracy of future burden of disease estimates.

References for unpublished work and manuscripts *in press* are contained at the end of this thesis. References for published work are listed within the published document in the relevant chapters.

Chapter Two: Evaluation of public health surveillance systems

Declarations for thesis Chapter 2

Declaration by candidate

In the case of Chapter 2.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, data cleaning and analysis, preparation of draft manuscript, preparation of manuscript for submission	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Lucinda Franklin	Revision of manuscript	
Nicola Stephens	Revision of manuscript	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature	[redacted]	**Date** 11th July, 2016

In the case of Chapter 2.2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Allen Cheng	Advice regarding statistical analysis; revision of manuscript from preliminary draft to submission	
Robert Hall	Initial concept of NNDSS review; sourcing data; revision of manuscript from preliminary draft to submission	
Karin Leder	Revision of manuscript from preliminary draft to submission	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature	[redacted]	**Date** 11th July, 2016

Aim: To better understand communicable disease surveillance in Australia and inform changes to relevant public health surveillance systems through evaluation of a state-based and a national public health surveillance system.

Preface

The need for regular evaluation of public health surveillance systems has been recognised since the inception of modern infectious disease surveillance. The *Updated Guidelines for Evaluation Public Health Surveillance Systems* published by the CDC identifies the purpose of such evaluations as ensuring efficient and effective monitoring of problems of public health importance.[55] This chapter contains two complementary manuscripts; the first has been accepted for publication and the second re-submitted for peer-review following revision.

The first manuscript examines notification practices for infectious diseases in Victoria through analysis of cases notified to Victoria's Public Health Event Surveillance System (PHESS) in 2013. It examines conditions notified, notification timeliness and data completeness by notification source (doctors vs. laboratories vs. both). Line-listed data from PHESS are uploaded into the National Notifiable Diseases Surveillance System (NNDSS). Therefore, a focussed evaluation of notifications to PHESS is beneficial at the jurisdictional level to identify necessary changes "to ensure that problems of public health importance are being monitored efficiently and effectively",[55] but also at the national level to understand how data are received and handled by jurisdictions prior to being uploaded to NNDSS. Although Victoria is just one of eight jurisdictions that contribute data to NNDSS, Victoria is the second most populous jurisdiction in Australia and accounts for 25% of the national population. Furthermore, PHESS is a customised version of a commercial product known as Maven Enhanced Disease Surveillance System (Maven EDSS), developed by Consilience Software, Austin Texas USA. Maven EDSS is used in both Victoria and New South Wales –

together accounting for more than half the national population. Therefore, familiarity with notification practices in Victoria was useful in the subsequent evaluation of the NNDSS, which relies on receipt of notification data from jurisdictional surveillance systems.

The second manuscript is an evaluation of NNDSS over its first 21 years of operation (1991–2011) using line-listed NNDSS data from that period. It examines changes in notifiable conditions, case definitions, notification sources, diagnostic tests, data completeness, and data timeliness over that period. This evaluation is significant in future planning of national public health surveillance in Australia, as well as informing interpretation of NNDSS data over the 21-year study period.

2.1 Infectious disease notification practices, Victoria 2013

This manuscript has been accepted for publication in *Communicable Disease Intelligence*.

2.1.1 Abstract

Background: Infectious disease notification practices in Victoria were reviewed to identify areas for potential improvement.

Methods: Confirmed or probable cases notified to the Department of Health & Human Services (DHHS) Victoria in 2013 (excluding elevated blood lead, food-borne or water-borne illness [≥2 related cases] and chlamydial infection) were analysed according to: notification source (doctor [± laboratory] vs. laboratory-only); follow-up by public health staff (routine for selected conditions vs. not routine); priority for Indigenous status reporting (18 priority conditions with target ≥95% completeness vs. other conditions with target ≥80% completeness); and urgency of notification (Group A conditions [immediate (same day) notification] vs. Groups B, C and D [notification within five days]).

Results: Almost half (49%) of the 34,893 confirmed and probable cases were notified by laboratory report alone. Indigenous status was complete for 48% of cases, more often for conditions with active vs. no active follow-up (RR 1.88 [95%CI 1.84–1.92]) and priority conditions for Indigenous status reporting vs. other conditions (RR 1.62 [95%CI 1.59–1.66]). Among conditions without active follow-up, doctor-notified cases had more complete Indigenous status reporting than laboratory-only notified cases (86% vs. 6%, RR 15.06 [95%CI 14.15–16.03]). Fewer Group A notifications were received within the legislated timeframe (59%) than Group B, C and D notifications (90%).

Discussion: DHHS Victoria handles a large volume of infectious disease notifications. Incomplete Indigenous status reporting (particularly conditions without active public health

follow-up) and delayed notification of Group A conditions warrant attention. These findings will be used to improve notification practices in Victoria.

2.1.2 Introduction

Infectious disease surveillance data are used to monitor disease epidemiology, detect and manage disease outbreaks, inform the need for public health interventions, and monitor the impact of these interventions. In Victoria, the *Public Health and Wellbeing Act 2008* requires doctors and laboratories to notify the Department of Health & Human Services (DHHS) when certain infectious diseases are diagnosed or suspected. Seventy-two conditions are specified in the *Public Health and Wellbeing Regulations 2009* as requiring notification; all except elevated blood lead levels are infectious diseases or complications of infectious diseases. Twenty-four notifiable conditions are classified as 'Group A' conditions and require immediate (same day) notification by telephone on initial diagnosis, whether presumptive or confirmed, followed by written notification within five days. This allows immediate public health action, for example providing prophylactic antibiotics to people who have had contact with a case with invasive meningococcal disease. The remaining 48 conditions require notification within five days of initial diagnosis. In Victoria, notifications are received centrally and entered into the state's notifiable diseases database – the Public Health Event Surveillance System (PHESS) – an electronic platform introduced in 2012, with 2013 the first full year of use. Although PHESS has capacity to receive electronic notifications directly,[56] in 2013 all notifications (clinical and laboratory) were entered manually. Active case follow-up by DHHS staff is undertaken for all Group A conditions and selected other conditions based on the need for additional (enhanced) data to inform public health action; for remaining conditions there is no active follow-up. Responsibility for public health response to these notifications lies with the DHHS. Additionally, for the purposes of national surveillance of infectious diseases, de-identified data regarding confirmed and probable cases are forwarded daily to the National Notifiable Diseases Surveillance System (NNDSS) for a nationally agreed set of 65 communicable diseases.[30]

This paper represents an audit of notifications received in 2013 by DHHS Victoria into PHESS. Such audits have been performed every one to three years since 2004[57-61] to inform Victorian public health staff and notifiers of notification practices in Victoria and identify notifier and system factors that need improvement. Findings of this audit will be used to optimise the utility and efficiency of disease notification in Victoria.

2.1.3 Methods

All notifications received by DHHS in 2013 were entered into PHESS; all notifications were included in this analysis, excluding the conditions of elevated blood lead (not an infectious disease), food-borne and water-borne illness [two or more related cases] (not a single pathogen and notified by certain institutions only), and chlamydial infection (notification process under review during 2013). De-identified case notification data were extracted from PHESS in April 2014. Cases were reported and analysed according to the following classifications: 'confirmed' and 'probable' cases met nationally agreed case definitions;[62] 'rejected' cases did not meet the national case definition; 'suspected' cases had not been assessed against the national case definition; 'at-risk' cases included contacts of known cases; and 'not notifiable' cases were residents of another Australian jurisdiction and were therefore counted in that jurisdiction. Fields relating to the notified case included event identification, disease-group, condition, onset date, sex, age, Aboriginal and Torres Strait Islander (Indigenous) status, and postcode of residence. Notification details included the notifier, date of specimen collection (for laboratory notifications), date the notification was authorised by notifying doctor or positive result authorised by the notifying laboratory (signature date), and date the notification was received by DHHS (notification received date).

Case classification, number of notifications per case, and notification source (doctor, laboratory, or both) were described for all notifications. All other analyses – including data completeness and time to notification – were restricted to confirmed and probable cases. The

Communicable Diseases Network Australia (CDNA) has set a target for Indigenous status reporting of ≥95% for 18 priority conditions and ≥80% for all other conditions;[30] confirmed and probable notifications were benchmarked against these targets.

Relative risks (RR) and 95% confidence intervals (95% CI) were calculated to compare notification outcomes for different groups, including cases notified by a laboratory but not a medical practitioner (laboratory-only notified cases) to cases notified by a medical practitioner ± laboratory (doctor-notified cases); follow-up by public health staff (routine for all notified cases for certain conditions [all Group A conditions and selected Group B, C and D conditions] vs. not routine); and priority for Indigenous status reporting (18 priority conditions vs. other). A p-value <0.05 was considered statistically significant.

Time to notification was calculated as the number of days between earliest signature date and earliest notification received date for each notified case. Cases with missing signature date or delay >365 days were excluded from the time to notification analysis. Median delay to notification and proportion of cases notified within the legislated timeframe of zero days for Group A conditions or five days for Group B, C and D conditions were reported.

Data were analysed using Stata version 13.1. This project was an audit of disease notifications made under state legislation and was not subject to human research ethics committee review.

2.1.4 Results

A total of 94,592 notifications were received by the DHHS relating to 39,389 cases of notifiable infectious diseases that met the inclusion criteria. Of these, 33,436/39,389 (85%) cases were classified as confirmed and 1,457 (4%) probable. The remaining cases were classified as rejected (1,885 cases, 5%), at-risk (1,477 cases, 4%), not-notifiable (1,103 cases, 3%), and suspected (31 cases, 0.08%). Varicella zoster infection, pertussis and dengue made

up 98% of the 1,457 probable cases, with psittacosis, legionellosis, HIV (newly acquired), meningococcal infection, and rubella also having cases classified as probable. The majority of the 1,477 cases classified as at-risk were tuberculosis (1,327 cases, 90%), followed by typhoid (86 cases, 6%), and paratyphoid (56 cases, 4%).

Of the total 94,592 notifications, 48,913 (52%) were from primary laboratories, 21,417 (23%) from reference laboratories, and 22,681 (24%) from medical practitioners. Seventy-eight notifications were laboratory results where the testing laboratory was not identified, and 1,503 notifications were generated by public health staff at DHHS or other public health units. Of the included 39,389 cases, 40% were notified on a single occasion, with a median two and maximum 64 notifications per case [interquartile range 1–3 notifications per case]. Multiple notifications for a single case could result from notification by both clinician and laboratory (according to the legislative requirement); notification by more than one clinician; and/or multiple laboratory tests which sometimes resulted in a high number of notifications for a single case.

Almost half of the 34,893 cases classified as confirmed or probable were attributable to three diseases: *Campylobacter* infection (5,898 cases, 17%), influenza (5,833 cases, 17%), and Varicella zoster infection (5,084 cases, 15%). More confirmed or probable cases were notified in 2013 than during the preceding decade (2003–2012) for cryptosporidiosis; dengue; gonococcal infection; hepatitis D; HIV – unspecified duration; Q fever; salmonellosis; syphilis – infectious (less than two years duration [includes primary, secondary and early latent]); syphilis – late (more than two years or unknown duration); and typhoid (Table 2:1). More confirmed and probable cases of chikungunya (notifiable from 2005) and Varicella zoster infection (notifiable from 2008) were notified in 2013 than in previous years.

Among the 34,893 confirmed and probable cases, 49% were notified by laboratory alone, 45% by both medical practitioner and laboratory, and 6% by medical practitioner alone. The remaining 97 (0.3%) cases were identified through other means, including active surveillance by DHHS staff and public health units. Four conditions were notified by both laboratory and doctor in all confirmed and probable cases—newly acquired HIV infection (110 cases), leprosy (three cases), cholera (one case) and congenital rubella (one case). More than 80% of confirmed and probable cases were notified by both laboratory and doctor for the following diseases: chikungunya; HIV – unspecified duration; listeriosis; meningococcal disease; paratyphoid; rubella; shigellosis; syphilis – infectious; tuberculosis; and typhoid (Figure 2.1).

Medical practitioners made 22,681 separate notifications relating to 19,047 cases. Of these, 17,594/19,047 (92%) doctor-notified cases were confirmed or probable. The most common methods of initial notification for medical practitioners were fax (50%), web and e-notification (23%), and post (19%) (Table 2:2). Medical practitioners were more likely to first notify Group A conditions by telephone than Group B, C or D conditions (51% vs. 5%, RR 10.5 [95% CI 9.1–12.2]).

Of the 70,408 separate notifications received from laboratories, 63,711 (90%) related to confirmed or probable cases. Sixty per cent of the 32,850 confirmed or probable cases notified by laboratories were notified using a single laboratory notification, 19% had two, 8% had three, and 7% had four or more separate laboratory notifications per laboratory-notified case.

Age, sex and postcode were complete in ≥99.5% of confirmed and probable cases notified. Country of birth was reported in 41% of cases; more often among cases notified by a doctor than by laboratory-report alone (75% vs. 6%, RR 11.7 [95%CI 11.0–12.4], $p<0.001$).

Indigenous status was complete in only 48% of confirmed and probable cases. Conditions with routine active follow-up by DHHS public health staff were more likely to have Indigenous status reported than those without active follow-up (83% vs. 44%, RR 1.88 [95% CI 1.84–1.92], p<0.001). This difference in Indigenous status completeness was less marked among conditions notified by a doctor (92% with active follow-up vs. 86% with no active follow-up, RR 1.07 [95% CI 1.05–1.08], p<0.001) than among laboratory-only notifications (63% vs. 6%, RR 10.97 [95% CI 10.13–11.89], p<0.001). Among conditions without routine active follow-up, doctor-notified cases were more likely to have Indigenous status reported than laboratory-only notified cases (86% vs. 6%, RR 15.06 [95%CI 14.15–16.03], p<0.001) (Table 2:3).

Notifications were received for 15 of the 18 priority conditions for Indigenous status data completeness identified by CDNA.[30] Among these, Indigenous status completeness ranged from 58% for gonococcal infection to ≥95% for hepatitis A, hepatitis B (newly acquired), HIV, leprosy, and tuberculosis (Table 2:4). These priority conditions for Indigenous status reporting were more likely to have Indigenous status complete than other conditions (71% vs. 44%, RR 1.62 [95%CI 1.59–1.66], p<0.001). Indigenous status was complete for 89% of notified priority condition cases for which active follow-up by DHHS public health staff is routine compared to 58% for gonococcal infection (the only priority condition without routine active follow-up).

The median time to notification for confirmed and probable Group A conditions was zero days [range 0–52 days], with 59% of notifications received on the same day as the signature date and within the legislated timeframe for notification (Table 2:5). For Group B, C and D conditions the median delay from signature date to notification was one day, with 90% of cases notified within the legislated timeframe of five days from the signature date. Among medical practitioners, 100% of Group A conditions were notified within the legislated

timeframe (same day as diagnosis) when notified by web or e-notification, 79% when notified by telephone and 50% when notified by fax (Table 2:5). For Group B, C and D conditions notified by medical practitioners, ≥97% were notified within the legislated timeframe (within five days of diagnosis) when notified by web or e-notification, telephone or fax, and 77% when notified by post.

2.1.5 Discussion

A major finding of this audit was the low proportion of notified cases with completed Indigenous status. Reporting Indigenous status in health data is essential in order to quantify health disparities between Indigenous and non-Indigenous Australians, inform policy development and service delivery planning, and measure the effectiveness of interventions against targets of improved Indigenous health.[63] In 2011, CDNA set national targets for data completeness of Indigenous status at ≥95% for 18 priority conditions and ≥80% for all other notifiable conditions.[30] In Victoria, in 2013, Indigenous status was complete for 71% of the priority diseases and 42% of other diseases. The proportion of all confirmed and probable cases with complete Indigenous status was 48% in 2013, similar to previous Victorian reports of 45%–51% from 2004–2011.[57-59, 61] Overall, 48% of cases in the NNDSS in 2013 had Indigenous status reported, ranging from 18% in New South Wales to >90% in the Northern Territory, South Australia, and Western Australia.[30] Similarly, ethnicity was reported for 49% of cases notified to the U.S. National Notifiable Diseases Surveillance System from 2006 to 2010.[64] When restricted to doctor-notified confirmed and probable cases in Victoria, the proportion with complete Indigenous status was 87% in 2013, a slight improvement compared to 80–84% from 2006 to 2011.[57, 59-61] Despite awareness of the issue, there has not been substantial progress in improving completeness of Indigenous status reporting in Victoria. In this study we have provided more detailed analysis of Indigenous status reporting, highlighting higher completion rates among doctor-notified cases, conditions with

active follow-up, and priority diseases in order to highlight areas that require attention and potential strategies for improvement. In particular, more needs to be done to meet the CDNA targets for Indigenous status reporting for gonococcal infection, which is the only priority condition for which active case follow-up of laboratory notifications is not routine in Victoria. Indigenous status was complete for 83% of cases with active follow-up; therefore re-instituting routine active case follow-up for laboratory-notified cases of gonococcal infection is likely to improve completeness of Indigenous status reporting for gonococcal infection to >80%.

Ideally, Indigenous status would be ascertained at the time of notification. This requires educating clinician-notifiers of the importance of completing the Indigenous status field on the notification form. As Indigenous status was complete for 87% of doctor-notified cases in 2013, there is some scope for improvement as a result of clinician education. A DHHS communication strategy in 2009 aimed to increase the proportion of notified cases for which a notification was received from a doctor. This contributed to a temporary increase in this proportion to 58% in 2009,[65] but by 2013 this had fallen back to the baseline of 50%, indicating only modest gains in Indigenous status ascertainment are likely to be achieved through clinician education, and that such education needs to be ongoing to maintain these gains. Inclusion of an Indigenous status identifier on laboratory request forms has potential to do more to improve ascertainment,[66] particularly for laboratory-only notified cases without routine follow-up, such as gonococcal infection. Although this can be encouraged through clinician-education, changes to legislation and regulations requiring inclusion of Indigenous status on pathology request slips could prove more effective.[66] This requirement would also improve Indigenous status ascertainment in other datasets, such as cancer registries. Regardless of the method used to improve completeness of Indigenous status, individuals

should retain the right to withhold their Indigenous status through use of the "declined to answer" response.

Another potential approach is to undertake record linkage with other datasets to improve Indigenous status reporting completeness. In response to poor completeness of Indigenous status identified in previous audits of Victorian notification practices, a data-linkage pilot study was performed which aimed to improve Indigenous status reporting for three of the nominated priority conditions for Indigenous reporting completeness.[67] Data from newly acquired hepatitis B and C and gonococcal infection cases notified in Victoria in 2009–2010 were linked with Victorian hospitalisation data (1997–2011). Among the 82% of cases able to be linked, the proportion with missing Indigenous status decreased from 62% for hepatitis B, 68% for hepatitis C, and 33% for gonococcal infection to <0.2% for all conditions. Importantly, this resulted in a two- to four-fold increase in notification incidence among Indigenous Victorians for each of these conditions. Although the pilot data-linkage study illustrated potential use of other Victorian Government datasets to improve completeness of Indigenous status for data analysis and reporting, it was a retrospective study that did not update or correct the Indigenous status field in PHESS. The use of record linkage to update the Indigenous status field in PHESS raise ethical and privacy issues as people have the right to withhold their Indigenous status for some or all health-service interactions. At present, these ethical and privacy issues prevent updating the Indigenous status field in PHESS using information already contained in PHESS (related to an individual's previous disease notification[s]) or other health-related data-sources. However, such record linkage is routine in certain countries, indicating these issues may not be insurmountable. For example, a National Health Index (NHI) number is assigned to individuals accessing health and disability support services in New Zealand. The NHI holds various demographic and health data, including self-reported ethnicity. The NHI is included in the national notifiable

communicable diseases database (EpiSurv) which facilitates record linkage with the New Zealand Health Information Service.[68]

In Victoria, the *Public Health and Wellbeing Act 2008* requires both doctors and laboratories to notify all infectious diseases scheduled in the *Public Health and Wellbeing Regulations 2009*. In 2013, only 45% of confirmed and probable cases had both medical practitioner and laboratory notifications, similar to our findings for 2004 to 2011 (43%–52%).[58-61] A DHHS communication strategy contributed to a temporary increase in the proportion of notified cases for which a notification was received from a doctor to 58% in 2009,[65] but by 2013 this had fallen back to 50%. A 2008 survey of 152 Victorian medical practitioners identified the most common reasons for not notifying as: 1) assumption that the laboratory would notify; 2) belief that doctors notify confirmed, not suspected cases; and 3) notification was a time consuming process.[65, 69] The proportion of notifications received by laboratory alone increased from 38% in 2011 to 49% in 2013.[61] In comparison, in the proportion of notifications made by laboratory alone was estimated to be 4% in South Australia, 33% in Western Australia, and ≥95% in all other Australian jurisdictions in 2013.[30] This highlights the variability of surveillance practices in different Australian jurisdictions and potential issues with comparing notification data between jurisdictions. Unlike Victoria, in New South Wales, the Northern Territory, Queensland and Tasmania certain high-incidence conditions (e.g. chlamydial genital infection) require notification from the laboratory but not the doctor, and in each of these jurisdictions laboratory-only notifications account for ≥98% of all notified cases. The value of requiring dual notification by laboratories and clinicians for all notifiable conditions is currently under review in Victoria. If doctor notifications were not required for all conditions, the notification burden on clinicians and workload of DHHS surveillance staff would be reduced without impacting case ascertainment or timeliness of notification for high incidence diseases which require laboratory confirmation. However, the

trade-off associated with reliance on laboratory-only notifications is the potential loss of certain clinical, demographic and epidemiological information that can enable DHHS to identify sources of exposure and implement strategies to prevent further cases. For example, cases notified by a doctor were 12 times more likely to have completed country of birth compared to laboratory-only notifications. For several conditions, additional data were collected by public health officers during routine case follow-up with the treating doctor and/or case through telephone contact or a request to complete an enhanced surveillance form (ESF). To expedite this, DHHS are trialling a system for selected conditions whereby doctors making web notifications are immediately directed to the appropriate ESF so that enhanced data are collected at the time of notification. Active case follow-up also provides an opportunity to collect missing notification data. Among conditions with routine active case follow-up, the difference in completeness of reporting of Indigenous status between doctor-notified and laboratory-only notified cases (RR 1.88) were considerably less marked than among conditions with no routine active follow-up (RR 15.06). This suggests that for conditions with routine case follow-up, Indigenous status and other missing demographic information can be collected during case follow-up for laboratory-only notified cases.

As several high-incidence conditions are currently not routinely followed up, alternate ways to obtain data relevant to notified cases need to be considered. The modernisation of surveillance in Australia through formalised data linkages with existing datasets has been identified as a national surveillance strategic priority,[22] while development of secure and reliable record linkage has been identified in surveillance strategies in Australian and international jurisdictions.[70, 71] It might be possible to obtain demographic data, including Indigenous status, postcode of residence and country of birth from electronic medical records if this information was automatically included on electronically generated pathology request slips and notification forms.[66] This would result in more complete data without the need for

medical practitioners to separately notify each diagnosed case. Linkage of case notification data with extracts from other government databases has the potential to be more easily achieved. In New South Wales and Western Australia, linkage of the Australia Childhood Immunisation Register data with state-based disease notification data has been successfully piloted for a 17-year birth cohort (more than two million children) to improve vaccination status reporting.[72] This allows identification of vaccine failures and population-based assessment of vaccine effectiveness and can be used to evaluate and inform Australia's National Immunisation Program. Updating PHESS records regarding vaccination status using data obtained via record linkage is unlikely to raise the same ethical and privacy concerns as Indigenous status fields.

Electronic laboratory reporting (ELR), the automated transmission of laboratory results from laboratories to public health units, improves notification timeliness and accuracy and therefore public health response capacity.[73-75] PHESS is a customised version of a commercial product known as Maven Enhanced Disease Surveillance System (Maven EDSS), developed by Consilience Software, Austin Texas USA. In 2014, Maven EDSS was used in seven US states, five US cities (including New York City) and New South Wales – the most populous Australian state with 32% of the national population.[56] The use of ELR is expanding in New South Wales, with four laboratories commencing ELR in 2013 and additional laboratories added subsequently.[76] Electronic laboratory notifications from some laboratories are received directly into the New South Wales surveillance system, the Notifiable Conditions Information Management System (NCIMS). As yet, the Victorian PHESS database does not receive laboratory reports electronically; however, a pilot is underway for ELR from a Victorian public health laboratory with plans to expand this to other Victorian laboratories. As >90% of notified cases include a laboratory notification, this

has the potential to reduce notification delays as well as reducing data entry workload and errors within DHHS.

DHHS Victoria continues to receive and respond to a high number of notifications of communicable diseases. In 2013, fewer than half the notified cases had Indigenous status completed, although higher ascertainment was achieved for doctor-notified cases, priority conditions for Indigenous reporting, and conditions with active public health follow-up. An increasing proportion of cases were notified by laboratory alone in Victoria. This is in keeping with national trends, with the potential consequence of incomplete demographic and risk factor data for notified cases. Possible actions to ensure adequate data quality and completeness in this context include prioritisation of data fields and diseases for which data completeness is necessary; education and support of doctors to ensure appropriate and timely notification; automation of systems to pre-populate laboratory request slips and notification forms with relevant demographic data; and development of ELR and data linkage capacity. Notifying doctors should be reminded of the requirement for immediate notification by telephone for Group A conditions to facilitate rapid public health response and prevention of further cases. DHHS Victoria will continue to work with notifiers and data custodians on these issues to ensure timely, complete and efficient notification to inform and monitor public health actions.

Table 2:1: Conditions for which more confirmed and probable notifications were received in 2013 than for any single year in the preceding decade (2003–2012)

Condition	Notified cases	
	2013	**Range 2003–2012**
Chikungunya virus infection*	30	0–17
Cryptosporidiosis	1,261	215–1,142
Dengue virus infection	407	6–326
Gonococcal infection	2,992	922–2,438
Hepatitis D	23	4–16
HIV – unspecified duration	208	112–183
Q fever	50	16–35
Salmonellosis	2,944	1,160–2,743
Syphilis – infectious	655	55–467
Syphilis – late	572	293–537
Typhoid	46	12–41
Varicella zoster infection†		
Chickenpox	871	222–738
Shingles	1,209	168–1,111
Unspecified	3,004	146–2,626

*Notifiable from 2005 – comparative period 2005–2012

†Notifiable from 2008 – comparative period 2008–2012

Table 2:2: Method of first notification of doctor-notified cases by disease group*, Victoria 2013

Method of notification	Group A		Groups B, C, D		All	
	No.	(%)	No.	(%)	No.	(%)
Fax	49	(23)	8,704	(50)	8,753	(50)
Web/e-notification	34	(16)	3,933	(23)	3,967	(23)
Post	12	(6)	3,349	(19)	3,361	(19)
Telephone	107	(51)	847	(5)	954	(5)
Other	3	(1)	364	(2)	367	(2)
Unknown	4	(2)	188	(1)	192	(1)
Total	**209**		**17,385**		**17,594**	

Group A conditions require immediate notification by telephone followed by written notification; groups B, C, and D conditions require written notification within 5 days of initial diagnosis

*Confirmed and probable cases only, excludes elevated blood lead, chlamydial infection and food-borne or water-borne illness

Table 2:3: Completeness of Indigenous status reporting for conditions with and without active follow-up, by notifier

	All notifications			Doctor-notified			Lab-only notified			RR*	[95% CI]	P-value
	n	N	(%)	n	N	(%)	n	N	(%)			
Conditions with active follow-up of all notified cases												
Group A	232	293	(79)	172	209	(82)	60	84	(71)	1.15	[0.99–1.34]	0.038
Group B, C, D	2,464	2,936	(84)	1,961	2,121	(92)	503	815	(62)	1.50	[1.42–1.58]	<0.001
Conditions without active follow-up of all notified cases†												
Group B, C, D	14,054	31,664	(44)	13,118	15,264	(86)	936	16,400	(6)	15.06	[14.15–16.03]	<0.001
All conditions	16,750	34,893	(48)	15,251	17,594	(87)	1,499	17,299	(9)	10.00	[9.53–10.50]	<0.001

*Relative risk for having Indigenous status complete if notified by a doctor vs. laboratory only

†Barmah Forest virus infection, campylobacteriosis, cryptosporidiosis ≥6 months of age, gonococcal infection (laboratory notified), hepatitis B (unspecified duration), hepatitis C (unspecified duration), influenza, non-TB mycobacterium infection (excluding *M. ulcerans*), pertussis (aged ≥5 years), invasive pneumococcal infection (aged 5–49 years), Ross River virus infection, salmonellosis, syphilis – late (laboratory notified), and Varicella zoster infection

Group A conditions require immediate notification by telephone followed by written notification; groups B, C, and D require written notification within five days of initial diagnosis

Table 2:4: Completeness of Indigenous status reporting for priority diseases*, Victoria 2013

Priority condition	Cases notified	Indigenous status complete, %
Dengue virus (locally acquired)	0	--
Donovanosis	0	--
Gonococcal infection†	2,992	58
Haemophilus influenzae type b	4	75
Hepatitis A	57	96
Hepatitis B (newly acquired)	37	95
Hepatitis C (newly acquired)	141	64
HIV	369	95
Leprosy	3	100
Measles	37	92
Meningococcal disease (invasive)	26	81
Pertussis <5 years	227	79
Pneumococcal disease <5 years	38	89
Pneumococcal disease ≥ 50 years	235	89
Shigellosis	101	89
Syphilis – congenital	0	--
Syphilis – infectious	655	86
Tuberculosis	382	100
All priority conditions	5,304	71
Other (non-priority) conditions‡	29,589	44

*Target for priority diseases is ≥95% Indigenous status complete and ≥80% for all other diseases

†Gonococcal infection is the only priority condition for Indigenous reporting that is not routinely followed up by DHHS staff

Table 2:5: Proportion of cases notified within 0 days, 1–5 days, and >5 days of signature date, by condition group, Victoria, 2013

		Number of cases*	Percent of cases within timeframe		
			0 day	1–5 days	>5 days
Group A	**All cases**	285	59	30	11
	Notifier				
	Both doctor and laboratory	201	62	29	9
	Laboratory only	82	50	35	15
	Doctor only	2	100	0	0
	Method of doctor notifications (if known)				
	Fax	18	50	44	6
	Web/e-Notification	10	100	0	0
	Post	2	0	0	100
	Telephone	77	79	16	5
	Other[†]	3	67	33	0
Groups B, C and D	**All cases**	31,779	33	56	10
	Notifier				
	Both doctor and laboratory	14,659	38	53	9
	Laboratory only	15,250	27	61	12
	Doctor only	1,870	51	40	9
	Method of doctor notifications (if known)				
	Fax	6,702	64	32	4
	Post	1,090	8	69	23
	Web/e-Notification	1,610	79	18	3
	Telephone	326	86	14	0.6
	Other[‡]	80	59	34	7
TOTAL		30,325	47	48	5

Group A conditions require immediate notification by telephone followed by written notification; groups B, C, and D require written notification within five days of initial diagnosis

*Confirmed and probable cases only; elevated blood lead, chlamydial infection and food-borne or water-borne illness excluded. Excludes notified cases where signature date was missing, or the date difference between "signature date" and "date notified" was greater than 365 days or less than 0 days (assuming transcription errors by notifier or data entry errors).

†Number of days between earliest signature date and the earliest notification received date

‡All other methods of notification

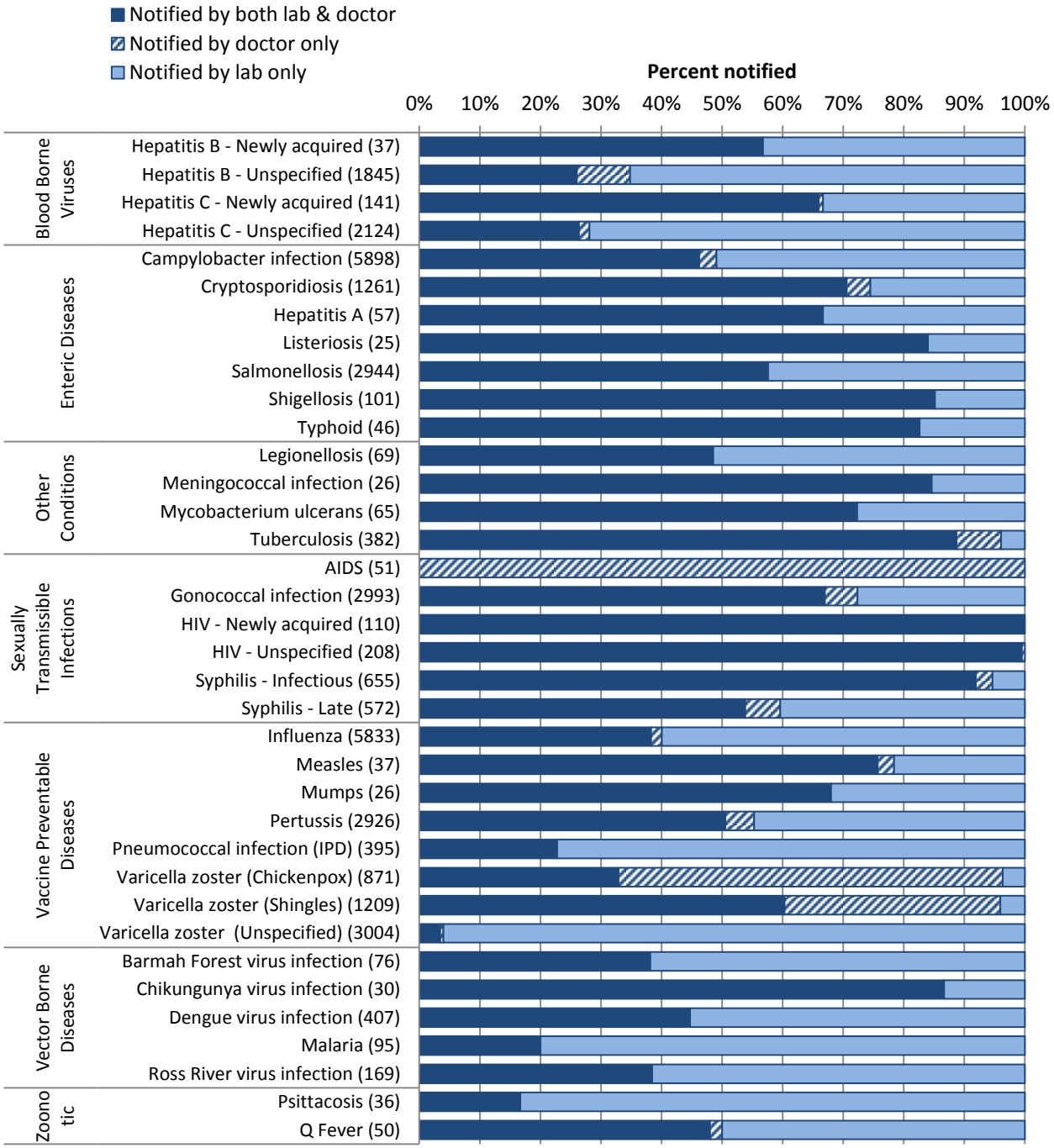


Figure 2.1: Method of notification for confirmed and probable cases notified to DHHS Victoria in 2013*

Number of confirmed and probable cases notified in 2013 in parentheses. The following conditions had fewer than 25 confirmed and probable cases notified: hepatitis D (23 cases), *Mycobacterium* infection [non-TB] (22), paratyphoid (19), Shiga-toxin and Vero-toxin producing *E. coli* (12), hepatitis E (9), leptospirosis (9), Creutzfeldt-Jakob disease [CJD] (7), rubella (5), *Haemophilus influenzae* type B (4), leprosy (3), botulism (2), haemolytic uraemic syndrome (2), cholera (1), rubella-congenital (1), tetanus (1).

2.2 Australia's National Notifiable Diseases Surveillance System 1991 to 2011: Expanding, adapting and improving

This paper has been re-submitted to *Epidemiology and Infection* following revisions made in response to reviewer comments.

2.2.1 Summary

We reviewed key attributes (flexibility, data quality and timeliness) of Australia's National Notifiable Diseases Surveillance System (NNDSS) over its first 21 years. Cases notified to NNDSS from 1991 to 2011 were examined by jurisdiction (six states and two territories) and sub-period to describe changes in the number of notifiable diseases, proportion of cases diagnosed using PCR tests, data quality (focussing on data completeness), and notification delays. The number of notifiable diseases increased from 37 to 65. The proportion of cases diagnosed by PCR increased from 1% (1991–1997) to 50% (2005–2011). Indigenous status was complete for only 44% of notifications [jurisdictional range 19%–87%]. Vaccination status was complete for 62% [jurisdictional range 32%–100%] and country of acquisition for 24% of relevant cases. Data completeness improved over the study period with the exception of onset date. Median time to notification was eight days [interquartile range 4–17 days; jurisdictional range 5–15 days]; this decreased from 11 days (1991–1997) to five days (2005–2011). NNDSS expanded during the study period. Data completeness and timeliness improved, likely related to mandatory laboratory reporting and electronic data transfer. A nationally integrated electronic surveillance system, including electronic laboratory reporting, would further improve infectious disease surveillance in Australia.

2.2.2 Introduction

Infectious disease surveillance involves the systematic collection of demographic, risk factor and event data on diagnosed cases of specified infectious diseases, combined with analysis and dissemination of disease information to provide information for action. Recent international examples of emerging infectious diseases, such as Zika virus, Middle Eastern respiratory syndrome Coronavirus, and Ebola virus, as well as ongoing domestic food-borne outbreaks,[77] highlight the importance of a robust and responsive public health infrastructure, of which infectious disease surveillance is a vital component.

In Australia (population 21.5 million in 2011), each of the six states and two territories has legislation mandating notification of selected infectious diseases; defines its own notifiable diseases list; collects surveillance information from notifying doctors and/or laboratories; and is responsible for the public health responses to notified cases. Although notifiable disease data have been reported nationally since 1917,[26] Australia lacked a national surveillance system until 1991 when the NNDSS was established by the Communicable Diseases Network Australia (CDNA), on behalf of state, territory and Australian governments. From 1991, de-identified notification data for diseases on the National Notifiable Diseases List (NNDL)[78] have been forwarded from Australian jurisdictions to the NNDSS. An evaluation published in 2004 concluded that NNDSS was a highly valued and well-used resource on communicable disease activity in Australia, with strengths of acceptability, stability and simplicity, plus relative weaknesses of inflexibility, lack of timeliness, and lack of clearly stated aims and objectives.[31] More recently, fragmentation of data collection, with jurisdictions collecting and storing information differently, has been identified as a barrier to effective national infectious diseases surveillance.[22]

The Australian Government funds several important public health programs, including the Immunise Australia Program, which provides free vaccination through the National

Immunisation Program (NIP), and is responsible for managing imported infectious disease risks and national health emergencies.[22] Despite a well-resourced healthcare system, a life-expectancy gap of 11.5 years for males and 9.7 years for females at birth persists between Aboriginal and Torres Strait Islander (Indigenous) Australians and non-Indigenous Australians.[79] In line with the National Indigenous Reform Agreement (Closing the Gap), CDNA has set targets to improve Indigenous status reporting in NNDSS. This will support more accurate reporting of the health of Indigenous Australians and measurement of progress toward closing the gap in Indigenous disadvantage for notifiable communicable diseases.[80] From 2008, this target has been 95% completeness of Indigenous status reporting for 18 priority diseases and 80% for the remaining notifiable diseases in NNDSS.[30] The purpose of this study was to describe selected system attributes and changes in surveillance practices over the first 21 years of the NNDSS to inform interpretation of NNDSS data and to identify aspects of NNDSS that could be improved.

2.2.3 Methods

Information regarding NNDSS and surveillance practices was obtained through discussion with Commonwealth and jurisdictional surveillance staff, annual NNDSS surveillance surveys (2001–2011), and published literature. Line listed data for all cases notified to NNDSS from 1 January 1991 to 31 December 2011 were reviewed. The study dataset, extracted from NNDSS in 2012, contained 2,438,054 case notifications and included case notifications received by NNDSS when the disease was not nationally notifiable and cases of Creutzfeldt-Jakob diseases, which are notifiable to a different national surveillance system.[78]

The NNDSS was briefly described, including CDNA goals for national surveillance and relevant legislation. Selected system attributes were evaluated using CDC's *Updated Guidelines for Evaluating Surveillance Systems*, including flexibility, data quality, and timeliness.[55] Within this structure, we highlighted changes in the NNDSS or in surveillance

practice that potentially impact NNDSS data, including diagnostic methods and testing practices. We reported changes in the proportion of notified cases diagnosed using different tests across three sub-periods (1991–1997, 1998–2004, and 2005–2011). These sub-periods were selected to allow meaningful summary comparison of changes in NNDSS across the entire study. Testing practices were examined using the data-field "reason for the diagnostic test", with the possible responses of "clinical presentation", "contact tracing or epidemiological link", and "screening". Cases notified in a jurisdiction and year in which >50% of cases had this data field complete were included in analysis of testing practices (Tasmania all years; Victoria from 1998; Western Australia from 2001; South Australia from 2007). Reason for testing was compared for the nine most frequently notified diseases (chlamydial infection, hepatitis C, campylobacteriosis, pertussis, salmonellosis, influenza, gonococcal infection, hepatitis B and Ross River virus), which made up 85% of all notifications.

Flexibility was assessed through description of changes in notifiable diseases, data fields, case definitions, and technology over the 21-year study period.

Data quality was assessed by examining completeness and validity of the study dataset. Missing data were defined as an observation field, which was blank; had non-informative data (e.g., "no information provided"); or had a value outside the plausible range (e.g., age <0 years or disease onset date after the study period). For certain variables, data completeness was analysed for a subset of all notifiable diseases as follows: vaccination history for cases aged <7 years and diseases included in the childhood vaccination schedule funded through the NIP; country of acquisition for diseases that are 'often travel-associated' based on disease epidemiology (brucellosis, chikungunya, cholera, dengue, hepatitis A, hepatitis D, hepatitis E, Japanese encephalitis, leprosy, malaria, measles, mumps, poliomyelitis, rubella, tuberculosis, tularaemia, and typhoid fever); and serogroup/organism for legionellosis,

malaria, meningococcal disease (invasive), pneumococcal disease (invasive), and salmonellosis.

Completeness of reporting of Indigenous status was assessed overall, as well as for 17 of 18 priority diseases for Indigenous status reporting identified by CDNA (excluding HIV which is not notifiable to NNDSS).[30] The 18 priority notifiable diseases for Indigenous status reporting are: dengue virus (locally acquired), donovanosis, gonococcal infection, *Haemophilus influenzae* type b, hepatitis A, hepatitis B (newly acquired), hepatitis C (newly acquired), HIV, leprosy, measles, meningococcal disease (invasive), pertussis (age <5 years), invasive pneumococcal disease (age <5 years), invasive pneumococcal disease (age ≥50 years), shigellosis, syphilis (congenital), syphilis (<2 years duration), and tuberculosis. Data validity was assessed by examining unexpected patterns in the study dataset and identifying values outside a plausible range, specifically age<0 years and ≥110 years; and date of disease onset, specimen collection, and notification outside the study period (before 1991 or after 2011). Due to an unexplained rise in notified cases, the number of cases notified from the Northern Territory in 1996 was compared between the study dataset (extracted from NNDSS in 2012) and online (live) NNDSS data that has undergone subsequent updates and data cleaning.[81]

Timeliness was assessed by calculating time to notification by disease, jurisdiction, and sub-period. Time to notification was calculated as the number of days from the date of symptom onset (onset date) to the date the notification was received by the jurisdiction (notification received date), where both these dates were reported and the notification received date was after the onset date. Time to notification was reported by diseases if it could be calculated for at least 100 cases.

NNDSS data were provided by the Australian Government's Office of Health Protection on behalf of CDNA jurisdictional members in March 2012 as an extract from the national data file. The project was approved by the Monash Human Research Ethics Committee and CDNA jurisdictional members. Data were analysed using Stata 12 (StataCorp, Texas USA).

2.2.4 Results

The CDNA has identified the following goals for national surveillance: identify national trends; guide national policy development and resource allocation; monitor the need for and impact of national disease control programs; coordinate response to national or multi-jurisdictional outbreaks; describe the epidemiology of rare diseases; meet international reporting requirements (e.g. to the WHO); and support federal government quarantine activities.[30] By 2011, 65 communicable diseases were notifiable to NNDSS (Table 2:6). The *National Health Security Act 2007* provides a legislative framework for the NNDL and exchange of public health surveillance information between Australian state/territory and federal governments and with other countries or the WHO.[25] All eight Australian jurisdictions have signed the National Health Security Agreement, which enacts the *National Health Security Act 2007* and enshrines the importance of national surveillance and the role of CDNA. Case notification data were sourced from jurisdictions and population data from the Australian Bureau of Statistics. Under their respective public health legislations, jurisdictions received notifiable diseases data from clinical sources (doctors and hospitals) and laboratories. To protect patient privacy, identifying information was removed from case records prior to submission to NNDSS, with the exception of postcode of residence. Jurisdictions were able to re-identify cases if required. Australian Government Department of Health staff were responsible for reviewing, cleaning, analysing, and interpreting NNDSS data, which were discussed at the fortnightly CDNA meetings. Aggregate data tables and

fortnightly summaries were available on the Internet, and quarterly and annual summaries were published in *Communicable Disease Intelligence.*

Flexibility

Notifiable diseases: In 1991, 37 diseases were nationally notifiable, increasing to 65 by 2006 (Table 2:6, Figure 2.2a). All 65 diseases were notifiable by all eight jurisdictions, with the exception of campylobacteriosis and varicella zoster virus infections, which were not notifiable in New South Wales. Two diseases were taken off the NNDL during the study period (chancroid and hydatid disease) and four diseases were not included on the NNDL but had cases notified (chikungunya virus disease, non-tuberculosis mycobacterial diseases, rotavirus, and yersiniosis). Some of the observed increase in annual notification numbers can be attributed to the addition of diseases to NNDL (Figure 2.2a). Twenty-one diseases were consistently notifiable across jurisdictions for the entire study period, accounting for 36% of all notifications (Table 2:6). There is an established process for adding and removing diseases to the NNDL.[82]

Case definitions: Case definitions were initially determined by jurisdictions. Uniform case definitions were recommended by the National Health and Medical Research Commission (NHMRC) in 1993,[83] however national surveillance case definitions were not used by all jurisdictions until 2005 and have been continually updated since.[31, 84]

Data fields: In 1991, NNDSS comprised 12 core data fields, expanding to 26 core data fields by 2011 (Table 2:7). Four of five mandatory fields – record reference number, notifying jurisdiction, disease, and notification received date – were included from 1991, with confirmation status (confirmed vs. probable case) added later. Of the non-mandatory fields, some were relevant to all notified cases (e.g. age, sex, Indigenous status) while others only to

selected notifications (e.g. species, vaccination status, outbreak reference). Twenty-three of 25 core NNDSS data fields were included in the study dataset (Table 2:7).

Notifier: Jurisdictions initially relied heavily on clinicians to notify cases, but during the study period this shifted toward notification by laboratories, supported by legislative changes. For example, laboratory notification was informal in Western Australia from 1991 to 2005 but was thereafter mandated by the *Health Amendment Act 2006*. By 2013, the proportion of cases notified by laboratory report alone was ≥95% in the Australian Capital Territory, New South Wales, the Northern Territory, Queensland and Tasmania but only 4% in South Australia.[30]

Technology: In 1991, jurisdictions received notifications by paper, telephone and fax, with several jurisdictions later developing capacity to directly import electronic notifications from clinicians. During the study period, electronic laboratory reporting (ELR) became well established in Queensland (covering 90% of the population from 2002 to 2006)[85] but not in other jurisdictions. Initially, jurisdictional notification data were sent to the Australian Government Department of Health fortnightly in paper form, on diskette or electronically and manually entered into the NNDSS. From 2004, NNDSS has received daily electronic uploads of standardised case notification data from the electronic jurisdictional surveillance systems using a Data Acquisition System.[31]

Data quality

Data completeness is summarised in Table 2:8. Indigenous status was complete for 44% of all notifications [jurisdictional range 19%–87%] and >75% in three jurisdictions (the Northern Territory, South Australia and Western Australia). For the 17 priority diseases assessed, Indigenous status was reported for 68% of cases [jurisdictional range 42%–92%]. Vaccination data were reported for 62% [jurisdictional range 32%–100%] of relevant cases

overall. Country of acquisition was reported for 24% of cases for diseases that are 'often travel associated'. Completeness of reporting improved for most data fields; however, onset date completeness dropped from 92% to 51% between the earliest and latest periods.

Laboratory testing methods were reported for 65% of all notified cases [jurisdictional range 0%–89%], with completeness increasing over the study period. The proportion of cases diagnosed using PCR increased over each sub-period (1% [1991–1997], 16% [1998–2007], and 49% [2005–2011]) but remained stable for serology (14%, 16%, 13%) and culture (22%, 19%, 19%) (Figure 2.2b). The median annual number of cases diagnosed using PCR increased from 492 (1991–1997) to 74,119 (2005–2011).

Testing practices were analysed for 756,434 (31%) cases. Of these, 'reason for diagnostic test' was complete in 89%, with ≥95% of campylobacteriosis, influenza, pertussis, Ross River virus infection and salmonellosis cases diagnosed because of clinical presentation. In comparison, 78%–80% of notified cases of chlamydial infection, gonococcal infection, hepatitis B and hepatitis C were reported as diagnosed through clinical presentation. The reported proportion of cases detected through clinical presentation also differed between Indigenous and non-Indigenous cases (52% vs. 90%).

Data validity: Reported age at onset was <0 years for four cases and >110 years for 36 cases. A spike of 1,381 cases aged 99 years likely indicates data entry errors (unknown age was coded as 999). Onset, specimen collection, and notification dates were complete in 62%–83% cases. When reported, these dates fell outside the study period for 0.06%–0.20% of cases. We identified a discrepancy between the study data extract and NNDSS data published online in data from the Northern Territory in 1994: 7,267 cases were included in the study dataset compared to 4,776 cases reported online. This discrepancy was caused by a change to the "notification ID" used by the Northern Territory in 2010/11, resulting in some existing

notifications from 1994 appearing again as new notifications; the error was noted and corrected after the study dataset was extracted in 2012.

Timeliness

Median time to notification (calculated for 1,509,073 [62%] cases) was eight days [interquartile range (IQR) 4–17 days] for all diseases, decreasing from 11 days [IQR 6–21 days] in the earliest period to five days [IQR 3–11 days] in the latest period, albeit with jurisdictional variability (Figure 2.3). Median time to notification was shortest for hydatid infection, influenza, invasive meningococcal disease, rotavirus, and varicella infection (three days) and longest for leprosy (31 days), tuberculosis (59 days), and CJD (99 days), potentially reflecting subacute disease onset and diagnostic challenges for these diseases.

2.2.5 Discussion

During its first 21 years of operation, Australia's NNDSS expanded dramatically in terms of number of notifiable diseases and data fields included (indicating system flexibility), as well as marked increases in annual case notifications. NNDSS performance improved over that time, evidenced by better data completeness and timeliness. The increase in notification numbers in the latest period appear partly attributable to improved case ascertainment resulting from changing diagnostic methods (e.g. adoption of PCR) and more frequent testing. Our results will help inform interpretation of NNDSS data, including observed changes in notification incidence for selected diseases.[86]

When compared to the CDNA's stated goals for national infectious diseases surveillance,[30] NNDSS data can be used to describe the epidemiology of rare diseases and meet international reporting requirements. The system's capacity to support quarantine activities and effectively coordinate response to national or multi-jurisdictional outbreaks is dependent on notification timeliness, which improved on two levels during the study period. First, the time from

disease onset to jurisdictional notification reduced. Second, data uploads from jurisdictions to NNDSS changed from fortnightly to daily. Data completeness likewise improved, which enhances the capacity of NNDSS to guide national policy development and resource allocation, and monitor the need for and impact of national disease control programs. Several factors likely contributed to improved case ascertainment during the study period, including the increased use of PCR testing. This potentially limits the ability to identify national trends in the epidemiology of infectious diseases using NNDSS data.

The addition (and removal) of diseases and fields, and ongoing case definition modifications indicates a flexible system. More recently however, the system has demonstrated greater constancy, evidenced by fewer changes to the list of nationally notifiable disease and data fields, and greater consistency between jurisdictions, evidenced by adoption of nationally agreed case definitions and development of the Series of National Guidelines (SoNGs) which promote nationally consistent responses to notifiable disease events.[30, 84, 87]

Data completeness improved over the study period for all data fields except onset date. This reflects increasing reliance on notifications from laboratories rather than clinicians. While automated electronic laboratory notifications improve the completeness and timeliness of notifications,[88-90] increased reliance on laboratory-only notifications could result in reduced data completeness and accuracy for certain clinical, demographic and risk factor fields including onset date and Indigenous status. Jurisdictions can contact the treating doctor and/or case patient and request further data, such as onset date; however active follow-up of cases does not occur routinely for all diseases and is not feasible in the era of ELR with jurisdictions receiving tens of thousands of notifications per year. Jurisdictions must decide which diseases warrant active follow-up for public health action, including identification and management of susceptible contacts.

Indigenous Australians, who account for approximately 3% of Australia's population, continue to have worse health outcomes and shorter life expectancy than non-Indigenous Australians.[79] Improving identification in communicable disease reporting should contribute to better health for Indigenous Australians,[91] with more accurate quantification of the differential burden of notifiable infectious diseases to inform development and evaluation of targeted policies. During the study period, the CDNA targets for completeness of Indigenous status reporting were not met, although completeness did improve. Additional strategies to improve Indigenous status identification in communicable disease reporting include legislation of mandatory reporting of Indigenous status; documentation of Indigenous status on pathology request forms; a non-defaulting, mandatory data item on Indigenous status in electronic health records; and data linkages with other health-related data sources.[66, 67, 91-93] In Victoria, linkage of hepatitis B, hepatitis C and gonococcal infection notification data with hospital datasets improved completeness of Indigenous status reporting from 38% to >99% and resulted in a two- to four-fold increase in notification incidence for these diseases among Indigenous Victorians.[67]

Completeness of vaccination history for relevant diseases improved during the study period, although missing data remained for 17% of cases in the most recent study period. The Australian Childhood Immunisation Register (ACIR) has recorded details of vaccinations received by children aged <7 years since 1996.[94] Recently, ACIR records for around two million children were linked to notification datasets in Western Australia and New South Wales to evaluate and inform Australia's immunisation program.[72] Until such data linkage is routinely available throughout Australia, NNDSS must continue to strive for complete and accurate vaccination status data for notified vaccine preventable disease cases.

Country of acquisition provides useful information about the epidemiology of infectious diseases in destination countries, as well as disease risks for travellers to those destinations.[95]

It is also important to identify when diseases, such as dengue, are locally acquired to facilitate appropriate public health interventions. Country of acquisition was only collected for one quarter of cases for diseases defined as 'often travel-associated', although this would have improved with retrospective addition of data from two jurisdictions after extraction of study data in 2012. Another risk factor for many infectious diseases, country of birth, is not collected in NNDSS core data fields but could be used to identify at-risk groups requiring targeted interventions to diagnose and/or prevent infection. Country of birth, country of acquisition and postcode data from England's national surveillance system were used to identify large communities of south Asian heritage at particular risk for *Plasmodium vivax* malaria, specifically when visiting friends and relatives (VFR-travel) in India and Pakistan.[96] Country of birth is collected in six of eight Australian jurisdictions,[97] and its addition to NNDSS could enhance the system without imposing significant additional work on notifiers or jurisdictional public health staff.

We identified a discrepancy between the study data extract and NNDSS data published online relating to notifications from the Northern Territory in 1994. Notification data is uploaded daily from jurisdictions to NNDSS and changes made at the jurisdictional level will affect the NNDSS dataset. The ongoing cleaning of NNDSS data, with identification and correction of data errors indicates a robust data quality system, which is essential for a passive national surveillance system.

The system improvement allowing daily electronic data uploads to NNDSS is critical to support coordinated responses to national or multi-jurisdictional outbreaks. Following introduction of an Internet-based communicable-disease reporting system in China in 2004, the mean length of time to report from county-level health facility to central level fell from 29 days to one day.[98] Our observed differences in time to notification between diseases reflect the acuteness of symptom onset; notification source and method also influence notification

delay.[90] In Sweden, shorter notification delay was noted for laboratory compared to clinical notifications and electronic compared to paper notifications,[89] with subsequent discouragement of paper-based notification.[99] The US CDC aim to receive 80% of laboratory reports to public health agencies electronically by 2016 to improve timeliness.[100] Transition of all Australian jurisdictions to ELR would further improve notification timeliness.

The *National Framework for Communicable Disease Control* (2014) highlights fragmentation of data collection and incompatible data systems as barriers to effective national infectious diseases surveillance in Australia.[22] Several countries, including China, Germany, Ireland, the Netherlands, and Sweden have introduced electronic communicable disease surveillance systems that are consistent between the national and sub-national jurisdictions.[90, 98, 99, 101, 102] Sweden's integrated surveillance system receives almost all notifications electronically.[99] In contrast, some Australian jurisdictions manually entered all case notification data, which is time and resource intensive. Electronic notification from both clinicians and laboratories in Australia has potential to improve system simplicity, sensitivity, data completeness, and timeliness. A nationally integrated system, which includes the same electronic platform and user interface across jurisdictions, would promote consistent collection and storage of notification data and contribute to a less fragmented system of national surveillance.

Evaluation of sensitivity, predictive value positive, and representativeness of NNDSS is beyond the scope of this study, particularly as these parameters vary markedly between different diseases. Even among bacterial gastrointestinal pathogens, it was estimated NNDSS detected one in seven salmonellosis but one in 10 campylobacteriosis cases.[36] Data from the ECDC-funded Burden of Communicable Diseases in Europe (BCoDE) project suggest that case ascertainment for salmonellosis and campylobacteriosis in European countries are disease-, country-, age- and sex-specific.[35] It is likely that case ascertainment improved over

the study period, including as a result of legislative changes mandating laboratory notification. We were not able to quantify case ascertainment for all diseases and jurisdictions, however there was no apparent increase in notification incidence in Western Australia as a result of legislation mandating laboratory notification introduced in 2006.[86] Our data also suggest that case ascertainment improved over the study period through improved diagnostic tests (particularly PCR) and an increase in testing. Other Australian studies have attempted to quantify the effect of more frequent testing on increased notification rates for chlamydial infection, gonococcal infection, pertussis and influenza.[41, 103-105]

In summary, the NNDSS expanded and evolved over its first 21 years, demonstrating flexibility along with improvements in data quality and notification timeliness. Data linkage strategies designed to improve completeness of Indigenous status and vaccination status should be explored to optimise planning and assessment of public health interventions. An increasing proportion of notified cases were diagnosed by PCR, and NNDSS will need to continue to accommodate evolving laboratory diagnostics and testing practices, including whole genome sequencing and antibiotic resistance data, to support optimal public health prevention and control activities. International experience supports the benefits and feasibility of an electronic communicable disease surveillance system that is consistent between the national and sub-national jurisdictions, as well as electronic reporting from laboratories and clinicians. Our findings support the *National Framework for Communicable Disease Control*'s recommendations for an integrated platform that enables real-time assessment of potential outbreaks, automatic ELR of notifiable diseases to jurisdictional and federal health departments, and formalised linkages with existing data to assure optimised prevention and control of communicable diseases.[22]

Table 2:6: Diseases included in NNDSS in 1991 (foundation year) and diseases subsequently added to NNDSS by year, Australia 1991–2011

Diseases included in NNDSS in 1991	Study year	Diseases added in NNDSS after 1991
Arbovirus infection (NEC)	1993	Botulism
Brucellosis†		
Campylobacteriosis*†	1994	Hepatitis B – newly acquired
Chancroid		Ross River virus infection
Cholera†		Rubella
Dengue		
Diphtheria†	1995	Chlamydial infection†
Donovanosis		
Gonococcal infection†	1996	Barmah Forest virus
Haemophilus influenzae type b		Hepatitis C – newly acquired
Hepatitis (NEC)		Hepatitis C – unspecified
Hepatitis A virus†		Mumps
Hepatitis B – unspecified		
Hydatid infection	2000	Haemolytic uraemic syndrome
Legionellosis†		Hepatitis D
Leprosy†		Hepatitis E
Leptospirosis†		Shiga-/Vero-toxin producing *Escherichia coli*
Listeriosis		
Malaria†	2002	Australian bat lyssavirus/Lyssavirus (NEC)
Measles†		Cryptosporidiosis
Meningococcal disease†		Influenza
Ornithosis		Japanese encephalitis
Pertussis†		Kunjin / West Nile virus
Plague†		Murray Valley encephalitis virus
Poliomyelitis†		Pneumococcal disease (invasive)
Q fever†		
Rabies	2004	Severe acute respiratory syndrome (SARS)
Rubella – congenital†		Smallpox
Salmonellosis†		Tularaemia
Shigellosis		
Syphilis	2005	Highly pathogenic avian influenza in humans
Syphilis – congenital†		Syphilis >2 years / unspecified duration
Tetanus		Syphilis <2 years duration
Tuberculosis		
Typhoid†	2006	Varicella zoster – chickenpox*
Viral haemorrhagic fever		Varicella zoster – shingles*
Yellow fever†		Varicella zoster – unspecified*

NEC – not elsewhere classified
†diseases which were consistently notifiable across states for the entire study period
* not notifiable in New South Wales

Table 2:7: Core data fields of the National Notifiable Diseases Surveillance System, Australia 1991–2011

Data field (all included in the study dataset)	Included in			Mandatory field	Comments
	1991	2003*	2011		
Age / Date of birth	Yes	Yes	Yes	No	Only 'age' included in study dataset
Case identification number	Yes	Yes	Yes	Yes	*Not included in study dataset*
Confirmation status	Yes	Yes	Yes	Yes	'Confirmed' or 'Probable'
Date of symptom onset	Yes	Yes	Yes	No	
Disease	Yes	Yes	Yes	Yes	
Fortnight of report to CDNA	Yes	No	No		*Not included in study dataset*
Indigenous status	Yes	Yes	Yes	No	Aboriginal and/or Torres Strait Islander
Jurisdiction	Yes	Yes	Yes	Yes	
Notification date	Yes	Yes	Yes	No	Date notifying doctor or laboratory signed / authorised the notification
Notification received date	Yes	Yes	Yes	Yes	Date jurisdiction received the notification
Postcode of residence	Yes	Yes	Yes	No	
Sex	Yes	Yes	Yes	No	
Case found by	No	Yes	Yes	No	Reason for diagnostic test: Clinical presentation, contact tracing or epidemiologic link, screening
Country of acquisition	No	Yes	Yes	No	
Died from disease	No	Yes	Yes	No	
Laboratory diagnosis method	No	Yes	Yes	No	
Organism	No	Yes	Yes	No	From 1995, e.g. malaria, legionellosis
Outbreak reference	No	Yes	Yes	No	Selected cases only
Serogroup	No	Yes	Yes	No	From 1995, e.g. *Neisseria meningitides, Streptococcal pneumoniae, Salmonella*
Specimen date	No	Yes	Yes	No	Date diagnostic specimen was collected
Vaccination status	No	Yes	Yes	No	Older vaccination fields
Doses of vaccine	No	Yes	Yes	No	Older vaccination fields
Vaccination validation	No	Yes	Yes	No	Older vaccination fields
Date of last vaccination	No	No	Yes	No	Newer (replacement) vaccination fields
Combined vaccination schedule	No	No	Yes	No	Newer (replacement) vaccination fields

*Data from Miller et. al. 2004[31]

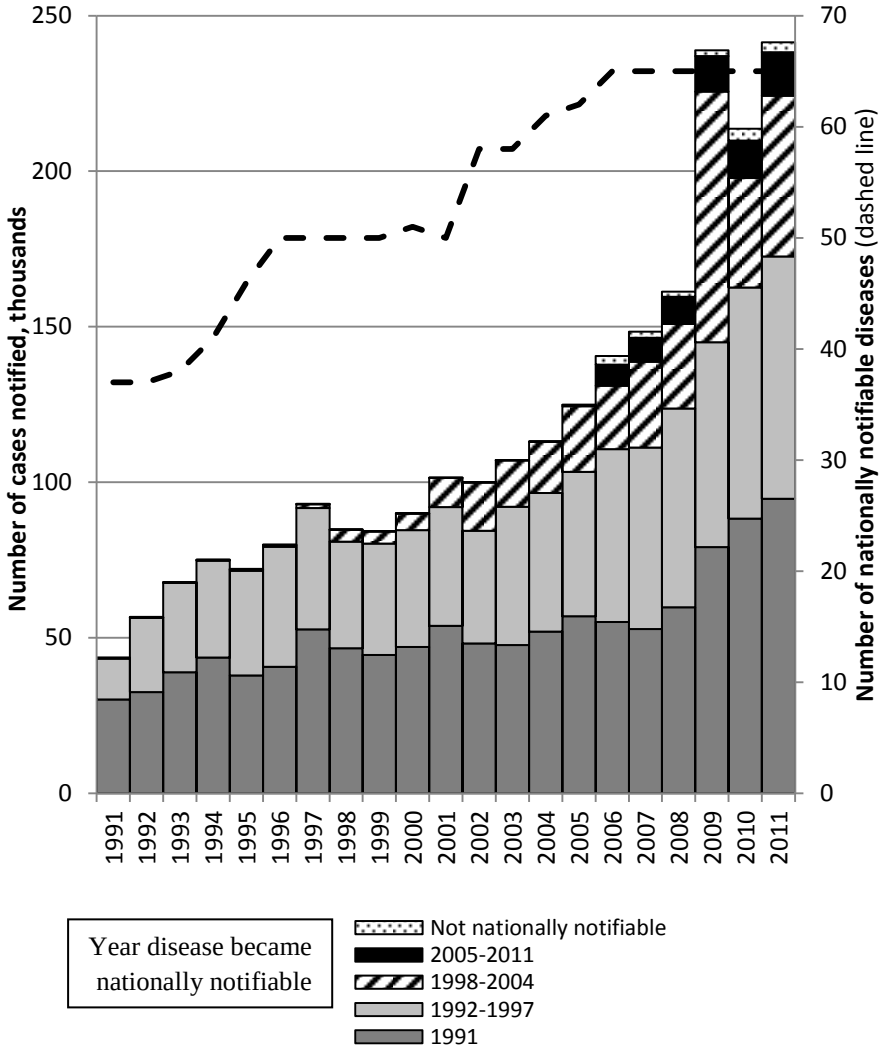
Table 2:8: Data completeness by sub-period, National Notifiable Diseases Surveillance System—Australia, 1991–2011

	Completeness, % [jurisdictional range]					
	1991–1997		1998–2004		2005–2001	
Case found by	3.2	[0–100]	28.6	[0–99.4]	38.2	[0–99.99]
Country of acquisition*	8.8	[0–89.0]	29.6	[0–60.6]	59.1	[0–80.2]
Death	17.3	[0–100]	29.1	[0.1–99.97]	44.0	[0.3–100]
Indigenous status	30.4	[2.1–78.8]	43.4	[21.7–89.4]	50.0	[19.8–93.2]
Lab diagnosis method	20.8	[0.9–69.2]	56.0	[89.8–2.1]	88.1	[30.3–99.7]
Notification date	59.5	[0.8–100]	82.0	[9.6–100]	92.9	[63.6–99.8]
Onset date	92.2	[70.1–99.99]	61.9	[29.5–100]	50.6	[9.9–100]
Outbreak reference no.	12.1	[0–99.8]	9.8	[0–99.9]	6.3	[0–100]
Serogroup*	19.4	[5.5–53.8]	50.1	[26.2–71.0]	47.5	[16.9–68.6]
Specimen date	59.0	[0–99.8]	74.1	[0–99.99]	94.9	[0.6–99.8]
Vaccination status*	36.8	[0–100]	56.9	[38.4–100]	83.2	[71.5–100]

Data complete for 97.6%–100% of cases for the following fields: Age, confirmation status, disease, jurisdiction, notification received date, postcode of residence, sex, and organism
*Completeness assessed for relevant subset of notified cases

Figure 2.2: Cases notified to the National Notifiable Diseases Surveillance System (NNDSS) by year, Australia 1991–2011

2.2a. According to year the disease became nationally notifiable



2.2b. According to year and diagnostic test used

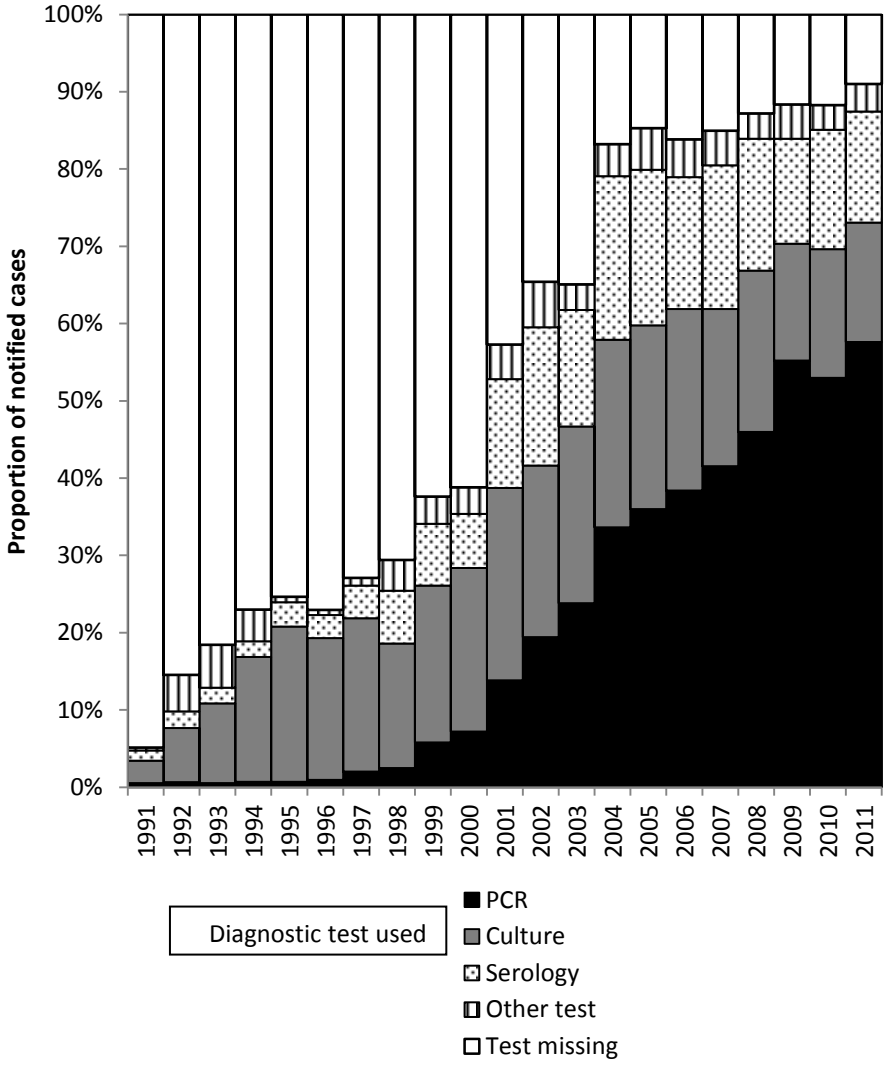
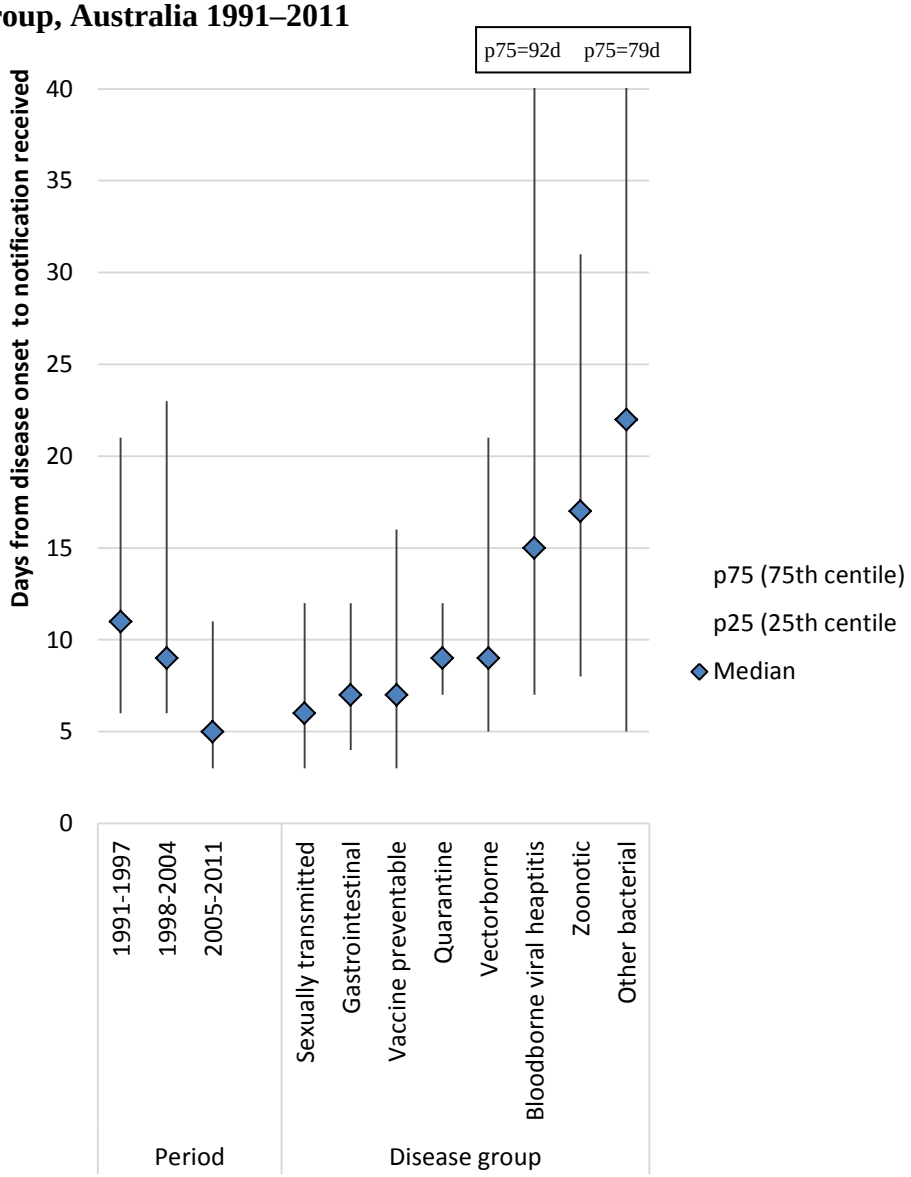


Figure 2.3: Time (in days) from disease onset to notification received, period and disease group, Australia 1991–2011



Chapter Three: Overview of the epidemiology of nationally notifiable infectious diseases in Australia

Declaration for thesis Chapter 3

Declaration by candidate

In the case of Chapter 3.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Allen Cheng	Advice regarding statistical analysis; revision of manuscript from preliminary draft to submission	
Robert Hall	Initial concept of NNDSS review; sourcing data; revision of manuscript from preliminary draft to submission	
Karin Leder	Revision of manuscript from preliminary draft to submission	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature	[redacted]	**Date** 11th July, 2016

Aim: To understand the epidemiology of nationally notifiable diseases in Australia over a 21-year period using data from NNDSS in order to inform changes to communicable disease surveillance and control in Australia.

Preface

In keeping with the reporting requirement of a public health surveillance system, NNDSS data are freely available online in the form of aggregate data tables which are updated daily; fortnightly summary reports; and annual reports. More detailed longitudinal analyses of selected individual diseases have also been published. However, in Australia there has been no overview of all notifiable conditions since NNDSS began collecting data in 1991. Longitudinal and inclusive analyses of national surveillance data can highlight the value of public health programmes. In a recent dramatic demonstration of this, analysis of communicable disease surveillance data in the US from 1888 to 2011 (Project Tycho) estimated that immunisation programmes in the US prevented 103 million cases of childhood vaccine preventable diseases (95% of those that would have otherwise occurred) from 1924 to 2011, including 26 million cases (99% of those that would otherwise have occurred) from 2002 to 2011.[106] The objective of Project Tycho – to advance the availability and use of public health data for science and policy – is echoed in the analyses presented in this thesis which, despite not being solely focussed on vaccine preventable diseases, aims to inform changes to communicable disease surveillance and control in Australia.

Chapter 3 contains a manuscript accepted for publication in *Epidemiology and Infection,* which summarises the first 21 years of NNDSS notifications for all nationally notifiable diseases. This represents a unique longitudinal overview of notifiable diseases in Australia, including analyses of temporal trends and comparisons between disease groups and diseases. Such analyses can be used by policymakers to prioritise conditions requiring public health

intervention, due either to high notification incidence, increasing notification incidence, or observed differences in incidence between jurisdictions or populations.

3.1 An overview of the epidemiology of notifiable infectious diseases in Australia, 1991–2011

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An overview of the epidemiology of notifiable infectious diseases in Australia, 1991–2011

K. B. GIBNEY*, A. C. CHENG, R. HALL AND K. LEDER

Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, Melbourne, Victoria, Australia

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SUMMARY

We reviewed the first 21 years (1991–2011) of Australia's National Notifiable Diseases Surveillance System (NNDSS). All nationally notified diseases (except HIV/AIDS and Creutzfeldt–Jakob disease) were analysed by disease group ($n = 8$), jurisdiction (six states and two territories), Indigenous status, age group and notification year. In total, 2 421 134 cases were analysed. The 10 diseases with highest notification incidence (chlamydial infection, campylobacteriosis, varicella zoster, hepatitis C, influenza, pertussis, salmonellosis, hepatitis B, gonococcal infection, and Ross River virus infection) comprised 88% of all notifications. Annual notification incidence was 591 cases/100 000, highest in the Northern Territory (2598/100 000) and in children aged <5 years (698/100 000). A total of 8·4% of cases were Indigenous Australians. Notification incidence increased by 6·4% per year (12% for sexually transmissible infections and 15% for vaccine-preventable diseases). The number of notifiable diseases also increased from 37 to 65. The number and incidence of notifications increased throughout the study period, partly due to addition of diseases to the NNDSS and increasing availability of sensitive diagnostic tests. The most commonly notified diseases require a range of public health responses addressing high-risk sexual and drug-use behaviours, food safety and immunization. Our results highlight populations with higher notification incidence that might require tailored public health interventions.

Key words: Analysis of data, Australia, epidemiology, public health, surveillance system.

INTRODUCTION

Surveillance is the cornerstone of public health efforts to minimize morbidity and mortality resulting from preventable infectious diseases. Infectious disease surveillance was instrumental in smallpox eradication and in current efforts towards global polio eradication and measles elimination. National surveillance systems allow examination of the epidemiological profile of important infections at a country level and provide oversight to ensure consistent reporting across jurisdictions [1].

In Australia, notification of selected infectious diseases is required by public health legislation in the six states and two territories. Each jurisdiction defines its own notification list and receives data from doctors and/or laboratories. Primary responsibility for public health action lies with the state/territory health departments. Jurisdictions forward de-identified

* Author for correspondence: Dr K. B. Gibney, The Peter Doherty Institute for Infection and Immunity, 792 Elizabeth Street, Melbourne 3000 Victoria, Australia.
(Email: Katherine.Gibney@unimelb.edu.au)

notification data for cases meeting national case definitions for diseases on the National Notifiable Diseases List (NNDL) to the National Notifiable Disease Surveillance System (NNDSS), a passive surveillance system operational since 1991.

A summary of national notifiable disease surveillance data from 1917 to 1991 highlighted the lack of consistency, detail, and methodical reporting of nationally notifiable diseases before the introduction of the NNDSS [2]. Annual reports of NNDSS data have been produced since 1991; however, trend analysis of all nationally notifiable diseases has not previously been performed. We present an overview of the epidemiology of all notifiable infectious diseases in Australia [excluding HIV/AIDS and Creutzfeldt–Jakob disease (CJD)] during the first 21 years of the NNDSS, with a view to highlighting diseases and population groups with greatest need of public health intervention to reduce disease incidence.

METHODS

All case notifications of nationally notifiable diseases to the NNDSS from 1 January 1991 to 31 December 2011 were analysed according to their diagnosis date [3]. HIV/AIDS and CJD are under different national surveillance systems and were excluded from this analysis [4]. Notifications were reported by disease and categorized into eight disease groups (as per the NNDL) based on mode of acquisition and/or public health strategies for control and prevention: bloodborne viral hepatitis (BBVH), gastrointestinal, other bacterial, quarantinable, sexually transmissible infections (STIs), vector-borne diseases (VBDs), vaccine-preventable diseases (VPDs), and zoonotic diseases. Diseases included in each group and the year they became notifiable are summarized in Table 1. NNDSS diseases were analysed by pathogen for hepatitis B, hepatitis C, rubella, syphilis, and varicella zoster.

We report the number and annual incidence of notified cases nationally and by jurisdiction. For all-cause and disease-group incidence calculations, all notified cases were included and Australian Bureau of Statistics (ABS) population estimates at 30 June for each study year were used [5]. Data from the Northern Territory (NT) were excluded from both the numerator (number of cases notified) and denominator (population) of incidence calculations for 1994 due to large discrepancies between the study dataset (extracted in 2012) and online (live) NNDSS data that has undergone subsequent data cleaning [6]. For disease-specific incidence calculations, diseases notifiable both nationally and in that jurisdiction were included (Table 1) with the exceptions of hepatitis B and C (Victoria 1991–1997), hepatitis B [South Australian (SA) 1991–1995], tuberculosis (Victoria 1991), and varicella zoster (Victoria 2006–2007) due to discrepancies with online NNDSS data; the denominator comprised the combined populations for included years and jurisdictions. Relative risks (RRs) were calculated for univariate comparison of notification incidence between study sub-periods (1991–1997, 1998–2004, 2005–2011), age groups (<5, 5–19, 20–64, 65–98 years) and jurisdictions for diseases with >400 notifications during the 21-year study period. Three sub-periods were selected to allow more meaningful comparison between disease groups/diseases within a sub-period as well as analysis of change in notification incidence across these sub-periods for a single disease or disease group.

Average changes in annual notification incidence over the study period were investigated by Poisson regression for all diseases combined and by disease group from 1991 to 2011; for individual diseases this calculation was confined to years the disease was nationally notifiable. Tests for statistical significance were not performed as population-based data were used. To allow international comparison, age-standardized incidence rates were calculated using the WHO world standard population distribution [7].

Incidence rates for Aboriginal and Torres Strait Islander ('Indigenous') Australians were calculated for the three jurisdictions reporting Indigenous status for >75% of notified cases [NT, SA, and Western Australia (WA)] using ABS population estimates [8, 9]; cases with unknown Indigenous status were presumed non-Indigenous.

NNDSS data were provided by the Australian Government's Office of Health Protection on behalf of Communicable Diseases Network Australia (CDNA) jurisdictional members in March 2012 as an extract from the national data file.

Ethical considerations

The project was approved by the Monash Human Research Ethics Committee (project no. CF11/2357–201) and CDNA jurisdictional members. Data were analysed using Stata v. 12 (StataCorp., USA). This work did not involve human or animal experimentation.

Table 1. *Diseases included in the National Notifiable Diseases Surveillance System (NNDSS) by disease group and year introduced, Australia 1991–2011*

	Year*	Variation by jurisdiction
Bloodborne viral hepatitis		
Hepatitis B (newly acquired)	1993	1994 in Qld and WA, 1995 in ACT
Hepatitis B (unspecified)	1991	2005 in NT
Hepatitis C (newly acquired)	1993	1995 in ACT, Tas and WA, 2005 in NT, not notifiable in Qld
Hepatitis C (unspecified)	1995	Included incident cases until hepatitis C newly acquired introduced
Hepatitis D	1999	2002 in WA
Hepatitis (NEC)	1991	2001 in WA. Included reports of hepatitis D and E 1991–1998
Gastrointestinal diseases		
Botulism	1992	1993 in SA, 1998 in NT and NSW, 2001 in WA
Campylobacteriosis	1991†	Not notifiable in NSW
Cryptosporidiosis	2001	
Haemolytic uraemic syndrome	1999	
Hepatitis A	1991†	
Hepatitis E	1999	2001 in WA
Listeriosis	1991	1992 in SA, 1994 in NT
Salmonellosis (non typhoidal)	1991†	
Shiga-/Vero-toxin-producing *E. coli*	1999	2001 in Qld and WA
Shigellosis	1991	2001 in NSW
Typhoid fever	1991†	Includes paratyphoid in NSW, Qld and Vic
Quarantinable diseases		
Cholera	1991†	
Highly pathogenic avian influenza (human)	2004	Reported under influenza in WA
Plague	1991†	
Rabies	1991	1993 in ACT, 1997 in NSW
Severe acute respiratory syndrome	2003	
Smallpox	2004	
Viral haemorrhagic fever	1991	1993 in ACT
Yellow fever	1991†	
Sexually transmissible infections		
Chancroid	1991	No longer nationally notifiable from 2000
Chlamydial infection	1994	1999 in NSW
Donovanosis	1991	1993 in Tas, 2002 in NSW and SA
Gonococcal infection	1991†	
Syphilis	1991	Includes syphilis <2 and >2 years/unknown duration to 2004
Syphilis (<2 years duration)	2004	
Syphilis (>2 years or unknown duration)	2004	Not reported in SA
Syphilis (congenital)	1991†	
Vaccine-preventable diseases		
Diphtheria	1991†	
Haemophilus influenzae type b	1991	1994 in WA
Influenza (laboratory confirmed)	2001	2008 in SA
Measles	1991†	
Mumps	1995	Not reported by Qld in 1995–96, 1999–2000
Pertussis	1991†	
Pneumococcal disease (invasive)	2001	
Poliomyelitis	1991†	
Rubella	1993	1995 in Tas
Rubella (congenital)	1991†	
Tetanus	1991	1994 in Qld
Varicella zoster (chickenpox)	2006	Not notifiable in NSW
Varicella zoster (shingles)	2006	Not notifiable in NSW
Varicella zoster (unspecified)	2006	Not notifiable in NSW

Table 1 (*cont.*)

	Year*	Variation by jurisdiction
Vector-borne diseases		
Arbovirus infection (Not elsewhere classified)	1991	1991–2000 included Japanese encephalitis, Kunjin, and Murray Valley encephalitis (MVE) notifications
Barmah Forest virus infection	1995	
Dengue virus infection	1991	1993 in ACT, 1995 in WA
Japanese encephalitis virus infection	2001	
Kunjn virus infection	2001	Reported as MVE in ACT
Malaria	1991†	
Murray Valley encephalitis virus infection	2001	
Ross River virus infection	1993	
Zoonoses		
Anthrax	2001	2002 in SA
Australian bat lyssavirus infection	2001	
Brucellosis	1991†	
Hydatid infection	1991	No longer nationally notifiable from 2001
Leptospirosis	1991†	
Lyssavirus (not elsewhere classified)	2001	
Ornithosis	1991	2001 in NSW, Qld did not report 1991, 1997–2001
Q fever	1991†	
Tularaemia	2003	
Other bacterial diseases		
Legionellosis	1991†	
Leprosy	1991†	
Meningococcal disease (invasive)	1991†	Includes conjunctival cases from ACT and NSW
Tuberculosis	1991	

Source: NNDSS online (live) data and 2012 NNDSS annual report [3, 6].
Excludes HIV/AIDS and Creutzfeldt–Jakob disease which are notified to other surveillance systems.
ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; Qld, Queensland; SA, South Australia; Tas, Tasmania; Vic, Victoria; WA, Western Australia.
* Year became nationally notifiable – listed as 1991 for diseases that were nationally notifiable when NNDSS began in 1991; diseases introduced after 1991 might have cases notified to NNDSS prior to becoming nationally notifiable.
† Diseases which were consistently notifiable across states for the entire study period.

RESULTS

The NNDSS contains 2 421 134 notified cases of 60 diseases from 1991 to 2011. STIs were most common [790 990 (32·7%) notifications] and quarantinable diseases least common (79 notifications, all cholera) (Table 2, Fig. 1). Chlamydial infection, notifiable from 1994, was the most commonly notified disease [621 431 (26%) notifications]. The 10 pathogens with highest notification incidence were *Chlamydia trachomatis, Campylobacter*, varicella zoster virus, hepatitis C virus, influenza virus, *Bordetella pertussis, Salmonella*, hepatitis B virus, *Neisseria gonorrhoeae*, and Ross River virus (RRV) (Tables 3 and 4); these comprised 88% of all notifications despite campylobacteriosis and varicella zoster infection not being notifiable in New South Wales (NSW), the most populous state. Fewer than 20 notifications were received for eight diseases and no notifications were received for seven diseases (Table 3).

Notification numbers increased over the study period, from 43 443 in 1991 (37 notifiable diseases) to 238 164 in 2011 (65 notifiable diseases) (Fig. 1). The national annual notification incidence increased by an average of 6·4% per year (Fig. 2), rising from 386/100 000 in the earliest sub-period (1991–1997) to 853/100 000 in the latest sub-period (2005–2011) (Table 3). Annual notification incidence fell most markedly for rubella (average 30% decrease/year), followed by *Haemophilus influenzae* type B (Hib, 25%), measles (23%), and donovanosis (17%) (Table 3). Rubella and hepatitis A were among the 10 highest incidence diseases in the earliest study sub-period (Table 4). Conversely, influenza (average 33%

Table 2. *Number, incidence, and demographics of notified cases by disease group and jurisdiction, Australia, 1991–2011*

	Notifications		Age, median	Male,	Indigenous*,	Crude incidence (/100 000 per year)		Age-standardized incidence		Crude incidence, Indigenous cases*†	
	N	(%)	years	%	%	Mean	(range)	Mean	(95% CI)	Mean	(range)
All notifications	2 421 134	(100)	27	51·0	8·4	591	(251–1092)	621	(620–622)	3764	(2211–4910)
Disease group											
Bloodborne viral hepatitis	431 608	(17·8)	34	61·1	3·4	106	(43–150)	104	(103–104)	195	(70–278)
Gastrointestinal diseases	518 808	(21·4)	24	52·8	4·5	127	(88–147)	136	(135–136)	490	(309–819)
Other bacterial diseases	36 960	(1·5)	37	55·5	5·1	9·0	(6·4–11·3)	8·7	(8·6–8·8)	27	(9–59)
Quarantinable diseases	79	(0·0)	42	50·7	2·5	0·02	(0–0·03)	0·0	(0·0–0·0)	—	—
Sexually transmissible infections	790 990	(32·7)	23	45·7	17·8	193	(50–428)	210	(210–211)	2758	(1312–3525)
Vaccine-preventable diseases	487 176	(20·1)	25	47·5	3·8	119	(17–470)	126	(126–126)	267	(22–1395)
Vector-borne diseases	137 817	(5·7)	40	51·3	2·0	34	(16–53)	31·9	(31·7–32·0)	26	(7–58)
Zoonoses	17 696	(0·7)	40	79·3	2·4	4·4	(2·4–6·6)	4·1	(4·1–4·2)	—	—
Jurisdiction											
Australian Capital Territory	38 083	(1·6)	26	51·5	0·5	560	(129–1098)	555	(549–561)		
New South Wales	584 382	(24·1)	29	53·7	1·8	430	(114–812)	449	(448–450)		
Northern Territory	110 930	(4·6)	23	47·9	58·1	2598	(1824–3653)	2512	(2497–2523)	5121	(3609–7204)
Queensland	644 556	(26·6)	26	49·1	9·7	850	(491–1504)	880	(877–882)		
South Australia	218 624	(9·0)	27	49·3	5·7	694	(291–1653)	740	(736–743)	2085	(972–4417)
Tasmania	48 633	(2·0)	24	47·6	1·1	483	(245–991)	526	(523–531)		
Victoria	501 335	(20·7)	28	52·3	0·5	494	(184–995)	507	(506–509)		
Western Australia	274 591	(11·3)	25	50·6	18·1	684	(251–1262)	713	(711–716)	3353	(1535–4340)

CI, Confidence interval.

* Assumes all cases without Indigenous status reported were non-Indigenous.

† Only calculated for jurisdictions with Indigenous status reported for >75% of notified cases (Northern Territory, South Australia, Western Australia); –, <50 Indigenous cases notified.

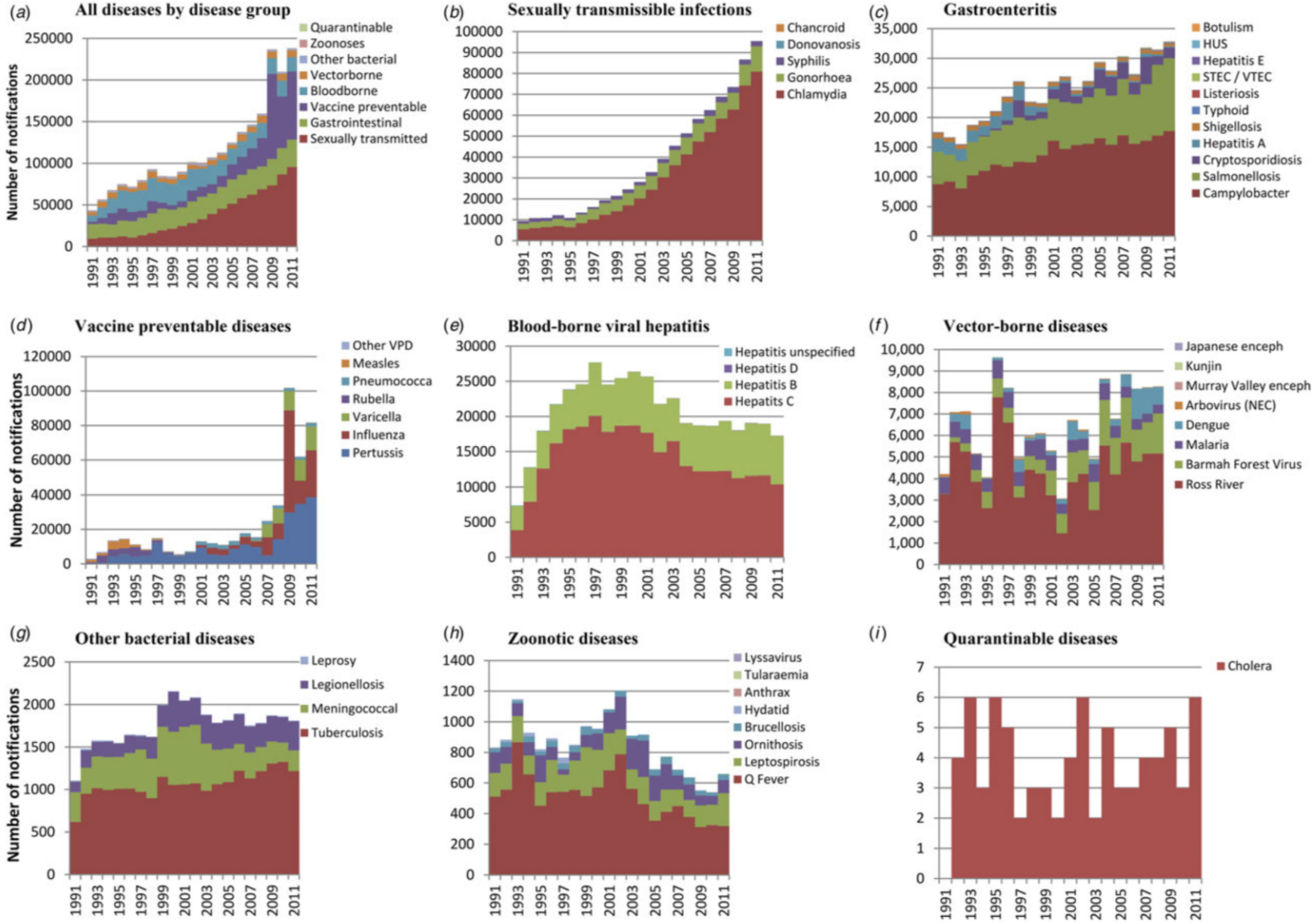

Fig. 1. Number of notifications by disease group and year, Australia 1991–2011. HUS, Haemolytic uraemic syndrome; NEC, not elsewhere classified; STEC/VTEC, Shiga/Vero-toxin-producing *Escherichia coli*; VPD, vaccine-preventable disease.

Table 3. *Infectious disease notification incidence by sub-period and age group, Australia 1991–2011*

	Overall		Average change annual inc.	Sub-period						Age group							
				1991–1997		1998–2004		2005–2011		<5 years		5–19 years		20–64 years		65–98 years	
	Cases notified	Inc.		Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR
All diseases	2 421 134	591·2	6·4%	385·9	0·5	504·5	0·6	853·0	Ref.	698·4	1·1	564·6	0·9	653·9	Ref.	262·6	0·4
Bloodborne viral hepatitis	431 608	105·6	−1·1%	108·6	1·2	122·7	1·4	87·4	Ref.	5·9	0·04	28·5	0·2	158·6	Ref.	28·6	0·2
Hepatitis B	134 797	35·8	−1·5%	41·2	1·3	36·0	1·1	32·5		2·4	0·0	14·9	0·3	51·6		11·8	0·2
Hepatitis C	296 022	73·9	−5·3%	100·2	1·8	86·9	1·6	54·8		3·3	0·0	15·6	0·1	113·0		17·4	0·2
Hepatitis D	573	0·1	3·1%	–	–	0·1	0·8	0·2		0·006	0·0	0·04	0·2	0·2		0·02	0·1
Hepatitis (NEC)	216	0·06															
Gastrointestinal diseases	518 808	126·7	2·0%	105·0	0·7	129·8	0·9	142·0	Ref.	440·4	4·2	109·4	1·1	104·2	Ref.	88·2	0·8
Botulism	16	0·005															
Campylobacteriosis	286 865	105·4	2·0%	85·9	0·7	112·4	1·0	115·2		255·3	2·6	86·7	0·9	97·2		89·4	0·9
Cryptosporidiosis	33 157	11·9	0·0%	–	–	9·9	0·8	12·9		79·0	12·2	12·9	2·0	6·5		1·8	0·3
Haemolytic uraemic syndrome	260	0·08															
Hepatitis A virus	23 506	5·7	−12·9%	11·9	8·7	4·8	3·5	1·4		4·9	0·8	7·0	1·1	6·2		1·5	0·2
Hepatitis E virus	346	0·1															
Listeriosis	1295	0·3	0·4%	0·3	1·0	0·3	1·1	0·3		0·4	1·8	0·01	0·1	0·2		1·3	5·9
Salmonellosis	157 428	38·4	3·0%	30·5	0·7	37·4	0·8	45·9		195·7	7·7	32·4	1·3	25·4		24·3	1·0
Shiga/Vero-toxin-producing *E. coli*	1035	0·4	5·7%	–	–	0·3	0·6	0·5		0·9	3·1	0·4	1·5	0·3		0·6	2·1
Shigellosis	13 297	3·8	−5·5%	6·2	2·1	3·1	1·1	2·9		17·3	5·7	3·0	1·0	3·0		1·2	0·4
Typhoid fever	1603	0·4	1·8%	0·4	0·9	0·3	0·7	0·5		0·4	1·0	0·5	1·1	0·4		0·09	0·2
Quarantinable diseases	79	0·02															
Cholera	79	0·02															
Sexually transmissible infections†	790 990	192·9	11·8%	64·4	0·2	156·3	0·5	333·8	Ref.	6·1	0·03	228·7	1·0	239·1	Ref.	11·2	0·05
Chancroid	8	0·005															
Chlamydial infection	621 431	185·1	12·5%	64·4	0·2	119·8	0·4	280·3		3·3	0·01	234·3	1·0	226·7		2·9	0·01
Donovoanosis	426	0·09	−17·5%	0·3	46·3	0·09	15·4	0·006		0·03	0·3	0·10	0·9	0·11		0·02	0·2
Gonococcal infection	130 008	31·5	5·6%	18·4	0·4	32·4	0·8	41·8		1·8	0·05	33·2	0·8	40·4		1·4	0·03
Syphilis (incl. congenital $n = 54$)	39 117	9·4	3·4%	6·8	0·6	9·3	0·8	11·7		0·9	0·07	5·2	0·4	12·2		7·1	0·6
Vaccine-preventable diseases	487 176	119·0	14·7%	57·5	0·2	51·8	0·2	241·6	Ref.	229·3	2·5	178·1	2·0	90·7	Ref.	95·9	1·1
Diphtheria	358	0·09															
Haemophilus influenzae type b	2081	0·5	−24·7%	1·4	15·7	0·1	1·5	0·09		5·6	75·2	0·3	3·5	0·07		0·2	2·6
Influenza (laboratory confirmed)	137 940	60·6	32·6%	–	–	13·4	0·2	87·8		143·0	2·8	90·5	1·8	50·9		35·1	0·7
Measles	16 780	3·9	−22·9%	11·6	29·8	0·7	1·8	0·4		17·0	18·3	10·4	11·3	0·9		0·2	0·2
Mumps	3363	1·0	0·7%	1·0	0·8	0·7	0·6	1·2		1·3	1·3	1·3	1·3	1·0		0·2	0·2
Pertussis	220 541	53·9	13·4%	25·6	0·3	33·4	0·3	96·3		86·6	2·1	87·3	2·1	41·8		39·3	0·9
Pneumococcal disease (invasive)	21 813	8·8	−4·5%			11·2	1·5	7·6		31·5	5·3	3·0	0·5	6·0		19·9	3·3

Table 3 (*cont.*)

	Overall		Average change annual inc.	Sub-period						Age group							
				1991–1997		1998–2004		2005–2011		<5 years		5–19 years		20–64 years		65–98 years	
	Cases notified	Inc.		Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR	Inc.	RR
Poliomyelitis	1	0·000															
Rubella (incl. congenital $n = 4$)	24 388	5·3	−30·4%	19·5	99·5	1·5	7·7	0·2		6·5	1·6	11·6	2·9	4·0		0·3	0·07
Tetanus	120	0·03															
Varicella zoster	59 791	77·9	4·1%	–	–	–	–	77·9		91·6	1·5	92·0	1·5	62·1		123·2	2·0
Vector-borne diseases	137 817	33·7	0·5%	36·1	1·0	28·5	0·8	36·3	Ref.	3·2	0·07	13·3	0·3	46·6	Ref.	21·1	0·5
Arbovirus infection (NEC)	869	0·2	−9·1%	0·3	3·7	0·3	2·9	0·09		0·02	0·06	0·08	0·3	0·3		0·2	0·6
Barmah Forest virus infection	21 815	6·1	6·0%	4·3	0·5	4·7	0·6	8·1		0·2	0·03	1·8	0·2	8·4		5·1	0·6
Dengue virus infection	8691	2·1	8·1%	1·2	0·4	1·9	0·6	3·2		0·3	0·09	1·1	0·4	2·9		1·1	0·4
Japanese encephalitis	11	0·001															
Kunjin virus infection	60	0·02															
Malaria	13 733	3·3	−3·3%	4·0	1·5	3·4	1·3	2·7		1·8	0·5	3·5	0·9	4·0		0·8	0·2
Murray Valley encephalitis virus	79	0·01															
Ross River virus infection	92 559	22·3	−1·0%	28·7	1·3	18·1	0·8	22·2		0·7	0·02	7·0	0·2	31·5		14·5	0·5
Zoonoses	17 696	4·4	−3·2%	5·1	1·6	5·1	1·7	3·1	Ref.	0·3	0·04	1·8	0·3	6·0	Ref.	2·7	0·4
Anthrax	4	0·001															
Australian bat lyssavirus	1	0·0															
Brucellosis	724	0·2	0·3%	0·2	1·0	0·2	1·0	0·2		0·01	0·04	0·08	0·3	0·3		0·07	0·3
Hydatid infection	136	0·07															
Leptospirosis	3544	0·9	−2·1%	0·9	1·3	1·1	1·7	0·7		0·02	0·02	0·4	0·3	1·2		0·3	0·3
Ornithosis	2480	0·8	−4·5%	0·9	1·9	1·0	2·0	0·5		0·06	0·06	0·09	0·10	1·0		1·3	1·3
Q fever	10 805	2·6	−4·1%	3·3	1·9	3·1	1·8	1·7		0·2	0·04	1·2	0·3	3·7		1·2	0·3
Tularaemia	2	0·001															
Other bacterial diseases	36 960	9·0	0·1%	8·7	1·0	10·1	1·2	8·8	Ref.	13·2	1·5	4·9	0·6	8·8	Ref.	14·8	1·7
Legionellosis	5658	1·4	2·3%	1·0	0·6	1·7	1·1	1·5		0·03	0·02	0·06	0·04	1·3		4·7	3·6
Leprosy	200	0·05															
Meningococcal disease (invasive)	8766	2·1	−2·7%	2·2	1·6	3·0	2·2	1·4		11·5	11·0	3·1	3·0	1·0		0·8	0·8
Tuberculosis	22 336	5·5	0·4%	5·4	1·0	5·4	0·9	5·7		1·7	0·3	1·7	0·3	6·4		9·3	1·4

Inc., Incidence per 100 000 person-years; Avg change inc., % average percentage change in annual incidence per year of the study period (while disease was nationally notifiable; Table 1); RR, relative risk; Ref., reference group for RR calculations; NEC, not elsewhere classified; –, not notifiable for that sub-period.

Annual change in notification incidence, sub-period and age-group analysis for diseases with >400 cases notified.

† Chlamydial and gonococcal infections and syphilis include non-sexually acquired infections (especially in children) such as perinatal and eye infections.

Diseases with zero notifications: highly pathogenic avian influenza in humans (HPAIH), plague, rabies, severe acute respiratory syndrome (SARS), smallpox, viral haemorrhagic fevers, yellow fever.

Table 4. *Pathogens with highest notification incidence, Australia 1991–2011, by sub-period and age group*

		Sub-period			Age group			
Rank	Overall	1991–1997	1998–2004	2005–2011	<5 years	5–19 years	20–64 years	65–98 years
1	*Chlamydia*	Hepatitis C virus	*Chlamydia*	*Chlamydia*	*Campylobacter*	*Chlamydia*	*Chlamydia*	Varicella zoster
2	*Campylobacter*	*Campylobacter*	*Campylobacter*	*Campylobacter*	*Salmonella*	Varicella zoster	Hepatitis C virus	*Campylobacter*
3	Varicella zoster	*Chlamydia*	Hepatitis C virus	*B. pertussis*	Influenza	Influenza	*Campylobacter*	*B. pertussis*
4	Hepatitis C virus	Hepatitis B virus	*Salmonella*	Influenza	Varicella zoster	*B. pertussis*	Varicella zoster	Influenza
5	Influenza	*Salmonella*	Hepatitis B virus	Varicella zoster	*B. pertussis*	*Campylobacter*	Hepatitis B virus	*Salmonella*
6	*B. pertussis*	Ross River virus	*B. pertussis*	Hepatitis C virus	***Cryptosporidium***	*N. gonorrhoeae*	Influenza	***S. pneumoniae***
7	*Salmonella*	*B. pertussis*	*N. gonorrhoeae*	*Salmonella*	***S. pneumoniae***	*Salmonella*	*B. pertussis*	Hepatitis C virus
8	Hepatitis B virus	**Rubella**	Ross River virus	*N. gonorrhoeae*	***Shigella***	Hepatitis C virus	*N. gonorrhoeae*	Ross River virus
9	*N. gonorrhoeae*	*N. gonorrhoeae*	Influenza	Hepatitis B virus	**Measles**	Hepatitis B virus	Ross River virus	Hepatitis B virus
10	Ross River virus	**Hepatitis A**	***S. pneumoniae***	Ross River virus	***N. meningitidis***	***Cryptosporidium***	*Salmonella*	***M. tuberculosis***

Incidence calculated for years each disease was nationally notifiable and jurisdictional data available.
Bold text indicates pathogens not in the overall top 10.

increase/year, notifiable from 2001), pertussis (13%), and chlamydial infection (13%, notifiable from 1994) increased the most across the study period. Twenty-one diseases were consistently notifiable across jurisdictions for the entire study period (Table 1); annual incidence of these increased by 4·1% per year.

The median age of notified cases was 27 [interquartile range (IQR) 19–40] years, younger for STIs and in the NT (both with median age 23 years) (Table 2). Median age at onset was $\leqslant 7$ years for congenital rubella, congenital syphilis, botulism, Hib, cryptosporidiosis, chickenpox and haemolytic uraemic syndrome; and $\geqslant 62$ years for legionellosis, listeriosis and tetanus. Notification incidence (/100 000 per year) was highest for young children aged <5 years (698) and adults aged 20–64 years (654) and lowest for older adults aged 65–98 years (263) (Table 3). Cryptosporidiosis, invasive pneumococcal disease, shigellosis, measles and invasive meningococcal disease were among the 10 highest-incidence diseases for young children; cryptosporidiosis for older children and adolescents (aged 5–19 years); and pneumococcal disease and tuberculosis for older adults (Table 4). Compared to adults (aged 20–64 years), notification RR was highest for Hib (75), measles (18), cryptosporidiosis (12) and invasive meningococcal disease (11) for young children; measles (11) for older children and adolescents; and listeriosis (6) for older adults (Table 3). Fifty-one percent of notified cases were male, ranging from 46% for STIs to 79% for zoonoses (Table 2).

Overall, 202 584 (8·4%) cases were identified as Indigenous – ranging from 0·5% in the Australian Capital Territory (ACT) and Victoria to 58% in the NT (Table 2) – 36% of cases identified as non-Indigenous and for 56% Indigenous status was not reported. STIs comprised 70% of Indigenous case notifications. In the three jurisdictions with Indigenous status completed for >75% of cases, notification rates for all diseases were six times higher and STIs 14 times higher in Indigenous Australians compared to the total population.

Queensland had the greatest number of notifications (644 556 notifications, 27%), despite ranking third in population behind NSW and Victoria. The NT had the highest annual notification incidence (2598/100 000) (Fig. 2); age-standardized notification rates remained four times higher in the NT than the national average (2512 *vs.* 621/100 000 per year). Notification rates were highest in the NT for all disease groups except quarantinable and zoonotic diseases; however, the NT made the best progress in

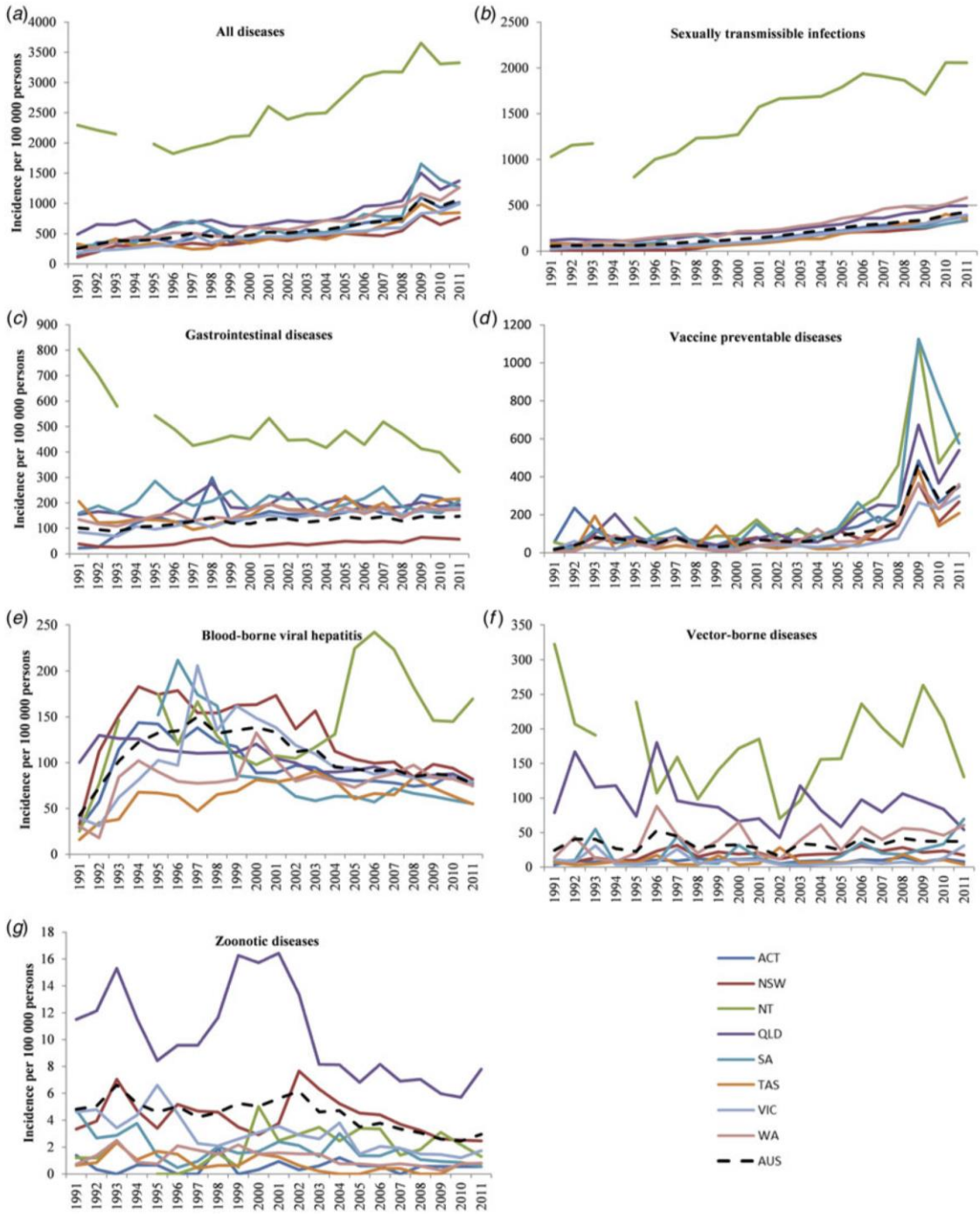

Fig. 2. Annual notification rate by jurisdiction and year for all diseases groups, Australia 1991–2011. NT notifications from 1994 not included in incidence calculations.

reducing (or limiting increase of) notifications overall (Supplementary Appendix Fig. A1). Compared to notification incidence in NSW, RR was $\geqslant 15$ for shigellosis, gonococcal infection, and syphilis in the NT; brucellosis in Queensland; and Shiga- or Verotoxin-producing *Escherichia coli* (STEC/VTEC) in SA (Supplementary Appendix Table A1).

STIs

STIs comprised 33% of all notifications, increasing fivefold from 64/100 000 per year in 1991–1997 to 334/100 000 per year in 2005–2011 (Table 3). Chlamydial infections (notifiable from 1994) accounted for 79% of STI notifications, gonococcal

disease 16% (32/100 000 per year), and syphilis 5% (9/100 000 per year) (Fig. 1*b*). Annual incidence of STIs was highest in those aged 20–29 years (239/100 000) and was eightfold higher in the NT than the national average (1527 *vs.* 193/100 000) (Fig. 2*b*).

Gastrointestinal diseases

Gastrointestinal diseases comprised 21% of notifications, with campylobacteriosis accounting for 55% despite not being notifiable in NSW (Fig. 1*c*). The national incidence of notified gastrointestinal diseases increased by 2% per year. Gastrointestinal disease notifications in the NT were nearly four times the national incidence (481 *vs.* 127/100 000 per year, Fig. 2*c*). NSW had the lowest notification incidence (Supplementary Appendix Fig. A1); however, national notification incidence of gastrointestinal diseases excluding campylobacteriosis (55/100 000 per year) was similar to NSW (43/100 000 per year).

VPDs

Just under half a million VPD cases were notified (Table 2), of which 45% were pertussis, 28% influenza (notifiable from 2001), and 12% varicella zoster (notifiable from 2006) (Fig. 1*d*). VPD notifications increased 15% per year, from 3016 in 1991 to a peak of 101 942 cases in 2009 during the H1N1 influenza pandemic. Median age at disease onset increased from 14 years in 1991–1997 to 30 years in 2005–2011. National incidence of VPD notifications was 119/100 000 per year, highest in the NT (239/100 000) and lowest in Victoria (77/100 000) (Fig. 2*d*).

BBVH

BBVH comprised 18% of notifications nationally and 30% of notifications in NSW (Supplementary Appendix Fig. A1). Annual incidence of notified BBVH cases was higher in the NT and NSW (144 and 128 notifications/100 000, respectively) than other jurisdictions (64–101/100 000, Fig. 2*e*). Hepatitis C, notifiable from 1995, accounted for 69% and hepatitis B 31% (Fig. 1*e*). BBVH notification incidence increased threefold from 43/100 000 per year persons in 1991 to 150/100 000 per year in 1997 before dropping to 77/100 000 per year in 2011, reflecting changes in hepatitis C notifications.

VBDs

There were 137 817 VBD notifications (5·7% of notifications), 67% being RRV infections (notifiable from 1993), 16% Barmah Forest virus infections (notifiable from 1995), 10% malaria, and 6% dengue (Fig. 1*f*). VBD notification incidence was 34/100 000 per year for Australia, highest in the NT (175/100 000) and Queensland (92/100 000) and lowest in Tasmania (9/100 000) (Fig. 2*f*).

Other bacterial diseases

There were 36 960 notifications of other bacterial diseases, of which 60% were tuberculosis, 24% invasive meningococcal disease, and 15% legionellosis. Other bacterial disease notification incidence was 9/100 000 per year, highest in the NT (27/100 000) and lowest in Tasmania (5/100 000) (Fig. 2). Tuberculosis notification incidence was 6/100 000 per year for Australia (range 21/100 000 in the NT to 2/100 000 in Tasmania) and was stable over the study period (Supplementary Appendix Fig. A1). Fifty-five percent of notified cases were male; highest for *Legionella* (67%) and leprosy (62%).

Zoonotic diseases

There were 17 696 zoonotic disease notifications (0·7% of all notifications). Q fever was most common (61%), followed by leptospirosis (20%) and ornithosis (14%). Males predominated, especially for anthrax (100% of four cases notified), leptospirosis (90%), brucellosis (84%), and Q fever (80%). Queensland notified 43% of all zoonotic cases, 83% of brucellosis and 56% of leptospirosis cases. Zoonotic disease notification incidence was 4·4/100 000 per year; highest in Queensland (10·0/100 000) and lowest in the ACT (0·6/100 000) (Fig. 2*h*). Zoonotic disease notifications fell by an average 3% annually (Supplementary Appendix Fig. A1).

DISCUSSION

Intelligence obtained from national communicable disease surveillance regarding infectious disease epidemiology guides national policy development, resource allocation, disease control programmes and quarantine activities, as well as allowing identification of and coordinated responses to national or multijurisdictional outbreaks [3]. This paper provides the first trend analysis of all nationally notifiable diseases in

Australia (except HIV/AIDS and CJD) since the inception of the NNDSS in 1991. Both the number and incidence of notifications increased steadily over the 21 years, partly due to the addition of diseases to the system. Incidence rates were highest in the NT and in Indigenous and young Australians. The ten diseases with highest notification incidence accounted for nearly 90% of notifications and required a range of public health strategies for disease prevention and control; including safe sex, contact tracing, harm-reduction for people who inject drugs, food safety, and immunization [10–14]. This highlights the complex challenges facing state, territory, and federal health departments in preventing and controlling infectious diseases in Australia.

Indigenous people comprised 8% of notified cases but only 3% of the Australian population [15]. Significant under-reporting of Indigenous status among notified cases means likely underestimation of this proportion. Indigenous Australians have poorer health outcomes: life expectancy is 9·7 and 11·5 years lower for Indigenous females and males, respectively [16], and disease burden measured in years of life lost was 2·6 times that of non-Indigenous Australians for all causes and 3·8 times for infections in 2010 [17]. Childhood vaccination coverage is lower for Indigenous children [18], potentially explaining some difference in VPD notification rates. In a previously published study, the notification RR for Indigenous compared to non-Indigenous Australians from 2000 to 2009 was 24 for chlamydial infection and 174 for gonococcal infection [19], and higher positivity rates for Indigenous patients tested for *Chlamydia* confirm greater STI burden rather than ascertainment bias [20].

Higher notification rates in the NT reinforce previous findings that the health adjusted life expectancy for the NT population was 5 years less than the Australian average in 2003 (67·7 *vs.* 72·9 years) [21]. The NT is the least populous Australian jurisdiction (estimated resident population 231 000 in 2011) [5]. The NT population is younger and has a high proportion of Indigenous persons (30% in NT *vs.* 3% nationally) than other jurisdictions [15, 22]; factors reflected in NT notifications. However, age-standardized notification rates were higher in the NT than elsewhere and notification rates in Indigenous people were higher in the NT than SA and WA. As NT data from 1994 were excluded from both the numerator (number of cases notified) and denominator (population) of incidence calculations, this would not have substantially impacted our RR calculations comparing notification incidence between the NT and other jurisdictions. It is likely that climactic and environmental diseases also impact disease incidence in the NT, while variability in health-seeking, diagnostic and notification practices might further contribute to the interjurisdictional differences.

Importantly, our results highlight some major public health achievements. The marked reduction in notification incidence for rubella, measles and Hib demonstrate the impact of Australia's National Immunization Programme. In 2014 Australia was recognized by the WHO to have eliminated measles [23]. Similarly, the reduction in donovanosis cases results from sustained public health programmes such as the National Donovanosis Eradication Project [24].

The annual number of notifications increased more than fivefold over the 21-year study period. The reasons for this are multifactorial, including addition of notifiable diseases to national and jurisdictional notification lists, population growth, introduction of screening programmes (e.g. for chlamydial infection), and improved diagnostics as well as true changes in disease incidence. There were 37 nationally notifiable diseases in 1991 and 65 in 2011. The number of nationally notifiable diseases has also increased internationally; from 56 to 87 (1992–2011) in the United States and from 41 to 58 (1991–2011) in Canada [25, 26]. The number of nationally notifiable diseases varied between European countries, ranging from 26 in France to 82 in Hungary in 2005 [27]. Some differences are due to increased number of disease categories associated with a single pathogen (e.g. syphilis has eight categories in the US system and three in the Australian NNDSS), but also reflect inclusion of diseases that are endemic in selected countries (particularly VBDs).

While many diseases are common between national surveillance systems, some differences are seen. In Australia, 10 diseases accounted for 88% of NNDSS notifications. National surveillance systems in the United States and Canada as well as the European Surveillance System (TESSy) receive notifications for eight of these diseases; varicella is not notifiable in to the Canadian or European surveillance systems and RRV is not notifiable to any [25–28]. In New Zealand, chlamydial infection, influenza, varicella and RRV are not nationally notifiable [29]. Conversely, some common infectious diseases are not notifiable in Australia and their inclusion on the Australian

NNDL may increase the burden on notifiers and public health departments. For example, rotavirus and norovirus diseases have high notification rates in Germany [30, 31]. National notification rates for all diseases or by disease group are generally not published and the variable inclusion of high-incidence diseases limit direct comparisons, but different notification rates for individual diseases could indicate differential disease burden between countries.

A major limitation of notification data is that they underestimate the number of infections, particularly for diseases that cause mild or no clinical symptoms. Despite uniform national case definitions [32], disease notification rates are influenced by jurisdictional and local diagnostic, screening, case follow-up, and notification practices. For example, disproportionately high STEC notification rates in SA have been linked to differences in diagnostic practices with a very high number of STEC toxin gene tests performed in SA [33]. Additionally, over the 21-year study period, sensitive diagnostic tests (particularly PCR) have become widely available and marked changes to testing practices among doctors and laboratories have been documented [34–37]. These factors potentially account for much of the observed change for several diseases, including chlamydial infection, influenza and pertussis which had the greatest increase in notification incidence over the study period [34, 36, 37]. As notification fractions vary between diseases, jurisdictions, population subgroups and over time, notification rates represent the frequency of disease diagnosis but not necessarily disease incidence. Similarly, as it is impossible to determine disease severity, notification incidence alone cannot determine the population burden of infectious diseases. A European study of seven infectious diseases found foodborne diseases (campylobacteriosis and salmonellosis) had the highest notified incidence, tuberculosis the highest mortality, and HIV infection and tuberculosis the greatest disability-adjusted life years burden [38].

The NNDSS dataset provides comprehensive coverage of national infectious disease notifications over two decades. Previously, annual Australian and international reports have been produced but this paper is unique in reporting the entire dataset of nationally notifiable diseases (excluding HIV/AIDS and CJD) for a 21-year period across all Australian jurisdictions. While we provide an overview of diseases reported, we have not reported system performance or data completeness and quality. However, this analysis highlights the breadth of diseases notified in Australia and complexity of public health responses required to reduce associated morbidity and mortality. Understanding the increasing number of notifiable diseases and notified cases is crucial for informing surveillance and public health workforce planning at a jurisdictional and national level.

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SUPPLEMENTARY MATERIAL

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DECLARATION OF INTEREST

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3.1.1 Supplementary material

Table 3.3: Annual incidence of disease notification by jurisdiction, Australia 1991–2011 *(Supplementary Appendix Table)*

	ACT		NSW		NT		QLD		SA		TAS		VIC		WA	
	Inc	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**
All diseases	560·1	1·3	429·8	Ref	2,598·5	6·0	849·9	2·0	693·6	1·6	482·7	1·1	493·9	1·1	684·2	1·6
Blood-borne viral hepatitis	94·5	0·7	128·1	Ref	144·4	1·1	101·0	0·8	74·7	0·6	64·4	0·5	101·2	0·8	81·9	0·6
Hepatitis B	24·6	0·5	46·5		90·8	2·0	26·6	0·6	26·5	0·6	10·9	0·2	37·4	0·8	26·1	0·6
Hepatitis C	71·9	0·9	83·4		109·8	1·3	73·1	0·9	66·3	0·8	58·9	0·7	69·1	0·8	59·7	0·7
Hepatitis D	0·0		0·2		0·04	0·2	0·2	1·2	0·005	0·03	0·0	0·0	0·2	1·0	0·08	0·4
Gastrointestinal diseases	151·7	3·5	42·8	Ref	481·4	11·2	189·5	4·4	202·7	4·7	161·3	3·8	137·1	3·2	156·4	3·7
Campylobacter†	103·7	1·1	NN	--	130·4	1·3	102·7	1·1	147·1	1·5	118·0	1·2	96·9	Ref	93·5	1·0
Cryptosporidiosis	8·4	1·1	7·8		59·3	7·6	19·6	2·5	8·8	1·1	9·2	1·2	10·0	1·3	13·0	1·7
Hepatitis A virus	4·5	0·7	6·5		24·9	3·8	8·1	1·3	3·1	0·5	1·2	0·2	3·7	0·6	5·1	0·8
Listeriosis	0·3	1·0	0·3		0·2	0·5	0·3	0·8	0·3	0·9	0·3	1·0	0·3	1·1	0·4	1·3
Salmonellosis	29·3	1·0	29·0		206·7	7·1	59·9	2·1	39·1	1·3	34·4	1·2	27·7	1·0	41·5	1·4
STEC/VTEC	0·11	0·8	0·14		0·3	1·8	0·4	2·9	2·5	17·6	0·06	0·4	0·14	1·0	0·2	1·3
Shigellosis	1·5	1·0	1·6		73·4	47·3	3·3	2·1	4·1	2·6	0·6	0·4	1·8	1·2	7·8	5·0
Typhoid	0·3	0·6	0·5		0·5	1·1	0·3	0·5	0·2	0·5	0·2	0·3	0·4	0·8	0·6	1·2
Sexually transmissible infections	159·0	1·3	125·9	Ref	1,527·3	12·1	263·0	2·1	165·7	1·3	151·2	1·2	155·9	1·2	284·8	2·3
Chlamydia	164·4	1·1	156·3		749·9	4·8	234·1	1·5	153·5	1·0	157·1	1·0	147·3	0·9	236·1	1·5
Donovanosis	0·0		0·0		6·8		0·0		0·0		0·0		0·0		0·08	
Gonococcal infection	9·2	0·5	18·4		656·7	35·7	33·0	1·8	21·7	1·2	3·5	0·2	17·0	0·9	66·5	3·6
Syphilis	4·9	0·8	6·4		164·7	25·8	13·2	2·1	2·8*	0·4	2·9	0·5	7·6	1·2	9·1	1·4
Vaccine preventable disease	138·6	1·4	99·8	Ref	239·4	2·4	187·8	1·9	217·9	2·2	91·3	0·9	76·9	0·8	110·2	1·1
Haemophilus influenza type B	0·5	0·9	0·6		1·6	2·8	0·6	1·0	0·6	1·1	0·5	0·8	0·4	0·8	0·15	0·3
Influenza	64·6	1·7	38·9		165·3	4·3	105·7	2·7	313·0	8·1	49·1	1·3	31·7	0·8	58·0	1·5
Measles	8·0	1·6	4·9		7·2	1·5	5·7	1·2	1·9	0·4	10·8	2·2	1·8	0·4	1·5	0·3
Mumps	1·3	1·2	1·1		5·0	4·7	0·8	0·7	0·8	0·8	0·4	0·4	0·7	0·6	1·6	1·5
Pertussis	58·5	1·0	61·2		51·3	0·8	60·3	1·0	97·0	1·6	30·2	0·5	36·1	0·6	33·8	0·6
Pneumococcal disease	8·8	1·0	9·1		36·6	4·0	8·8	1·0	9·0	1·0	9·6	1·1	7·5	0·8	8·3	0·9
Rubella	8·1	2·0	4·1		1·4	0·3	10·0	2·4	3·6	0·9	3·0	0·7	3·8	0·9	5·4	1·3
Varicella zoster †	32·3	0·7	NN	--	116·5	2·4	96·3	2·0	115·8	2·3	41·7	0·8	49·4	Ref	73·2	1·5
Vector-borne diseases	9·2	0·5	18·8	Ref	175·2	9·3	91·9	4·9	20·3	1·1	8·6	0·5	9·9	0·5	40·4	2·2
Arbovirus infection (NEC)	0·01	0·3	0·06		0·8	14·5	0·5	8·5	0·2	4·0	0·00		0·3	5·4	0·00	
Barmah Forest virus infection	0·8	0·14	5·4		24·1	4·4	17·2	3·2	2·3	0·4	0·2	0·0	0·7	0·1	4·1	0·8

	ACT		NSW		NT		QLD		SA		TAS		VIC		WA	
	Inc	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**	**Inc**	**RR**
Dengue	1·7	1·9	0·9		11·5	13·2	6·5	7·5	0·6	0·7	0·3	3 0·3	0·4	0·5	3·8	4·3
Malaria	4·9	2·2	2·2		19·2	8·7	7·4	3·4	1·7	0·8	2·3	1·1	1·9	0·9	2·8	1·3
Ross River virus	2·3	0·2	11·6		111·0	9·5	58·4	5·0	17·1	1·5	6·1	0·5	6·6	0·6	31·1	2·7
Zoonoses	0·6	0·1	4·2	Ref	3·4	0·8	10·0	2·4	2·8	0·7	0·7	0·2	3·1	0·7	1·2	0·3
Brucellosis	0·03	0·6	0·05		0·05	1·0	0·8	15·9	0·03	0·5	0·01	0·2	0·04	0·8	0·01	0·3
Leptospirosis	0·09	0·2	0·5		1·2	2·4	2·6	5·4	0·2	0·4	0·4	0·9	0·7	1·4	0·2	0·5
Ornithosis	0·3	0·3	0·9		0·3	0·3	0·10	0·11	0·5	0·5	0·2	0·3	1·4	1·5	0·2	0·2
Q fever	0·2	0·06	3·2		0·6	0·2	6·6	2·1	1·1	0·3	0·03	0·0 09	0·7	0·2	0·6	0·2
Other bacterial diseases	6·6	0·7	10·1	Ref	27·4	2·7	6·7	0·7	9·5	0·9	5·1	0·5	9·7	1·0	9·1	0·9
Legionellosis	0·6	0·6	1·1		1·2	1·1	1·0	0·9	2·8	2·6	0·5	0·5	1·4	1·3	2·5	2·3
Meningococcal disease	1·7	0·7	2·3		4·6	2·0	2·2	1·0	1·5	0·7	2·3	1·0	1·9	0·8	2·3	1·0
Tuberculosis	4·3	0·6	6·6		20·8	3·1	3·4	0·5	3·8	0·6	2·3	0·3	6·6	1·0	4·1	0·6

Hib – *Haemophilus influenzae* type B; Inc – Incidence per 100,000 person-years; RR – relative risk compared to NSW (most populous jurisdiction); NEC – not elsewhere classified; NN – not notifiable; Ref – reference state for RR; STEC/VTEC – Shiga- or Vero-toxin producing *E. coli* ;

†RR compared to Victoria (not notifiable in NSW); *SA only reported infectious syphilis (primary, secondary or early latent)

ACT – Australian Captial Territory; NSW – New South Wales; NT – Northern Territory; Qld – Queensland; SA – South Australia; Tas – Tasmania; Vic – Victoria; WA – Western Australia; Aus - Australia

Table 3.2: Disease group notifications across jurisdictions, Australia 1991—2011 *(Supplementary Appendix Figure)*

a· Notification relative risks (RR) for jurisdictions compared to NSW, by disease group

	Blood-borne viral hepatitis	Gastrointestinal*	Other bacterial	Sexually transmissible	Vaccine preventable	Vector-borne	Zoonotic	All diseases
ACT	0·7	3·5	0·7	1·3	1·4	0·5	0·1	1·3
NSW	1·0	1·0	1·0	1·0	1·0	1·0	1·0	1·0
NT	1·1	11·2	2·7	12·1	2·4	9·3	0·8	6·0
QLD	0·8	4·4	0·7	2·1	1·9	4·9	2·4	2·0
SA	0·6	4·7	0·9	1·3	2·2	1·1	0·7	1·6
TAS	0·5	3·8	0·5	1·2	0·9	0·5	0·2	1·1
VIC	0·8	3·2	1·0	1·2	0·8	0·5	0·7	1·1
WA	0·6	3·7	0·9	2·3	1·1	2·2	0·3	1·6

b· Average annual change in notification incidence over study period, by disease group and jurisdiction, %

	Blood-borne viral hepatitis	Gastrointestinal	Other bacterial	Sexually transmissible	Vaccine preventable	Vector-borne	Zoonotic	All diseases
ACT	-2	4	1	15	9	1	0	6·8
NSW	-2	3	-1	18	12	3	-2	6·6
NT	3	-3	-4	4	19	0	-6	3·3
QLD	-2	1	0	9	16	-2	-3	5·0
SA	0	0	-2	8	22	6	-10	7·2
TAS	2	2	-1	13	11	2	-8	6·7
VIC	0	4	2	15	15	0	-7	7·2
WA	1	2	0	11	18	4	-5	7·3
AUS	-1	2	0	12	15	1	-3	6·4

c· Percentage of all disease notifications in each disease group by jurisdiction, %

	Blood-borne viral hepatitis	Gastrointestinal*	Other Bacterial	Sexually transmissible	Vaccine preventable	Vector-borne	Zoonoses
ACT	17	27	1·2	28	25	2	0·1
NSW	30	10	2·4	29	23	4	1·0
NT	6	19	1·0	58	10	7	0·1
QLD	12	23	0·8	31	21	11	1·2
SA	11	30	1·2	24	31	3	0·3
TAS	13	34	1·1	32	18	2	0·2
VIC	21	28	2·0	32	16	2	0·6
WA	12	23	1·3	42	15	6	0·2
AUS	18	21	1·5	33	20	6	0·7

a. Relative risk (reference state NSW = 1); red = higher notification incidence, green = lower notificatoin incidence· – no notifications recived

b. Change in disease incidence dark red=greatest increase in incidence, white = no significant change in incidence, dark green = greatest decrease in incidence of notifications over study period; numbers show average annual change (%) in disease incidence over study period

c. Dark red = greatest proportion of jurisdiction's total notifications in that disease group; White = lowest proportion of jurisdiction's totatl notifications in that disease group

*Campylobacteriosis not notifiable in NSW

ACT – Australian Captial Territory; NSW – New South Wales; NT – Northern Territory; Qld – Queensland; SA – South Australia; Tas – Tasmania; Vic – Victoria; WA – Western Australia; Aus - Australia

Chapter Four: Socio-demographic determinants of notifiable infectious diseases in Australia

Declaration for thesis Chapter 4

Declaration by candidate

In the case of Chapter 4.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study concept and design; data cleaning and analysis; preparation of draft manuscript; preparation of manuscript for submission	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Allen Cheng	Advice regarding statistical analysis; revision of manuscript from preliminary draft to submission	
Robert Hall	Initial concept of NNDSS review; sourcing data; revision of manuscript from preliminary draft to submission	
Karin Leder	Revision of manuscript from preliminary draft to submission	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature	[redacted]	**Date** 11th July, 2016

Aim: To explore the socio-demographic determinants of notifiable communicable diseases in Australia.

Preface

Health inequalities are differences in health status between different population groups. In certain situations these inequalities are attributable to biological variations and are therefore considered unavoidable. Health inequities refer to differences in health status between different population groups, which are unnecessary and avoidable as well as unjust and unfair.[107] Social determinants of health – the conditions in which people are born, grow, live, work and age – are responsible for most health inequities.[108] One of the most striking health inequities in Australia relate to the shorter life expectancy of Indigenous Australians compared to non-Indigenous Australians (a gap of 10.6 years for boys and 9.5 years for girls at birth).[109] Australians in remote areas also have shorter life expectancy and poorer health, relating to social determinants of health, access to goods and services, and health behaviours.[109] Socioeconomic disadvantage in Australia is likewise associated with poorer health. Compared to those in the least disadvantaged areas, Australians living in the most socioeconomically disadvantaged areas are more likely to: have poorer self-reported health status; have very high levels of psychological distress; be obese; smoke; be teenage parents; have children who are developmentally delayed; and have lower five-year survival rates following cancer diagnosis.[110] In 2011, the DALY burden of all infectious diseases was 2.9 times higher among Australians living in very remote areas compared to those living in major cities, and 1.7 times higher among those in the lowest compared to highest socioeconomic group.[49]

Socioeconomic status and access to services can be measured at the individual, household or area-based (neighbourhood, state, country) level. Use of area-based analysis of surveillance

data permits examination of the social distribution of communicable diseases and temporal trends, although the associations between socioeconomic status and specified health outcomes tend to be underestimated when using area-level rather than individual- or household-level socioeconomic status as the health determinant.[111] NNDSS data are de-identified but include postcode of residence. The Australian Bureau of Statistics (ABS) census data include area-based measures of a socioeconomic status and remoteness (determined by distance to services), which can be accessed at the postcode-level.

The following analysis of socioeconomic disadvantage and remoteness used ABS census data but applied these to non-census postcode defined areas. Postcodes are maintained for mail processing purposes only, however the line-listed NNDSS data provided only postcode of residence for geolocation. For analysis of remoteness, we used a '2012 Postcode to 2011 Remoteness Area' concordance file provided by the ABS and applied 2011 Remoteness Area classifications to all study years. This could lead to misclassification of the remoteness of certain areas early in the study period. Postal area-level population data by Indigenous status were only available for 2011 and these were retrospectively applied to the entire study period. Results of remoteness and Indigenous status analyses would be more accurate in the latter years of the study.

This chapter contains a manuscript that examines the socio-demographic influences on incidence of nationally notifiable infectious diseases in Australia. By combining the NNDSS and ABS variables relating to age-group, sex, Indigenous status, socioeconomic disadvantage and remoteness we undertook an area-based analysis of social determinants of health for all nationally notifiable infectious diseases in Australia.

4.1 Socio-demographic and geographic inequalities in notifiable communicable diseases in Australia: An analysis of 21-years of national disease surveillance data

This paper has been accepted for publication in *Lancet Infectious Diseases*.

4.1.1 Abstract

Background: Australia is a high-income country with a well-established and largely publically-funded health care system. Despite this, certain populations within Australia experience shorter life expectancy and worse health outcomes. We aim to explore geographic variations and socio-demographic inequities in infectious disease notifications in Australia.

Methods: National Notifiable Diseases Surveillance System (NNDSS) notifications from 1991–2011 (n=2·4 million) were analysed by disease group and disease (eight most commonly notified diseases) at postcode-level. The impact of socioeconomic disadvantage and remoteness of residence on notification incidence was examined nationally. We reported Gini co-efficients; adjusted relative risks (aRRs); population attributable fractions (PAF); and attributable notifications. We reported aRRs for Indigenous status in three jurisdictions with completeness of Indigenous status reporting >75% (the Northern Territory, South Australia and Western Australia).

Findings: Of the eight most commonly notified diseases, gonococcal infection was the most concentrated and campylobacteriosis the most evenly distributed. Overall notification incidence was higher in remote/very remote areas compared to major cities (aRR 3·37) and the most socioeconomically disadvantaged compared to less disadvantaged quintiles (aRR 1·15). PAF for socioeconomic disadvantage remained high for blood-borne viral hepatitis but

fell in other disease groups. In 2011, sexually transmissible infections had 11,093 notifications attributed to remoteness and 5,597 notifications attributable to socioeconomic disadvantage. Notification incidence was higher among Indigenous Australians (aRR 5·3).

Interpretation: Diseases had differing geographic concentration and sociodemographic risk. Overall, sociodemographic inequities in infectious disease notifications have reduced but remain unacceptably high. National communicable disease control is complex, requiring both targeted and population-wide interventions.

4.1.2 Introduction

Australia is one of the most privileged countries in the world, ranking second on the United Nation's Human Development Index.[112] With six states and two territories, the Australian population in 2011 was 22·5 million,[113] of whom 27% were born overseas, 70% lived in major cities and 1% lived in remote or very remote areas.[109] Aboriginal and Torres Strait Islander (Indigenous) Australians comprise 3% of the national population (~670,000 people) but up to 16% of the population in remote and 45% in very remote areas.[109]

Social and economic circumstances affect health, even in wealthy nations, with higher disease burden and shorter life expectancy among disadvantaged populations.[114] Despite government-funded health care and education, social and health inequalities persist in Australia. Life expectancy of Indigenous Australians is approximately 10 years lower than non-Indigenous Australians at birth. Indigenous Australians, people living in rural and remote areas, the lowest socioeconomic status groups, and people with disabilities experience poorer health outcomes.[109] Improvements in living standards, along with public health programmes such as vaccination, have resulted in lower burden of communicable diseases in recent decades; the proportion of deaths in Australia attributed to infections fell from 13% in 1907

to 1.3% in 2009.[110] Despite this, notification incidence of some communicable diseases is both increasing and unequally distributed.[86, 115, 116]

National communicable disease surveillance in Australia is achieved through aggregation of line-listed surveillance data provided by the states and territories; responsibility for public health action resulting from these notifications lies with the jurisdictions. From 1991, de-identified case notification data for diseases on the National Notifiable Disease List (NNDL) have been transmitted to Australia's National Notifiable Diseases System (NNDSS).[78] HIV/AIDS and Creutzfeldt-Jakob disease are notifiable to other national surveillance systems. [117, 118] A separate analysis of NNDSS notification data from 1991–2011 provides an overview of the time trends in incidence of disease notifications (3.1). We reviewed the first 21 years of NNDSS data to quantify inequalities in communicable disease notification incidence in Australia based on geography and sociodemographic factors.

4.1.3 Methods

Cases notified to the NNDSS from 1991–2011 were included. We analysed sociodemographic factors by disease group for all notified cases (blood-borne viral hepatitis [BBVH], gastrointestinal diseases, STIs, vaccine-preventable diseases [VPDs], and other diseases [incorporating other bacterial, quarantinable, vector-borne and zoonotic disease groups from the NNDL]).[78] We separately analysed the eight most commonly notified diseases which each had >100,000 cases notified over the study period (campylobacteriosis [not notifiable in New South Wales], chlamydial infection, gonococcal infection, hepatitis B [newly acquired and unspecified], hepatitis C [newly acquired and unspecified], influenza, pertussis, and salmonellosis). Data were analysed for the entire study period (1991–2011) and by sub-period (1991–1997, 1998–2004, and 2005–2011).

Annual notification incidences per 100,000 population were calculated using mid-year populations nationally and by postal area (matched to >2,300 postcodes). Notification and population data were included for all years in which a disease was notifiable at both the national and jurisdictional levels with the exceptions (as described in 3.1) listed in Table 4:1. The proportion of eligible cases included in the analyses is outlined in the Appendix (4.1.7).

The Australian Bureau of Statistics' (ABS) Index of Relative Socioeconomic Disadvantage (IRSD) and Accessibility/Remoteness Index of Australia (ARIA+) were used to examine the impact of socioeconomic disadvantage and remoteness on notification incidence at the small-area (postcode) level. [119, 120] The population was divided into quintiles based on IRSD scores, with the first quintile (Q1) representing the most socioeconomically disadvantaged areas. Remoteness was reported in five groups (major cities, inner regional, outer regional, remote and very remote) and dichotomised for analysis (remote [remote and very remote areas] vs. non-remote [major cities, inner regional and outer regional areas]). Postal area-level population and IRSD data were available for census years (1991, 1996, 2001, 2006 and 2011) and interpolated for inter-census year estimates. Postcode-level remoteness data for 2011 was applied to all study years.

Geographical variability: Notification incidence was analysed at postcode level to identify diseases with a high degree of geographical concentration. Postcodes were sorted from lowest to highest incidence to generate Lorenz curves, plotting cumulative proportion of the population (x-axis) against cumulative proportion of notified cases (y-axis)(Figure 4.1). The diagonal 'line of equality' demonstrates a theoretical situation whereby notifications are equally distributed across the population; the further the Lorenz curve deviates from this line of equality, the more unequal (or concentrated) the distribution of notifications. We calculated Gini coefficients (equivalent to twice the area between the line of equality and the Lorenz curve) for which higher values represent greater inequality (theoretical range from 0

[perfect equality] to 1 [absolute inequality]) using the –ineqdec0– code in Stata[121] for disease groups and most commonly notified diseases in 1991, 2001 and 2011, provided >1,000 cases were notified and the postcode population was >100 in that year.

Adjusted relative risks (aRRs). Relative risks for disease notification were calculated using multivariable Poisson regression models that adjusted for sex, age-group, socioeconomic disadvantage (most disadvantaged IRSD quintile [Q1] vs. other [Q2–5]) and remoteness (remote vs. non-remote). Separate models were constructed for each disease group and most commonly notified diseases.

Population attributable fraction (PAF) and attributable notifications: The relative contribution of socioeconomic disadvantage and remoteness to notification incidence was quantified using PAF, calculated separately for each by disease group and period. PAF indicates the expected percentage reduction in notifications if the entire population was at an ideal exposure level – namely the least disadvantaged IRSD quintile (Q5) or major city residence. The multivariable models above were re-run with dichotomous categorisation of socioeconomic disadvantage (IRSD Q1–4 vs. Q5) and remoteness (regional/remote vs. major city) and the resultant aRRs were included in the following:

$$PAF = \frac{p_c(RR - 1)}{RR}$$

where p_c is the proportion of cases in the suboptimal exposure level (IRSD Q1–4 or regional/remote residence).[122]

The absolute contribution of socioeconomic status and remoteness to case notifications in 2011 was estimated by disease group and disease, whereby:

$$Attributable\ notifications_{2011} = PAF_{2005\text{–}2011} \times\ notified\ cases_{2011}$$

Indigenous status sub-analysis: Incidence rates for Indigenous Australians were calculated for the three jurisdictions with >75% completeness of Indigenous status reporting among notified cases across the study period (the Northern Territory, South Australia, and Western Australia) using ABS population estimates; [123, 124] cases with unknown Indigenous status were presumed non-Indigenous. These jurisdictions included account for approximately 19% of the national population and 29% of the national Indigenous population. Postal area-level Indigenous population data were available for 2011 and applied retrospectively to all study years for analysis of socioeconomic disadvantage and remoteness. RRs for Indigenous compared to non-Indigenous Australians were calculated using univariate Poisson regression; multivariable Poisson regression models including Indigenous status, socioeconomic disadvantage and remoteness were used to generate aRRs for each disease group/disease.

Sensitivity analysis for cases with missing Indigenous status: Our primary analysis assumed all cases with missing Indigenous status were non-Indigenous. We also calculated RRs for the three included jurisdictions assuming Indigenous status was missing at random.

Exploratory analyses of co-linearity: A Spearman's correlation was used to assess the relationship between remoteness (remote vs. non-remote) and socioeconomic disadvantage (most disadvantaged IRSD quintile vs. other) nationally, with a weak positive correlation noted (r_s=0·22). For the Northern Territory, South Australia and Western Australia, a positive correlation was demonstrated between Indigenous status and remoteness (r_s=0·61); Indigenous status and socioeconomic disadvantage (r_s=0·36); and remoteness and socioeconomic disadvantage (r_s=0.29).

NNDSS data were provided by the Australian Government's Office of Health Protection in March 2012 as an extract from the national data file. The project was approved by the

Monash Human Research Ethics Committee and Communicable Diseases Network Australia (CDNA) jurisdictional members. Data were analysed using Stata 12 (StataCorp, Texas USA). Tests for statistical significance were not performed as population-based data were used and results are not being generalized to a larger target population.

4.1.4 Results

We analysed 2,421,134 cases notified to the NNDSS from 1991–2011, of which STIs comprised 33%, gastrointestinal diseases 21%, VPDs 20%, BBVH 18% and other diseases 8%.[86] The eight most commonly notified diseases analysed separately comprised 82% of all notified cases.

Geographical variations and remoteness: In 1991, gonococcal infection was the most concentrated of the commonly notified diseases, with a Gini coefficient of 0·936 and 87% of notified cases concentrated in areas occupied by 10% of the population (Table 4:2). By 2011, the 'other diseases' group (0·827), gonococcal infection (0·738) and hepatitis B (0·658) were the most concentrated, with gastrointestinal infections (0·417) and VPDs (0·403) the most equally distributed. Among STIs, chlamydial infections more equally distributed than gonococcal infections, and for BBVHs, hepatitis C was more equally distributed than hepatitis B (Figure 4.1). Distribution became more equal over the study period for all disease groups and commonly notified diseases.

Two-thirds (63%) of notifications were from residents of major cities and 8% from residents of remote/very remote areas. STI incidence was markedly higher among residents of remote and very remote areas (Figure 4.2). On multivariable analysis, notification incidence overall was three-fold higher for residents of remote/very remote areas; most marked for gonococcal infection (aRR 20·11) and salmonellosis (3·54) (Figure 4.3). Hepatitis B (aRR 1·44) was

more commonly notified and hepatitis C (0·63) less commonly notified among residents of remote/very remote areas.

Socioeconomic disadvantage: Notification incidence was highest in the most disadvantaged IRSD quintile (Q1) for BBVH and STIs (Figure 4.2). On multivariable analysis, residents of the most disadvantaged areas (IRSD Q1) had higher notification incidence overall (aRR 1·15), most marked for hepatitis B (2·40), gonococcal infection (1·83) and hepatitis C (1·73)(Figure 4.3).

Attributable notifications: The PAF for both socioeconomic disadvantage and living outside a major city decreased overall during the study period (Figure 4.4a). PAF for both socioeconomic disadvantage and non-city living was initially high for STI notifications with significant reduction for socioeconomic disadvantage (PAF 38% [1991–1997] to 6% [2005–2011]) and non-city residence (PAF 47% to 13%). For BBVH notifications, no reduction in PAF was seen for socioeconomic disadvantage. The number of notifications in 2011 attributable to socioeconomic disadvantage was highest for hepatitis C (PAF 35%, attributable notifications 3,680), followed by hepatitis B (34%, 2,351) and chlamydial infection (2%, 1,984)(Figure 4.4b). For non-city residence, gonococcal infection had higher PAF than chlamydial infection (31% vs. 9%) but fewer attributable notifications (3,801 vs. 7,660).

Indigenous status and other sociodemographic factors: Within the three jurisdictions analysed (Northern Territory, South Australia and Western Australia), notification RR for Indigenous compared to non-Indigenous Australians was 5·8 for all diseases – highest for STIs (14·5, gonococcal infection 64·7), females (6·4), ages 15–39 years (6·7), the most socioeconomically disadvantaged IRSD quintile (8·0), remote (7·8) and very remote (5·8) areas (Figure 4.5a). Overall, the RR for Indigenous Australians decreased from 7·0 [1991–

1997] to 4·7 [2005–2011]. STI notifications demonstrated the greatest decrease (RR 27·0 to 10·0) while notification RR increased for BBVH from 2·0 to 3·1. Indigenous status was missing for 20% of included notifications. On sensitivity analysis, the overall RR increased from 5·8 (assuming cases with missing data were non-Indigenous) to 7·8 (assuming Indigenous status was missing at random).

On multivariable analysis of all diseases, Indigenous status (aRR 5·3) had greater influence on notification incidence than remoteness (remote vs. non-remote aRR 1·9) or socioeconomic disadvantage (IRSD Q1 vs. Q2–5 aRR 0·9)(Figure 4.5 b). For Indigenous Australians, the greatest disparity in notification incidence was seen for gonococcal infection (aRR 25) followed by chlamydial infection (5·9), then influenza, hepatitis B, salmonellosis and hepatitis C (aRR 2·2–2·7).

4.1.5 Discussion

Our comprehensive analysis of 21 years of NNDSS data, incorporating 65 nationally notifiable communicable diseases and focussing on the most commonly notified diseases, reveals major inequalities in communicable disease burden in Australia. Australia's *National Framework for Communicable Disease Control* identifies populations suffering disproportionally high burden of communicable diseases as a high priority and recognises that disease- or population-specific strategies and programmes, in addition to an overarching national approach, are required to address these inequities.[22] Our analysis quantifies these inequalities and identifies diseases and populations in greatest need of targeted interventions, as well as diseases requiring community-based rather than targeted interventions.

Studies in Australia, Canada, the UK, and the US confirm our observation that notifications of gonococcal infection were more concentrated than chlamydial infection.[125-129] In a New South Wales study, 44% of gonococcal infection notifications concentrated in areas occupied

by 3.6% of the population.[129] Nationally, we found 87% of gonococcal infection notifications in 1991 and 61% in 2011 were concentrated in areas occupied by 10% of the population, confirming postcode of residence as an important risk factor for gonococcal infection. Gini coefficients can be influenced by notification incidence,[125-128] as we demonstrated with lower Gini coefficients for the highest compared to second-highest incidence diseases in each disease group (chlamydial/gonococcal infections; hepatitis C/B; and campylobacteriosis/salmonellosis). The observed reduction in geographic clustering over the study period might in part be attributable to an overall increase in notification incidence over the study period (3.1). Combined with notification incidence data, geospatial observations for disease concentration can inform the appropriateness of specific interventions.[130] In general, highly concentrated diseases require interventions targeted to high-incidence communities (e.g. gonococcal infection in remote Indigenous communities), while less concentrated diseases require population-wide interventions. (e.g. improving food safety nationally to prevent campylobacteriosis).

To identify and quantify drivers of geospatial disease concentration we examined the influence of socioeconomic disadvantage and remoteness on notification incidence. The impact of these factors differed between disease groups and even between high incidence diseases within the same disease group, highlighting the importance and novelty of our approach to compare these factors across all notifiable disease groups and high incidence diseases nationally. This also demonstrates the complexity of tailoring public health responses to the spectrum of notifiable diseases. Overall, socioeconomic disadvantage had less of an impact on notification incidence than remoteness (aRR 1·15 vs. 3·37, respectively). In the Australian Burden of Disease study, the DALY burden of all infectious diseases was 1·7 higher among Australians in the lowest compared to highest socioeconomic group and 2·9 times higher among those living in very remote areas compared to major cities.[49] One

strength of our study is that we examined high-incidence diseases separately. We found remoteness was an overwhelming risk factor for gonococcal infection notifications nationally (aRR 20). Furthermore, for the jurisdictions in which Indigenous status could be analysed, Indigenous status was even more strongly associated with gonococcal infection notifications than remoteness (aRR 25 vs. 7, respectively). This reflects our observed correlation between remoteness and Indigenous status; however it clearly identifies remote Indigenous communities as having the highest incidence of notified gonococcal infection. The complexities of appropriately targeting interventions are highlighted by a study indicating the observed gonococcal epidemics would not be sustained in small Indigenous communities without population movement,[131] and other reports that gonococcal infection incidence is also concentrated among men who have sex with men in urban settings.[115, 129] We found hepatitis C notification incidence was higher in non-remote areas, likely reflecting the distribution of people who inject drugs (PWID)–an important target population for public health interventions. The higher incidence of salmonellosis in remote areas (aRR 3·54) might reflect issues with food handling and food storage, particularly chicken meat and eggs.[132]

Socioeconomic inequalities in BBVH notifications persisted throughout the study period, indicating a need for public health action. Long-term sequelae to BBVH, namely cirrhosis and hepatocellular carcinoma (HCC), contribute significantly to mortality. Hepatitis C is now the leading cause of liver transplantation in Australia.[133] In Queensland, residence in an area where ≥10% of the population were Indigenous was associated with higher HCC incidence and poorer survival, while socioeconomic disadvantage was also associated with poorer survival.[134]

Indigenous Australians experience an unacceptable burden of communicable diseases.[109] The excess notification incidence for gonococcal infection in this study (aRR 25) echoes the findings of previous Australian surveillance-based reports but was ten-fold higher than for

American Indians/Alaskan Natives compared to whites in the United States from 2007–2011 (RR 2.4).[115, 116, 134] While it is encouraging that the relatively higher notification incidence for Indigenous compared to non-Indigenous Australians decreased over the study period, the gap persists and requires initiatives that target both upstream (e.g. education, employment and housing) and downstream (communicable disease screening and treatment programmes) determinants of health. Improving completeness of reporting of Indigenous status among notified cases in NNDSS has been identified as a surveillance priority.[30] As completeness improves, a better national picture of the true disparity in notification incidence based on Indigenous status will become available.

Importantly, geographic concentration of notifications and the relative inequalities attributed to socioeconomic disadvantage, remoteness and Indigenous status decreased over the study period. This contrasts with an increase in socioeconomic and ethnic inequalities in infectious disease hospitalisations in New Zealand from 1989–2008.[136] Proportionally, VPDs were the disease group least affected by sociodemographic disadvantage in our study, potentially reflecting a robust and successful national immunisation programme reaching children in remote and disadvantaged areas. Our analysis highlighted the marked reduction in PAF for STI notifications for both remoteness and socioeconomic disadvantage. However, the absolute number of STI notifications attributable to socioeconomic disadvantage and non-city residence in 2011 remained high (>5,000 and >11,000, respectively), indicating more needs to be done to reduce this inequity, particularly among Indigenous and remote-living Australians.

Our study has certain limitations. Differences in testing practices impact the observed notification incidences, distribution of notified cases and relative risks, thereby potentially biasing our results. Changing health seeking, testing and notification practices could each contribute to changes in case ascertainment over the study period. Laboratory notification of

relevant diseases is now mandated in all Australian jurisdictions. With widespread use of automated- (and increasing use of electronic-) laboratory reporting, near complete ascertainment of laboratory diagnosed notifiable disease cases in NNDSS is expected.[30] However, early in the study period notification by laboratories was not a legislative requirement and surveillance case definitions less frequently required laboratory confirmation.[27] For STIs in particular, introduction of duplex PCR testing for chlamydial and gonococcal infection using less invasive urine specimens, along with promotion of widespread testing and screening, have contributed to increased diagnoses.[115] The reduced inequalities in notification incidence that we observed might be partly explained by differential changes in case ascertainment between population groups. Between 2000 and 2009, chlamydial infection notification incidence increased by 80% among Indigenous Australians compared to 335% among non-Indigenous Australia.[116] If *Chlamydia* testing has shifted from primarily symptomatic testing in high risk populations to increased asymptomatic testing among a lower risk population, then our findings may be an artefact of changed testing practices rather than a true reduction in the inequality of infectious disease burden. Overall, notification data likely underestimate the true excess in disease incidence for people living in disadvantaged or remote areas. However, notifications resulting from targeted screening programmes (e.g. STIs in remote Indigenous communities or BBVH in inner-urban settings) might sometimes over-estimate geographic and sociodemographic inequalities.

We have not attempted to draw statistical conclusions from this descriptive study and we did not undertake formal spatial or temporospatial cluster analysis as the study summarized 65 diseases over a 21-year period. Use of postcode-defined areas for classifying social class composition has limitations as postcodes can span relatively large geographical areas, differ greatly in population size, and include markedly different types of neighbourhoods.[111]

Socioeconomic status and access to services can be measured at the individual, household or area-based (neighbourhood, state, country) level. Use of area-based analysis of surveillance data permits examination of the social distribution of communicable diseases and temporal trends, although the associations between socioeconomic status and specified health outcomes tend to be underestimated when using area-level rather than individual- or household-level socioeconomic status as the health determinant.[111] Spatial clustering and spatial autocorrelation are potential issues in small unit-area analyses. It is therefore possible that this analysis could conceal effects or generate false associations. More complex statistical analyses of one or more disease could generate detailed information for planning program or service delivery, taking into consideration issues such as increasing notification incidence, spatial autocorrelation and variation in population size between postcodes.[129]

Incomplete reporting of Indigenous status of notified cases precluded national analysis of the impact of Indigenous status on notification incidence. Interjurisdictional differences prevent generalisation of our findings nationally, particularly given our observed correlation between Indigenous status and remoteness in the included jurisdictions which likely differ in other jurisdictions. Sensitivity analysis suggests our reported RRs for Indigenous status underestimates the true gap in notification incidence between Indigenous and non-Indigenous Australians. Due to limitations in the NNDSS core data fields, other marginalized sub-populations with anticipated higher communicable disease burden could not be analysed, including PWID, sex workers, and culturally and linguistically diverse populations.

This analysis was designed to detect inequalities in notification incidence to better understand the determinants of communicable disease burden. As a high-level overview analysis, it was not designed to identify specific control programmes. However, our analysis of the eight most commonly notified diseases (all high-incidence) highlighted the following diseases as warranting public health intervention based on observed inequality: gonococcal infection

(higher notification incidence among Indigenous, remote-living, socioeconomically disadvantaged and males, along with marked geographic clustering); chlamydial infection (Indigenous and remote-living); influenza (Indigenous and geographic clustering); salmonellosis (remote-living and young children); hepatitis B (socioeconomic disadvantage and geographic clustering); and hepatitis C (socioeconomic disadvantage and males). The improved understanding of determinants of disease burden gained from this study is a starting point to identifying diseases and populations requiring targeted public health interventions. The next step is to identify evidence-based disease-, population-, and location-specific interventions that will reduce disease burden among vulnerable Australians. As an example of such a targeted intervention, in 2015 seasonal influenza vaccine was funded for Indigenous children under the National Immunisation Program.[94]

We present a population-based 21-year analysis of communicable disease notifications in Australia, comparing notification rates based on measurable social determinants of health. Infectious disease notification incidence remains high in remote areas and among Indigenous Australians, and although the relative disparities diminished over the study period, important differences remain. This analysis identifies high risk communities and high incidence/burden diseases that need to be a focus of public health interventions.

4.1.6 Research in Context

Evidence before this study

We aimed to identify national-level epidemiological studies addressing inequities in notifiable infectious disease burden in developed countries. PubMed search terms included 'communicable diseases', 'national', 'Indigenous', 'rural', 'remote', 'socioeconomic', 'health equity', 'health status disparities', 'spatial analysis', and 'Gini coefficient'. Reference lists and Australian Government websites were examined for relevant publications.

Australian Government reports highlighted shorter life expectancy among remote-living and Indigenous Australians. The recently published Australian Burden of Disease Study reported the disability adjusted life years (DALY) burden of all infectious diseases was 2.9 times higher among Australians living in very remote areas compared to major cities, and 1.7 higher among those in the lowest compared to highest socioeconomic group.[49] However, the impact of socioeconomic disadvantage on notification incidence has been variable in published literature. Higher notification incidence for selected infectious diseases has been noted for Indigenous people in Australia (particularly those living remotely), North America and New Zealand. Few studies reported trend analysis; however Indigenous status and lower socioeconomic status were associated with higher hospitalization rates for serious infections in New Zealand.[136] The Gini coefficient has predominately been used to assess geographic concentration of sexually transmissible infections.[125-129]

Added value of this study

Ours is the first study we are aware of to quantify sociodemographic health inequities and geographic concentration for all nationally notifiable infectious diseases over more than two decades. By reporting our results for all nationally notifiable diseases combined, by disease group, and by individual disease for the eight most commonly notified infections and by including trend analysis, some important (and novel) findings emerged. First, the risk patterns were quite different between the diseases / disease groups. Remoteness and Indigenous status were very strongly associated with STI (particularly gonococcal infection) notification incidence, and to a lesser extent gastrointestinal disease (particularly salmonellosis). Second, socioeconomic disadvantage was not associated with increased risk of gastrointestinal or vaccine preventable diseases, but was important for blood-borne viral hepatitis. Third, although in most areas the 'gap' was decreasing, this improvement was not seen for socioeconomic disadvantage and blood-borne viral hepatitis. Finally, Indigenous Australians

had higher notification incidence for all disease groups, although the 'gap' for gastrointestinal diseases and vaccine preventable diseases was less marked. Incomplete reporting of Indigenous status precluded national analysis of this important risk factor.

Implications of all the available evidence

Health inequities are apparent for notifiable infectious diseases in Australia, with broadly similar patterns as identified internationally. The relative disparity in notification incidence for gonococcal infection among Indigenous compared to non-Indigenous people was ten-fold higher in Australia from 1991–2011 (aRR 25) compared to the United States from 2007–2011 (RR 2.4).[135] We demonstrated some progress in 'closing the gap' in burden infectious diseases based on sociodemographic inequities, which contrasts with an observed increase in socioeconomic and ethnic inequalities in infectious disease hospitalisations in New Zealand from 1989–2008.[136] Lesser observed inequities for vaccine preventable diseases might be attributable to Australia's national funded vaccination program. Important health inequities persist in Australia and progress has not been made in reducing the inequity in blood borne viral hepatitis burden. The different patterns of geographic clustering and sociodemographic inequity highlight the need for disease-specific (and sometimes population-specific) prevention programmes. More complete documentation of Indigenous status will allow national analysis in the future, thus contributing to 'closing the gap' for health of Indigenous Australians.

Table 4:1 Included years for the eight most commonly notified diseases analysed in this study

Disease	Years included*	Variation by jurisdiction
Chlamydial infection	1994–2011	1999–2011 in New South Wales
Hepatitis C	1993–2011	1998–2011 in Victoria†; newly acquired and unspecified infections analysed together
Hepatitis C (newly acquired)	1993–2011	1995–2011 in the Australian Capital Territory, Tasmania and Western Australia; 2005–2011 in the Northern Territory; not notifiable in Queensland
Hepatitis C (unspecified)	1995–2011	Included incident cases until hepatitis C newly acquired introduced
Campylobacteriosis	1991–2011	Not notifiable in New South Wales
Pertussis	1991–2011	
Salmonellosis (non typhoidal)	1991–2011	
Influenza (laboratory confirmed)	2001–2011	2008–2011 in South Australia
Hepatitis B	1991–2011	1998–2011 in Victoria†; 1996–2011 in South Australia†; 2005–2011 in the Northern Territory; newly acquired and unspecified infections analysed together
Hepatitis B (newly acquired)	1993–2011	1994–2011 in Queensland and Western Australia; 1995–2011 in the Australian Capital Territory
Hepatitis B (unspecified)	1991–2011	2005–2011 in the Northern Territory
Gonococcal infection	1991–2011	

*Based on year the disease became nationally notifiable to the National Notifiable Diseases Surveillance System (NNDSS); †Earlier years excluded because of discrepancies with online (updated) NNDSS data – all notifications from the Northern Territory in 1994 excluded because of discrepancies with online (updated) NNDSS data

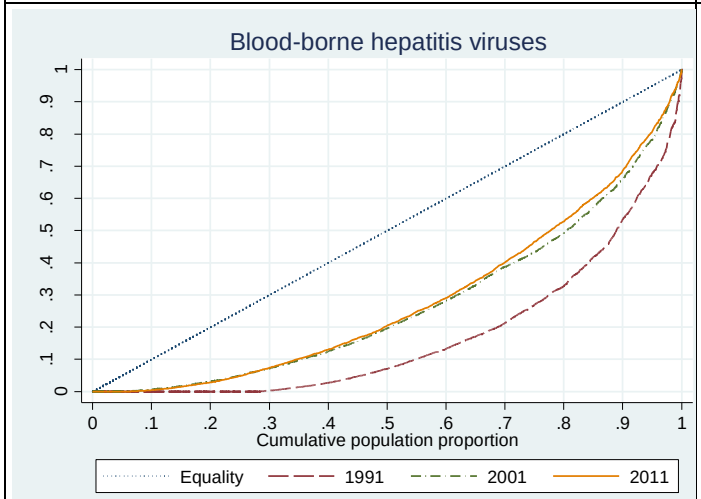
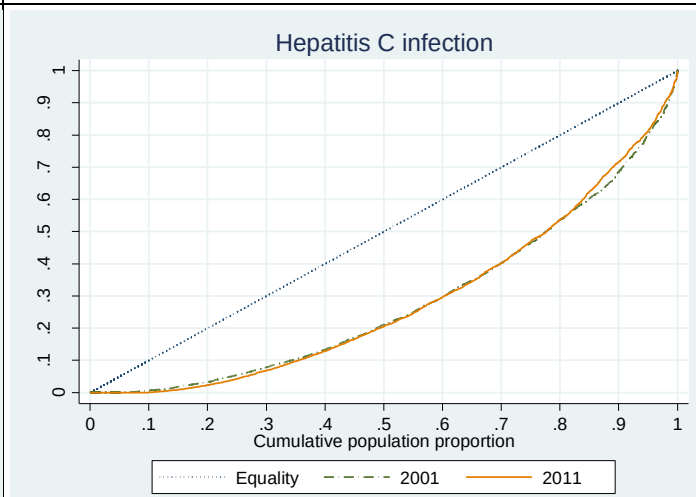
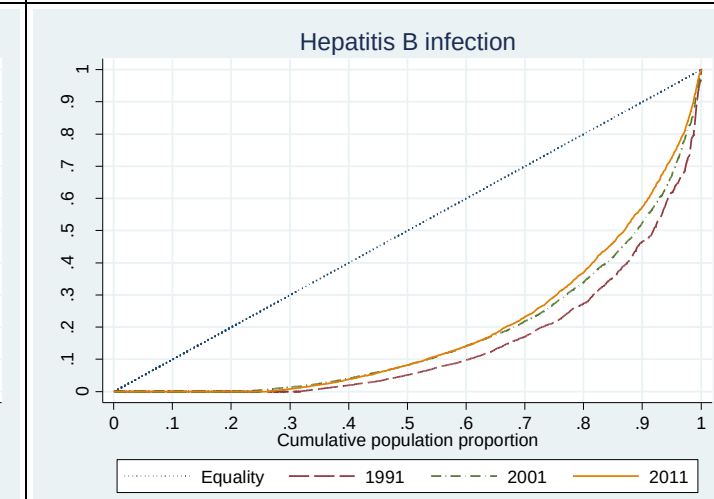
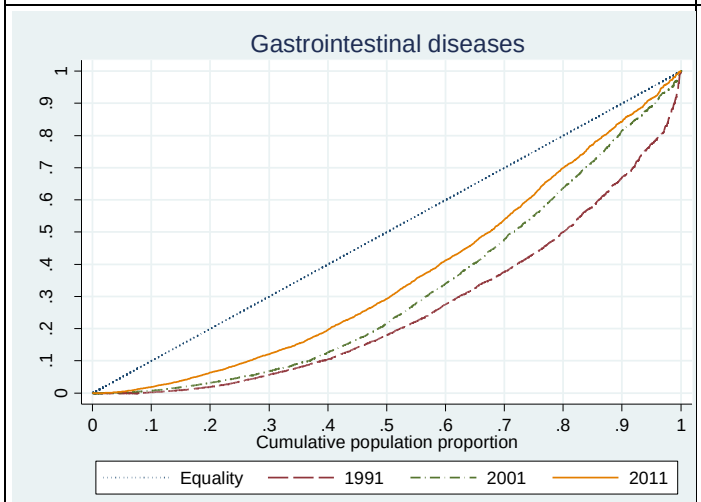
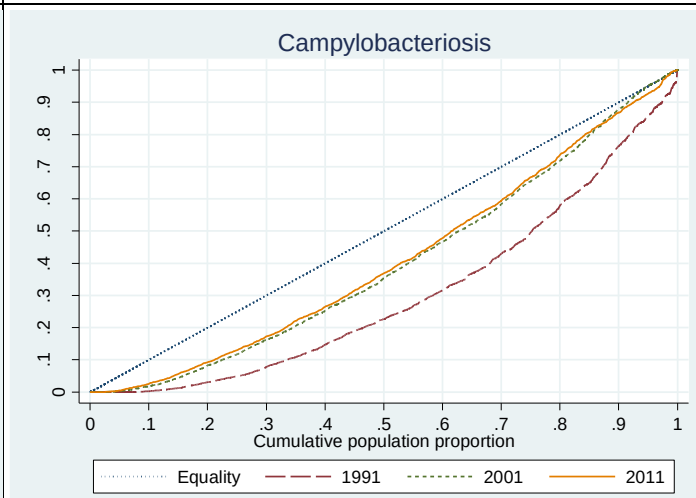
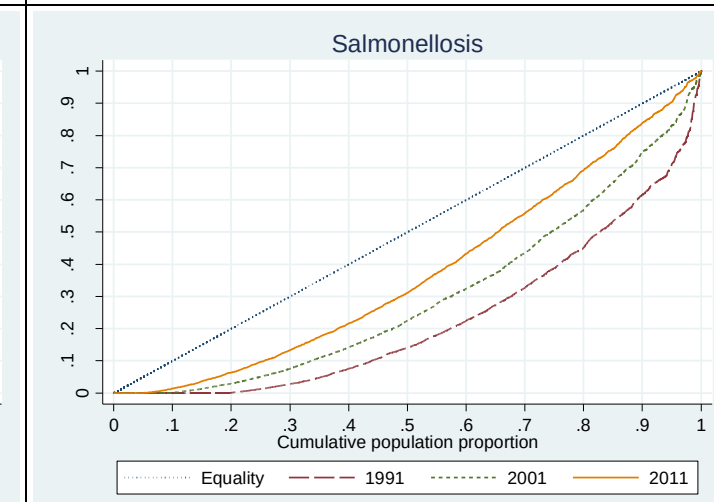
Table 4:2: Spatial inequality in disease notification according to postcode of residence for disease groups and highest-incidence diseases, by period, Australia 1991–2011

	Annual notification incidence per 100,000			Gini coefficient			% of all cases among 10% of population living in highest-incidence postcodes			% of total population living in postcodes with no cases notified		
Year	**1991**	**2001**	**2011**	**1991**	**2001**	**2011**	**1991**	**2001**	**2011**	**1991**	**2001**	**2011**
Disease group												
Blood-borne viruses	42.8	133.3	77.3	0.697	0.533	0.517	48	34	26	25	5	5
Gastrointestinal	101.3	135.3	147.0	0.568	0.494	0.417	33	18	16	8	3	2
Sexually transmitted	54.3	145.8	427.6	0.910	0.617	0.474	82	48	31	60	6	1
Vaccine preventable	17.4	68.0	366.1	0.637	0.512	0.403	44	26	19	34	8	0.8
Other diseases	11.8	11.4	14.6	0.876	0.825	0.827	72	62	62	69	62	62
Most commonly notified diseases												
Gonococcal infection	15.4	32.5	54.3	0.936	0.848	0.738	87	75	61	76	38	19
Hepatitis B	29.6	41.8	30.7	0.739	0.679	0.658	53	48	43	32	22	26
Influenza	NN	6.5	121.1	NN	0.724	0.529	NN	47	31	NN	53	5
Hepatitis C	NN	91.8	46.5	NN	0.520	0.522	NN	31	28	NN	6	10
Pertussis	1.9	49.4	172.9	--	0.592	0.446	--	31	21	--	16	3
Chlamydial infection	NN	104.8	361.9	NN	0.554	0.442	NN	37	27	NN	6	1
Salmonellosis	31.5	36.5	55.0	0.614	0.497	0.399	38	25	13	20	10	5
Campylobacteriosis	77.1	126.4	117.3	0.513	0.379	0.369	24	12	13	8	3	2

Notified incidence by postcode were used to calculate Gini coefficient and Lorenz curves

-- fewer than 1000 cases notified; NN – not notifiable

Figure 4.1: Lorenz curves demonstrating geographical inequality in disease notification incidence according to postcode of residence — Australia 1991, 2001 and 2011

Disease group	Most common disease within disease group	2nd most common disease within disease group
		
		

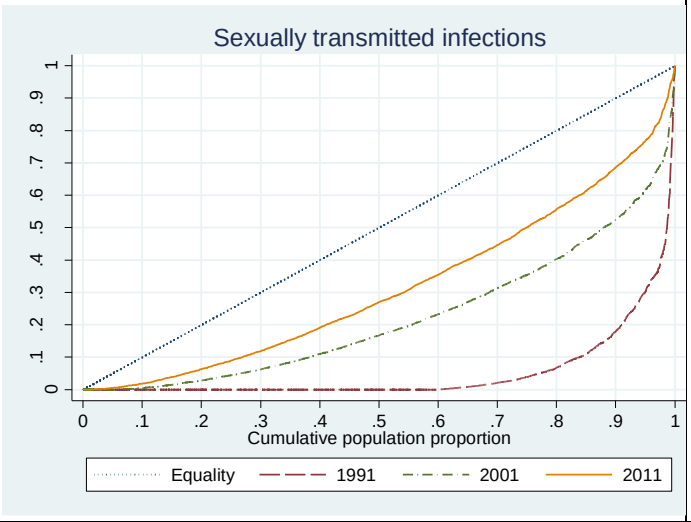
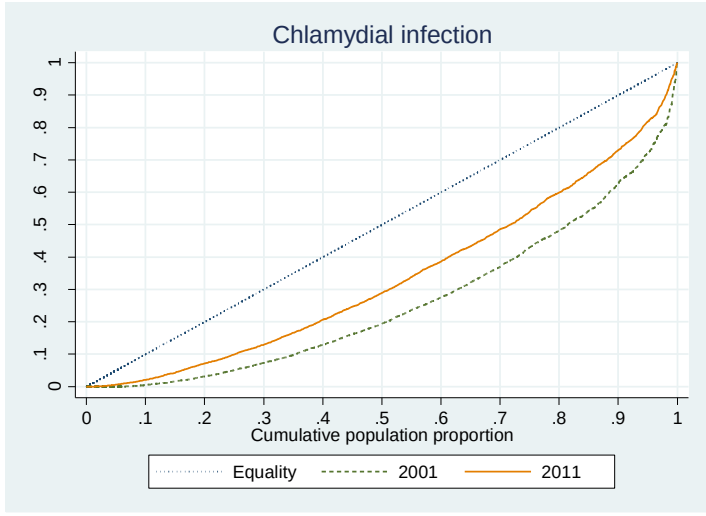
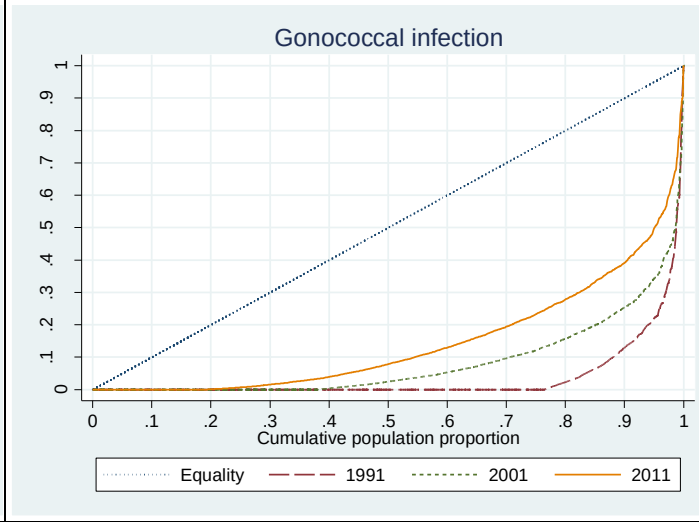
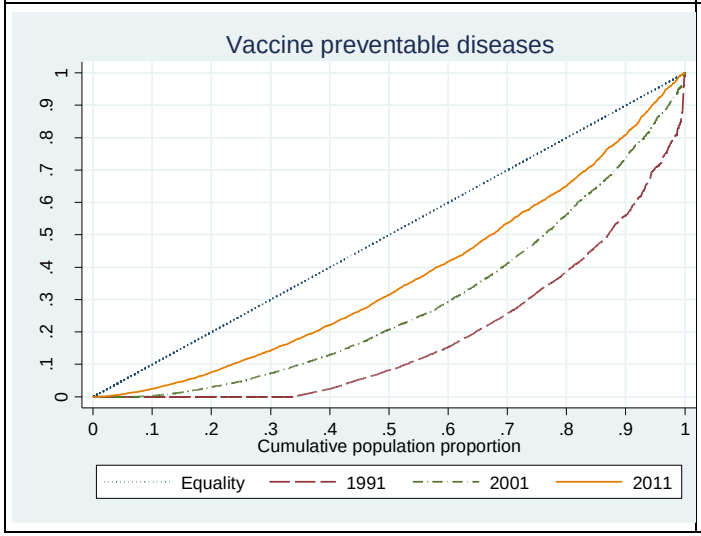
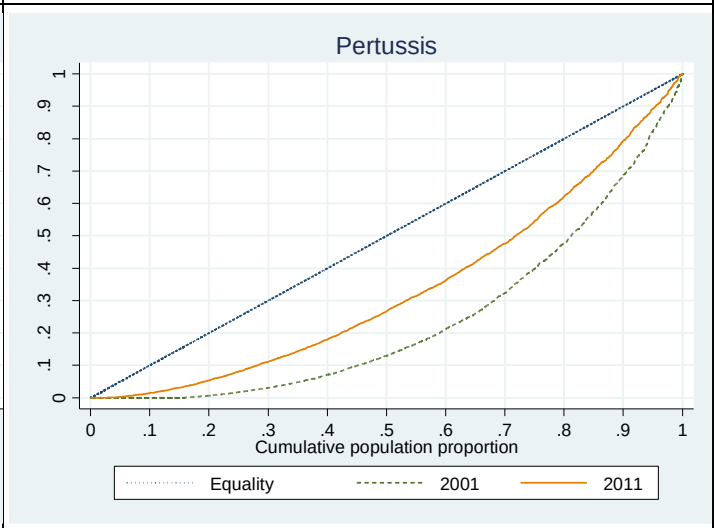
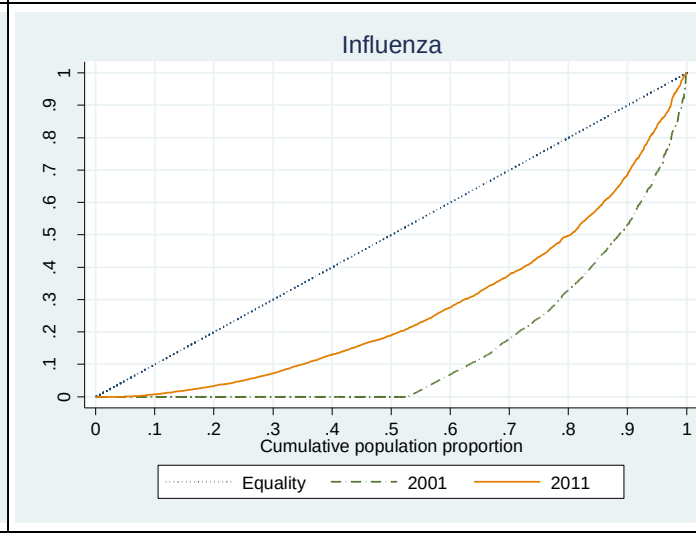
Disease group	Most common disease within disease group	2nd most common disease within disease group
		
		

Figure 4.2: Notification incidence by sociodemographic factors and disease group, Australia 1991–2011

Figure 4.2a. Socioeconomic disadvantage

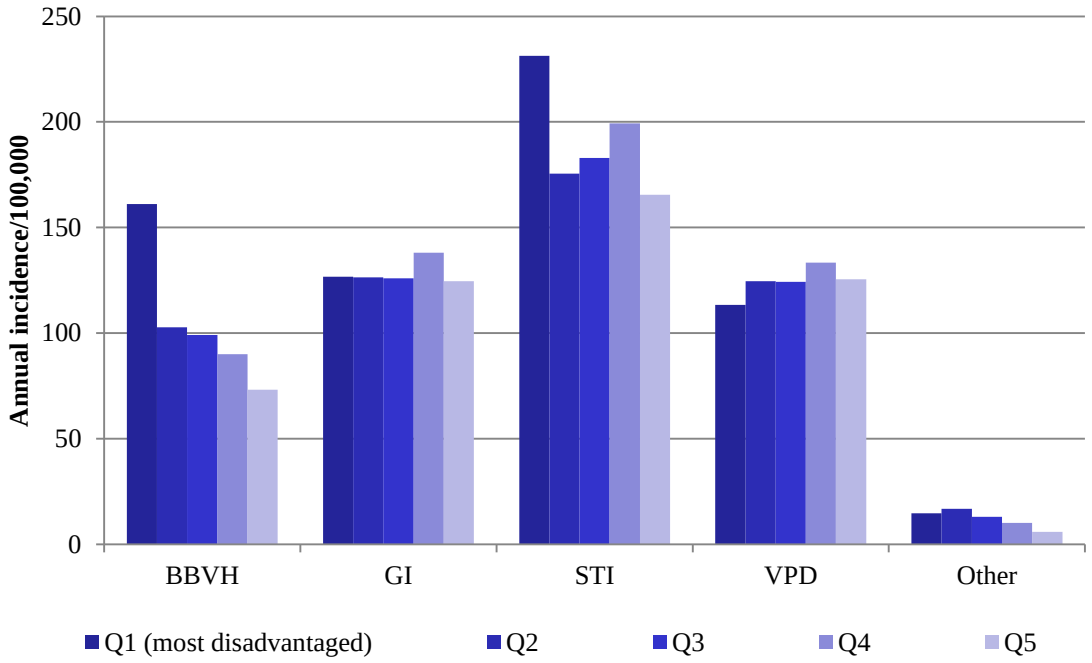
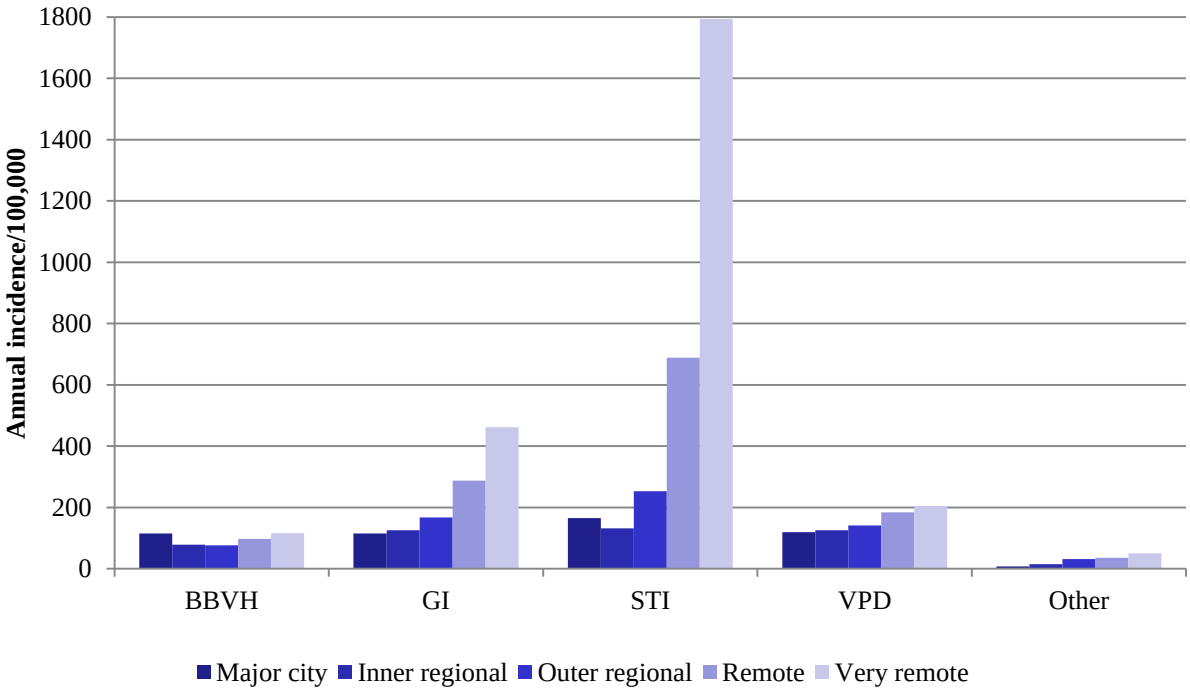


Figure 4.2b. Remoteness index



BBVH – blood-borne viral hepatitis; GI – gastrointestinal; IRSD – index of relative socioeconomic disadvantage; Q – quintile; STI – sexually transmissible infections; VPD – vaccine preventable diseases

Figure 4.3: Adjusted relative risks (aRR) for sociodemographic factors, by disease group and most common diseases, Australia 1991–2011

	All diseases	Blood-borne viral hepatitis			Gastrointestinal diseases			Sexually transmissible infections			Vaccine preventable diseases			Other diseases
		Group	Hep B	Hep C	Group	Camp	Salmo	Group	Chlam	Gono	Group	'Flu	Pertus	Group
Female (reference)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Male	1.03	1.56	1.29	1.75	1.12	1.19	1.00	0.82	0.67	1.98	0.91	0.95	0.78	1.22
Age <5 years	0.78	0.03	0.04	0.02	3.56	2.26	6.48	0.01	0.01	0.02	2.59	2.17	2.36	0.30
5–14 years	0.70	0.04	0.10	0.01	0.90	0.74	1.14	0.04	0.03	0.07	2.03	1.36	2.91	0.20
15–39 years (reference)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
40–64 years	0.42	0.55	0.60	0.59	0.67	0.72	0.70	0.11	0.07	0.20	0.74	0.62	1.32	1.12
≥65 years	0.28	0.15	0.18	0.13	0.72	0.8	0.82	0.02	0.01	0.02	0.97	0.52	1.03	0.70
IRSD Q2–5 (reference)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q1 (most disadvantaged)	1.15	1.86	2.40	1.73	0.91	0.87	1.05	1.14	1.08	1.83	0.87	1.04	0.89	1.23
City / regional (reference)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Remote / Very remote	3.37	0.84	1.44	0.63	2.87	1.11	3.54	6.62	3.38	20.11	1.63	2.06	0.98	3.64

Darker colours indicate greater relative difference in incidence rate – red indicates higher and green lower incidence rate than reference group (aRR >1 and <1, respectively)

Camp – campylobacteriosis; Chlam – chlamydial infection; 'flu – influenza; Gono – gonococcal infection; Hep – hepatitis (includes newly acquired and unspecified notifications); Other – other diseases group; Pertus – pertussis; Salmo – salmonellosis

Figure 4.4: Population attributable fraction and notifications attributable to remoteness and socioeconomic disadvantage adjusted for age and sex — Australia 1991–2011

Figure 4.4**a: Population attributable fraction by disease group and period**

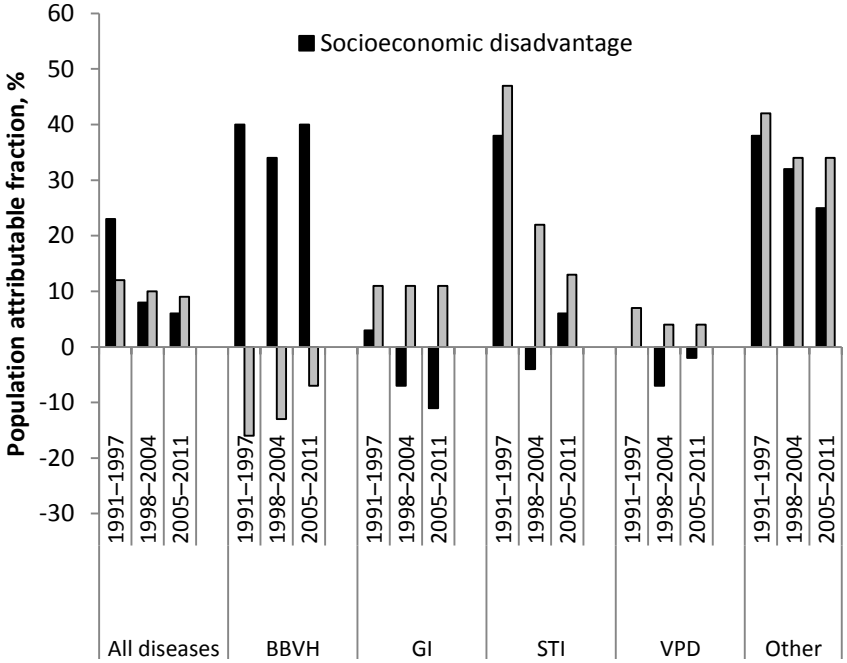
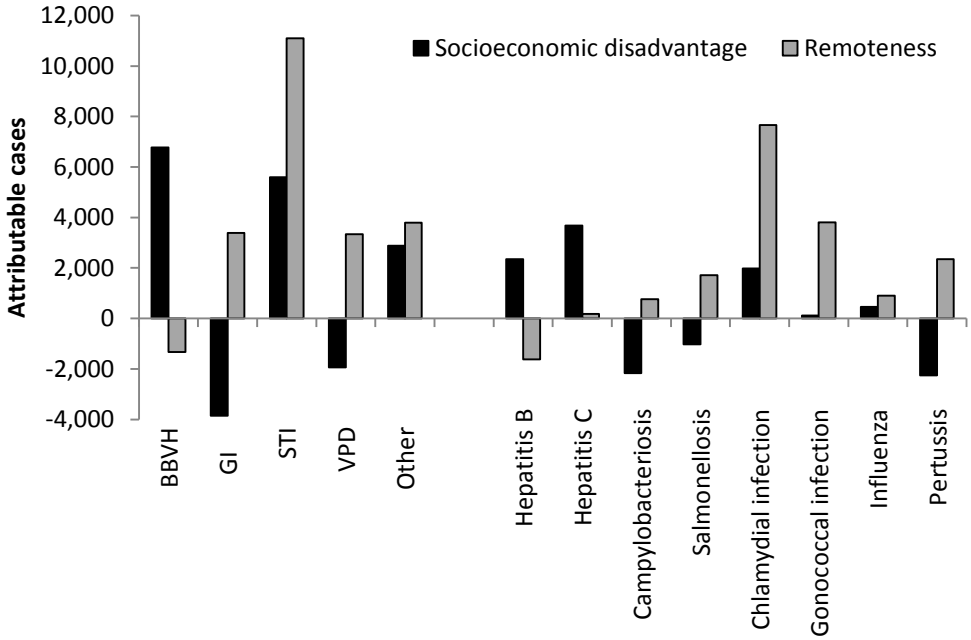


Figure 4.4b**: Attributable notifications by disease group and most commonly notified diseases, 2011**



'Ideal' exposure levels (reference groups) are the least disadvantaged Index of Relative Socioeconomic Disadvantage quintile (IRSD Q5) and residence in a major city; models also adjusted for age-group and sex. Negative values indicate higher notification incidence in the reference groups than in the comparison groups. BBVH – blood-borne viral hepatitis; GI – gastrointestinal; IRSD – index of relative socioeconomic disadvantage; Other – other disease groups; STI – sexually transmissible infection; VPD – vaccine preventable disease;

Figure 4.5: Notification relative risk based on sociodemographic factors and disease group—Northern Territory, South Australia and Western Australia, 1991–1998

Figure 4.5**a: Univariate analysis of Indigenous compared to non-Indigenous Australians**

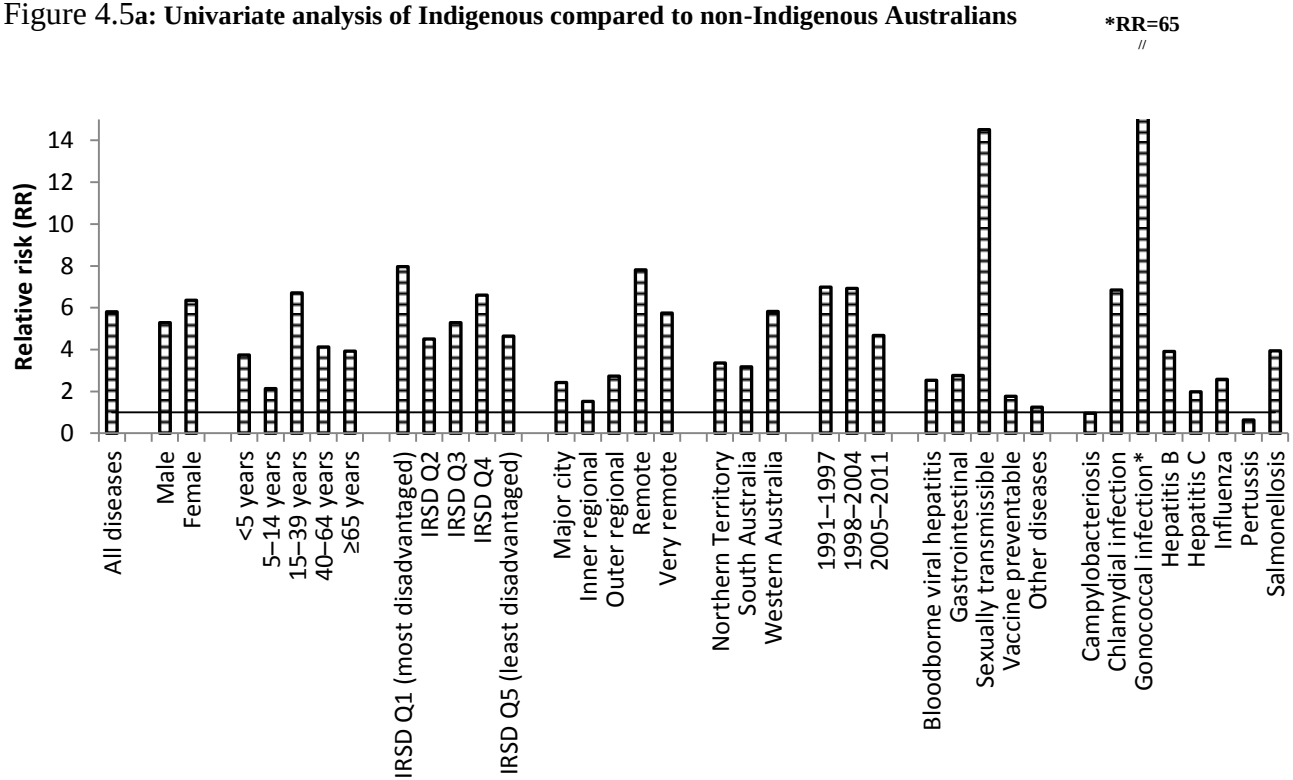
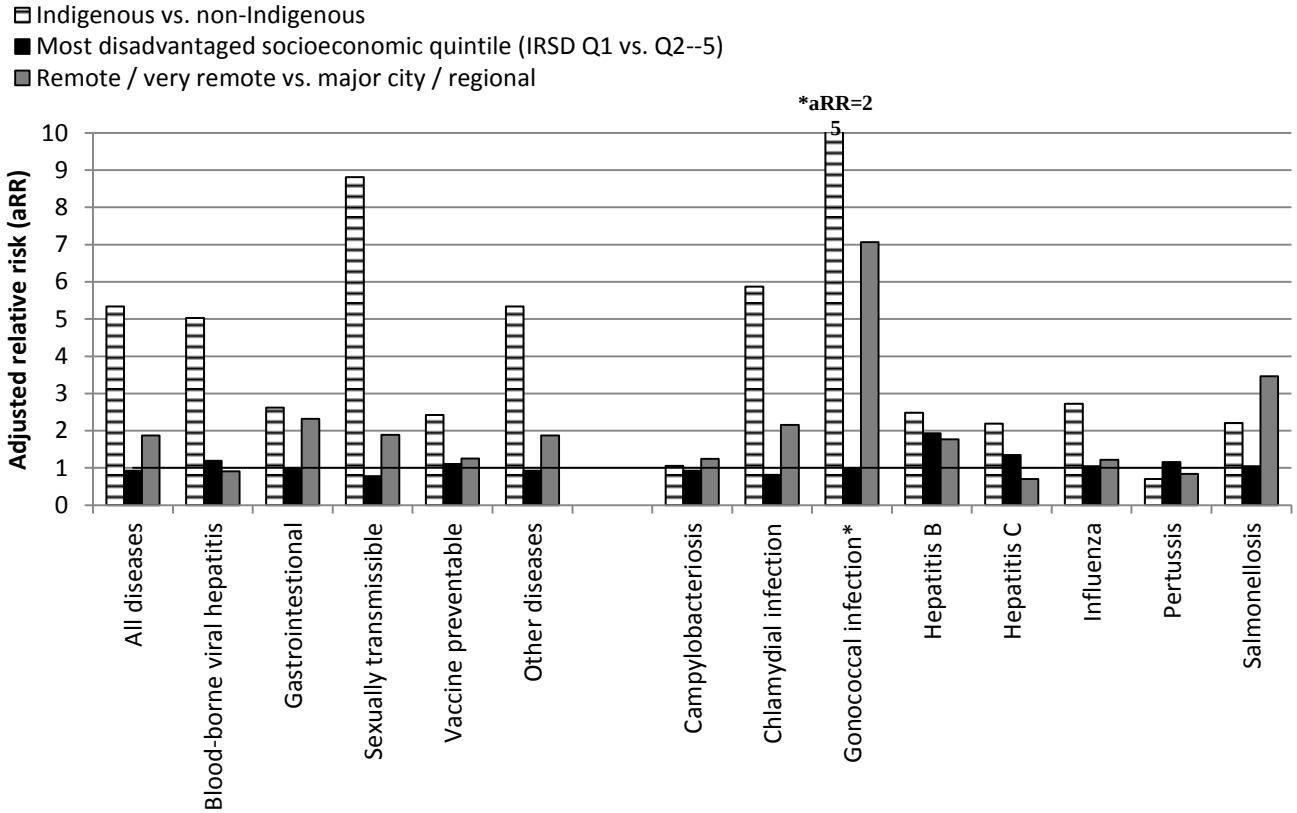


Figure 4.5b: Multivariable analysis including Indigenous status, remoteness and socioeconomic disadvantage, by disease group and disease



IRSD – Index of relative socioeconomic disadvantage; Q - quintile
Indigenous status missing for 20% of cases – these were assumed to be non-Indigenous

4.1.7 Appendix: Case definitions, data cleaning, and the proportion of eligible cases included in analyses.

Case definitions for notifiable diseases were initially determined by jurisdictions. Uniform case definitions were recommended by the National Health and Medical Research Commission (NHMRC) in 1993; however national surveillance case definitions were not used by all jurisdictions until 2005 and have been continually updated since.[31,83, 84]

NNDSS data were provided by the Australian Government's Office of Health Protection in March 2012 as an extract from the national data file. Staff in the Office of Health Protection undertook cleaning and de-duplication of NNDSS data prior to data extraction. Cases were eligible for inclusion in this analysis if they were notified in years when the disease was notifiable to NNDSS and included on the jurisdictional notifiable diseases list, with the following exceptions: cases notified in the Northern Territory in 1994; hepatitis B and C (Victoria 1991–1997); hepatitis B (South Australia 1991–1997); tuberculosis (Victoria 1991) and varicella zoster (Victoria 2006–2007). These exclusions were based on observed discrepancies between the study dataset and online (live) NNDSS data that has undergone subsequent additional data cleaning.[81] This reflects the fact that NNDSS data are dynamic with routine and targeted retrospective data cleaning processes occurring that may affect concordance between the dataset analysed and current NNDSS data.

In total, 2,421,134 notified cases were eligible for inclusion, of which 97.4% were successfully matched with Australian Bureau of Statistics data and analysed. Indigenous status analyses were restricted to the three jurisdictions with >75% completeness of Indigenous status reporting among notified cases – the Northern Territory, South Australia, and Western Australia – with 609,145 cases eligible for analysis. Of these, Indigenous status was missing for 20.4% (presumed non-Indigenous and included in the analysis), while age, sex, remoteness and socioeconomic disadvantage data were available for 95.4%.

Chapter Five: The burden of selected gastrointestinal pathogens in Australia

Declaration for thesis Chapter 5

Declaration by candidate

In the case of Chapter 5.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Literature review; data sourcing, collation and analysis; drafting manuscript; preparation of manuscript for submission	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Joanne O'Toole	Study concept and design; uncertainty analysis using @Risk; duplicate check of study results; revision of manuscript from preliminary draft to submission	
Martha Sinclair	Study concept and design; revision of manuscript from preliminary draft to submission	
Karin Leder	Project leader; study concept and design; revision of manuscript from preliminary draft to submission	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature		**Date** 11th July, 2016

Aim: To estimate and compare burden of six gastrointestinal pathogens in Australia using several burden of disease metrics, including collection of Australian data to inform these estimates.

Preface

Minimising the public health impact of gastroenteritis is a focus of the communicable disease control and prevention, food safety, and water units of jurisdictional health departments in Australia. Accurate burden of disease measures allow prioritisation and optimal use of limited resources and setting health based targets (HBTs) in guidelines and policies. There are a variety of metrics used to measure burden of disease; the choice of metric along with means of data acquisition, methods chosen and assumptions made will influence the resulting estimate.

This chapter has two parts. The first part comprises a published article that compares disease burden of six gastrointestinal pathogens in Australia using several different metrics – namely incidence, mortality, and disability adjusted life years (DALYs). Analysis of the impact of inclusion of sequelae is included in the DALY estimates for campylobacteriosis and salmonellosis. It is proposed that these DALY estimates be included in revised *Australian Drinking Water Guidelines*.

This article is based on an NHMRC Partnership Project report of which I was first author:

- **Gibney KB,** Sinclair M, O'Toole J, Leder M (2012). Establishing Australian health based targets for microbial water quality. Final Report Project 1004/09. Water Quality Research Australia, Adelaide.

The second part of Chapter 5 is a description of a planned doctoral study examining the frequency, severity and duration of sequelae following notified campylobacteriosis,

salmonellosis and cryptosporidiosis. This study was terminated by the Victorian Department of Health over concerns that release of data to researchers might contravene the *Health Records Act 2001*. The benefits and consequences of legislative restrictions on the use of health data for research are discussed.

5.1 Disease burden of selected gastrointestinal pathogens in Australia, 2010

This paper has been published in the *International Journal of Infectious Diseases*:

http://www.sciencedirect.com/science/article/pii/S1201971214016191

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Disease burden of selected gastrointestinal pathogens in Australia, 2010

Katherine B. Gibney *, Joanne O'Toole, Martha Sinclair, Karin Leder

Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne 3004, Victoria, Australia

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SUMMARY

Objective: To estimate and compare disease burden attributable to six gastrointestinal pathogens (norovirus, rotavirus, Campylobacter, non-typhoidal Salmonella, Giardia, and Cryptosporidium) in Australia, 2010.

Methods: We estimated the number of acute gastroenteritis (AGE) cases and deaths, disability-adjusted life years (DALYs), and DALY/case for each pathogen. We included AGE cases that did not require medical care. Sequelae were included for Campylobacter (Guillain–Barré syndrome, reactive arthritis (ReA), irritable bowel syndrome (IBS)) and Salmonella (ReA, IBS).

Results: We estimated 16 626 069 AGE cases in Australia in 2010 (population 22 million). Of the pathogens studied, most AGE cases were attributed to norovirus (2 180 145), Campylobacter (774 003), and Giardia (614 740). Salmonella caused the fewest AGE cases (71 255) but the most AGE deaths (90). The DALY burden was greatest for Campylobacter (18 222 DALYs) and Salmonella (3856 DALYs), followed by the viral and protozoal pathogens. The average DALY/case was greatest for Salmonella (54.1 DALY/1000 cases), followed by Campylobacter (23.5 DALY/1000 cases).

Conclusions: The pathogen causing the greatest disease burden varied according to the metric used, however DALYs are considered most useful given the incorporation of morbidity, mortality, and sequelae. These results can be used to prioritize public health interventions toward Salmonella and Campylobacter infections and to measure the impact of these interventions.

1. Introduction

Acute gastroenteritis (AGE) results in significant morbidity and mortality in Australia and worldwide.[1,2] Estimating AGE disease burden is an important element of estimating food-borne disease burden, a worldwide public health priority.[1,3] Disease burden can be measured in multiple ways, including number of cases, number of deaths, and more sophisticated metrics such as disability-adjusted life years (DALYs). The DALY takes into account disease mortality (years of life lost, YLL) and morbidity (years lost due to disability, YLD), where DALY = YLL + YLD. Specifically, DALYs incorporate information on the incident number of disease cases, illness duration, disease severity (disability weight), incident number of deaths, and life expectancy at age of death. Differing health outcomes can be incorporated into DALY disease models, including disease sequelae. In high-income countries where case fatality rates of AGE are low, sequelae to Campylobacter and Salmonella infection have been reported to cause greater DALY burden than the AGE itself.[4,5] One DALY equates to one lost year of 'healthy' life and the metric quantifies the gap between a population's current health status and an ideal where everyone lives to advanced age in perfect health. In addition to using the DALY to quantify the population disease burden, the average DALY/case can indicate the relative severity of disease caused by different pathogens.

We estimated the disease burden of six common gastrointestinal pathogens in Australia for the year 2010 and compared the number of cases, number of deaths, DALYs, and average DALY/case for each pathogen. We examined the two most common pathogens for high-income countries in each of the three major AGE pathogen groups:[4,6,7] viruses (rotavirus and norovirus), protozoa (Cryptosporidium and Giardia), and bacteria (Salmonella and Campylobacter). Comparing our results to international studies highlights the impact of environmental conditions, risk factors, and preventive measures on disease burden, with differences in disease burden estimates from specific AGE pathogens even between high-income countries; for example the incidence of Campylobacter

* Corresponding author. Tel.: +61 3 9903 0605; fax: +61 3 9903 0556.
E-mail address: Katherine.Gibney@monash.edu (K.B. Gibney).

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AGE is approximately nine-times higher in Australia than in the USA.[8] Therefore, there is the need for country-specific disease burden estimates. These results can be used to assess the burden of AGE illnesses caused by different pathogens and pathogen groups, to inform appropriate public health responses to specific pathogens and pathogen groups, and to rationalize optimal targets for disease prevention.

2. Methods

2.1. Overview

We first estimated the total number of all-cause AGE cases in Australia in 2010 and then the number of all-cause AGE cases in four severity categories based on the requirement for medical care: fatal, hospitalized (inpatient medical care), outpatient (outpatient medical care), and mild (no medical care). Next we estimated the number of AGE cases attributable to each study pathogen (norovirus, rotavirus, Campylobacter, non-typhoidal Salmonella, Giardia, and Cryptosporidium) in terms of total AGE cases as well as fatal, hospitalized, outpatient, and mild AGE cases (Figure 1). We then estimated the number of cases of sequelae attributable to the two bacterial pathogens and the proportion in each severity category. Sequelae were included for Campylobacter (Guillain–Barré syndrome, reactive arthritis (ReA), irritable bowel syndrome (IBS)) and Salmonella (ReA, IBS). Finally we estimated disease duration, disability weight, and average life expectancy at age of death in order to calculate the DALYs and DALY/case (Figure 2).

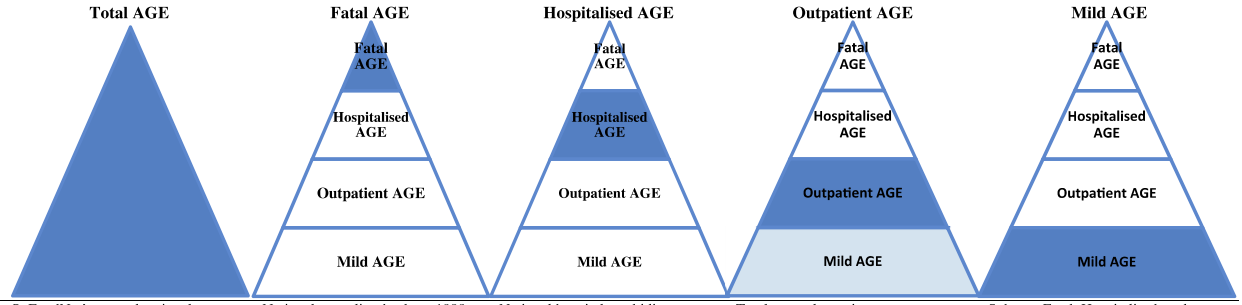
2.2. Population included

Our estimates were for all AGE cases, including those not requiring medical care, for the entire Australian population. For rotavirus, some previous DALY estimates have used a population of unvaccinated children <5 years of age.[9] However, because rotavirus cases are not confined to young children and rotavirus vaccine was added to Australia's National Immunisation Programme in July 2007,[10,11] we calculated the rotavirus burden in three Australian populations: (1) entire population, unvaccinated; (2) <5 years of age, unvaccinated; and (3) <5 years of age, vaccinated. Due to incomplete data on the impact of a partially vaccinated population, when comparing disease burden caused by the six AGE pathogens we used our estimates of rotavirus in the entire (unvaccinated) population.

2.3. Selecting data sources used in these DALY models

We used a combination of Australian administrative data (e.g., Australian notification/hospitalization/mortality data) and published and unpublished studies in our disease burden calculations. We obtained Australian administrative data through the websites of the relevant agencies and through formal data requests made to these agencies. Additionally, we submitted data requests to access unpublished data from OzFoodNet (a federally funded health network to enhance the surveillance of food-borne diseases in Australia) and the University of Sydney's 'Bettering the Evaluation And Care of Health' (BEACH) program, which collects information from Australian general practitioners (GPs).

To identify the published studies used in this report, we performed a literature review in PubMed using a combination of the following terms: 'gastroenteritis', 'community', 'hospital', 'deaths', 'epidemiology', 'Australia', 'norovirus', 'rotavirus', 'Campylobacter', 'Salmonella', 'Giardia', and 'Cryptosporidium'. We reviewed the titles of articles identified, and then based on perceived relevance we reviewed the abstracts before sourcing the full article. We reviewed the reference lists of articles to identify further relevant publications and reports. Only publications available in English were considered. The main literature review was performed in 2012; this was supplemented by targeted literature reviews until models were finalized. We selected data sources and studies based on certain criteria, including: (1) Study quality – size, duration, scientific rigor. These were the most important criteria for selecting studies to include in our DALY models. (2) Location – where possible we used Australian data, but if necessary we used data from other high-income countries (e.g., New Zealand, Europe, North America, and Japan). (3) Recency. (4) Internal consistency – where possible we used the same data sources for multiple pathogens. However, if the estimates for a particular pathogen deviated from other published estimates, we used judgement to choose an alternate data source to determine the most likely estimate. (5) Disease severity information, e.g., outpatient medical care, hospitalized, etc. (6) Age-group specific information – where available we included age-group specific data in our models.



All cause estimate	OzFoodNet's second national gastroenteritis survey (NGSII-2008)[65], 2008–2009	National mortality database 1998–2007, underlying cause A00–A09 (ICD 10)	National hospital morbidity database 1998/99–2007/08, principle diagnosis A00–A09 + 0.5 x total emergency department encounters x proportion due to AGE (Federal and State Health Departments)	Total general practice encounters (Medicare 2010) x proportion due to AGE (BEACH 2006–11)[18] + 0.5 x total emergency department encounters x proportion due to AGE (Federal and State Health Departments)	Subtract Fatal, Hospitalised, and Outpatient AGE from Total AGE
Pathogen specific estimate	Pathogen fraction (proportion of all-causes cases attributable to that pathogen)	Multiple methods: National Mortality Database data; National Notifiable Diseases Surveillance System data with case fatality rates; population mortality rates	Pathogen fraction	Pathogen fraction	Subtract Fatal, Hospitalised, and Outpatient AGE from Total AGE

Figure 1. Outline of methods used to estimate all-cause and pathogen-specific number of acute gastroenteritis (AGE) cases for each severity category.

DALY =	No. AGE deaths x average life expectancy at age of death	
	+	
	No. AGE cases x duration of illness x disability weight (for **mild** AGE)	
	+	All study pathogens
	No. AGE cases x duration of illness x disability weight (for **outpatient** AGE)	
	+	
	No. AGE cases x duration of illness x disability weight (for **hospitalized** AGE)	
	+	
	No. Reactive Arthritis (ReA) cases x duration of illness x disability weight (for **mild** disease)	
	+	
	No. ReA cases x duration of illness x disability weight (**outpatient** disease)	*Salmonella* and
	+	*Campylobacter* only
	No. ReA cases x duration of illness x disability weight (**hospitalised** disease)	
	+	
	No. Irritable Bowel Syndrome cases x duration of illness x disability weight	
	+	
	No. Guillain-Barré Syndrome (GBS) deaths x average life expectancy at age of death	
	+	
	No. GBS cases x duration of illness x disability weight (for **mild** disease)	*Campylobacter* only
	+	
	No. GBS cases x duration of illness x disability weight (for **severe** disease, <50 years of age)	
	+	
	No. GBS cases x duration of illness x disability weight (for **severe** disease, ≥50 years of age)	

Figure 2. Data points required to calculate disability-adjusted life years (DALY) for acute gastroenteritis (AGE) pathogens (ReA, reactive arthritis; GBS, Guillain–Barré syndrome).

2.4. Estimating AGE case numbers

2.4.1. Total all-cause infectious AGE cases

We applied age-weighted AGE rates from the national gastroenteritis survey NGSII-2008 study to the 2010 Australian population.[12] The NGSII-2008 study was a national cross-sectional telephone survey of 7578 participants conducted over 12 months in 2008–2009 in which infectious gastroenteritis was defined as at least three loose stools or two vomits in 24 h, in the absence of an identified non-infectious cause.[13] The full methodology of that study is a repeat of the earlier national gastroenteritis survey.[2]

2.4.2. All-cause AGE cases in each severity level

For each severity category we applied the estimated annual incidence of disease or death to the 2010 Australian population.[12]

For fatal AGE cases (all-cause), we determined average annual deaths with AGE as an underlying cause (International Classification of Diseases, 10th revision (ICD-10) codes A00–09) from the National Mortality Database (NMD, 1998–2007).[14]

For hospitalized AGE cases (all-cause), we combined the estimated number of AGE hospitalizations with half the estimated number of non-admitted emergency department (ED) encounters for AGE. Age-group specific hospitalization rates with a principal diagnosis of AGE (ICD-10 codes A00–A09) were obtained from the National Hospital Morbidity Database (1998/99–2007/08).[15] Total ED visits in 2010 was reported by the Australian Institute of Health and Welfare;[16] the proportion that were non-admitted ED encounters for AGE was obtained from state health departments (Queensland 2001/02–2009/10, New South Wales 1996/97–2009/10, Victoria 1999/2000–2009/10, and South Australia 2007/08–2009/10). We split the non-admitted ED encounters for AGE equally between the outpatient and hospitalized AGE categories, as we judged that some people attend ED with AGE because illness occurs when GP practices are closed (i.e., more like outpatient cases), while others go to the ED because they have severe symptoms (i.e., require intravenous fluid).

For outpatient AGE cases (all-cause), we combined GP visits for AGE with half the non-admitted ED encounters for AGE (see above). Total GP encounters for 2010 were obtained from Medicare, and the age-specific proportions attributable to AGE were derived from BEACH study data (2006–2011).[17,18] The BEACH study has been run by the University of Sydney since 1998. Each year, a random sample of 1000 GPs across Australia is surveyed with each recording details of 100 consecutive consultations.

With regard to mild AGE cases (all-cause), to account for AGE cases not requiring medical care and to ensure internal consistency in our disease models, mild AGE cases were estimated by subtracting fatal, hospitalized, and outpatient AGE cases from total AGE cases.

2.4.3. Pathogen-specific estimates of AGE cases and deaths

For total, hospitalized, and outpatient AGE cases (pathogen-specific), the proportions of all-cause AGE cases attributable to each pathogen (the pathogen fractions) were derived from studies listed in Table 1 and applied to the all-cause AGE estimate of each severity category. For total AGE cases we used the pathogen fraction from a population-based study from the Netherlands (the Sensor study) for all study pathogens other than Campylobacter,[19] for which we used the pathogen fraction from a British study (the IID2 study),[20] as this result was more consistent with other studies reviewed.[21–23] Similarly, for outpatient AGE cases we used the pathogen fraction from a GP-based study from the Netherlands (the NIVEL study) for the rotavirus, Cryptosporidium, Salmonella, and Campylobacter AGE estimates,[24] but the norovirus fraction from the IID2 study and the Giardia fraction from an Icelandic study (Hilmarsdóttir 2012),[20,25] as these were more consistent with the pathogen fraction reported in other studies reviewed.[26–31] As hospital-based studies were generally restrictive in terms of pathogens studied and age-groups included (paediatric vs. adult), a number of studies were used to estimate hospitalized AGE cases for each pathogen.[70–79]

With regard to fatal AGE cases (pathogen-specific), because of concerns about significant under-reporting of AGE deaths in the NMD, we used a combination of approaches to estimate AGE fatalities by different pathogens. For the protozoal study pathogens (Cryptosporidium and Giardia) we used vital registration data directly from the NMD (ICD-10 codes A00–A09, 1998–2007).[14] This is because, consistent with NMD data, published studies

Table 1
Data sources used to calculate number of cases and duration of illness for acute gastroenteritis and sequelae—Australia, 2010

Acute gastroenteritis	Number of cases			Duration		
	Total	Outpatient	Hospitalized[a]	Mild	Outpatient	Hospitalized
Norovirus	de Wit 2001[19]	Tam 2011[20]	Jansen 2008[70] Lorrot 2011[71] Patel 2008[72]	Sinclair 2005[23]	OzFoodNet outbreak registry[45]	Kemmeren 2006[49]
Rotavirus	de Wit 2001[19]	de Wit 2001[24]	Jansen 2008[70] Lopman 2011[73] Carlin 1998[74]	Kemmeren 2006[49]	Kemmeren 2006[49]	de Wit 2000[47]
Cryptosporidium	de Wit 2001[19]	de Wit 2001[24]	Tzipori 1983[75]	Sinclair 2005[23]	Sinclair 2005[23]	Robertson 2001[46]
Giardia	de Wit 2001[19]	Hilmarsdóttir 2012[25]	Jansen 2008[70] Essers 2000[76]	Nash 1987[77]	Homan 2012[50]	Nygård 2006[78]
Campylobacter	Tam 2011[20]	de Wit 2001[24]	Jansen 2008[70] Barnes 1998[79]	Kemmeren 2006[49]	Kemmeren 2006[49]	Kemmeren 2006[49]
Salmonella	de Wit 2001[19]	de Wit 2001[24]	Jansen 2008[70] Barnes 1998[79]	Sinclair 2005[23]	Food Standards Agency 2011[21]	McPherson 2006[48]
Sequelae (pathogen)	Number of cases			Duration		
	Total	In each severity group				
GBS (Campylobacter)	Poropatich 2010[40] Hankey 1987[39]	Mangen 2004[41]		Havelaar 2000[22]		
ReA (Campylobacter)	Hannu 2002[42]	Hannu 2002[42]		Mangen 2004[41]		
ReA (Salmonella)	Tuompo 2013[43]	Tuompo 2013[43]		Mangen 2004[41]		
IBS (Campylobacter, Salmonella)	Haagsma 2010[44]	-		Haagsma 2010[44]		

GBS, Guillain–Barré syndrome; ReA, reactive arthritis; IBS, irritable bowel syndrome.

indicate that fatalities attributable to these pathogens are rare.[32,33] However, for the other pathogens we chose alternate methods, as the number of registered deaths in the NMD was much lower than reported in the published literature. We used data from the Australian National Notifiable Disease Surveillance System (NNDSS, 2001–10)[34] to estimate the number of notified cases of Campylobacter and Salmonella in 2010, and multiplied this by the case fatality rates for these pathogens used in a study of the burden of food-borne diseases in the USA.[6] The viral study pathogens are not nationally notifiable in Australia, and so we applied population mortality rates for rotavirus and norovirus reported in two German studies to the 2010 Australian population.[35,36]

For mild AGE cases (pathogen-specific), we subtracted the sum of outpatient, hospitalized, and fatal AGE cases from total AGE cases for each pathogen. This ensured internal consistency in our pathogen-specific estimates.

For rotavirus cases and deaths in a vaccinated population <5 years old, the estimated percentage reduction in rotavirus cases of each severity as a result of vaccination[37,38] was applied to the estimated number of rotavirus cases among unvaccinated children.

2.5. Disease sequelae

We estimated the sequela fraction (proportion of Campylobacter or Salmonella AGE cases that develop relevant sequelae) and the proportion of sequelae cases in each severity category from the studies listed in Table 1. We estimated the number of all-cause GBS cases based on a study reporting GBS incidence in Australia,[39] and the number of all-cause GBS deaths from the NMD (ICD-10 code G61.0, 2000–2010), and multiplied these by the pathogen-fraction derived from a systematic review of Campylobacter-associated GBS.[40] For non-fatal GBS, the severity groupings (mild, severe <50 years, and severe ≥50 years) and proportion of non-fatal GBS cases in each severity group were derived from Dutch studies of the burden of Campylobacter-associated disease.[22,41] We estimated the ReA fraction (proportion of Campylobacter or Salmonella AGE cases that develop ReA) and severity of ReA from two Finnish population-based studies.[42,43] As these studies followed laboratory-confirmed AGE cases, we applied this ReA fraction to outpatient and hospitalized Campylobacter and Salmonella AGE cases. Finally, we applied the IBS fraction from a meta-analysis of post-infectious IBS studies to our total estimated Campylobacter or Salmonella AGE cases.[44]

2.6. Disease duration

Average disease duration was estimated for each pathogen for mild, outpatient, and hospitalized AGE and sequelae using the studies listed in Table 1. Because many studies do not record duration of AGE according to disease severity, we used a combination of data sources, including raw data from Australian registries and studies (e.g., the OzFoodNet national outbreak register and the community-based Water Quality Study),[23,45,46] estimates from published studies from Australia and Europe,[21,47,48] and estimates used in other studies examining the burden of food-borne disease.[49,50] Disease durations for sequelae were derived from Dutch studies of the burden of food-borne diseases.[22,41,44] We chose data sources to include in our models based on the criteria listed above.

2.7. Other DALY model input

Disability weights for mild, outpatient, and hospitalized diarrhoea from the Global Burden of Disease 2010 study (GBD2010) were used for all six AGE pathogens.[51] Disability weights for sequelae were derived from Dutch studies of the burden of food-borne diseases.[22,41,44] Average YLL for deaths due to each pathogen were calculated from the NMD (1997–1998 to 2007–2008) using Australian cohort life expectancies for 1996 without discounting.[52] To determine the average DALY/case, we divided the DALY burden by the number of AGE cases for each pathogen.

2.8. Age-specific inputs into DALY models

Rates of AGE are known to differ by age. Some data used to estimate all-cause AGE cases were available for specific age-groups (e.g., total AGE cases from the NGSII and hospitalizations), while other data only had whole-population estimates available

(e.g., emergency department encounters and deaths). Likewise, pathogen fractions were often available for specific age-groups, however the age-groups used varied by study. Where available, age-group specific data were used in our calculations and data stratified by age and then aggregated up to a total. However, we have reported our results for the whole population and not for specific age-groups.

2.9. Statistical analysis

Single input values were used to obtain the point estimate for the number of cases and deaths, DALY, and DALY/case estimates. These single input values were considered the 'most likely' values, based on assessment of the quality and recency of the study from which the values were derived and generalizability of results to the Australian population. In addition, Monte Carlo analyses (10 000 iterations) using PERT (Project Evaluation and Review Techniques) distributions were used to calculate 95% credible intervals (95% CrI) for DALY/case estimates. Minimum, mode, and maximum values used in the PERT distributions, along with the data sources and approaches to calculate these, are included in the **Supplementary Material**.

3. Results

We estimated 16 626 069 cases of AGE in Australia in 2010 (total population 22 million persons[12]), of which 26.6% were attributed to one of norovirus, rotavirus, Cryptosporidium, Giardia, Salmonella, and Campylobacter. The greatest numbers of cases were caused by norovirus (2 180 145, 13.1% of all-cause AGE cases), Campylobacter (774 003 cases, 4.7%), and Giardia (614 740 cases, 3.7%) (Table 2). Rotavirus was estimated to cause 592 745 AGE cases in the total population (unvaccinated), of which 223 370 (37.7%) cases were among unvaccinated children <5 years old.

The proportion of all-cause AGE cases that were mild was 91.4%, outpatient was 8.1%, and hospitalized was 0.6%, but the proportion of cases in each severity category varied between pathogens (Table 2). The proportion of total AGE cases that were mild ranged from 20.6% (Salmonella) to 92.2% (norovirus). Salmonella had the highest proportion of outpatient (65.6%), hospitalized (13.7%), and fatal AGE (case fatality rate 126/100 000 AGE cases); therefore, Salmonella caused the fewest AGE cases (71 255) but the most AGE fatalities (90). Conversely, Giardia and Cryptosporidium were estimated to cause no deaths in Australia in 2010.

For sequelae, it was estimated that IBS was most common (68 112 Campylobacter-associated and 6270 Salmonella-associated cases), followed by ReA (11 252 and 2505 cases, respectively) and GBS (102 Campylobacter-associated cases). Of these sequelae, only GBS was estimated to cause fatalities (three deaths). The average duration of AGE was shortest for the viral and longest for the protozoal pathogens studied (Table 2). The average duration of sequelae was shortest for ReA (0.6 years), followed by IBS (5 years), while symptoms of GBS were estimated to persist lifelong. Average YLL per AGE death ranged from 7.1 years (norovirus) to 31.9 years (rotavirus, total population) and 82.6 years (rotavirus, children <5 years).

The DALY burden was greatest for the bacterial pathogens, followed by viral and then protozoal pathogens (Figure 3). Campylobacter was estimated to cause 18 222 DALYs at an average of 23.5 DALY/1000 cases and Salmonella caused 3856 DALYs at an average of 54.1 DALY/1000 cases (Table 3). Rotavirus was more severe among children than adults (average 4.2 DALY/1000 cases among unvaccinated children vs. 2.5 DALY/1000 cases among the total unvaccinated population), and rotavirus vaccine not only reduced the number of cases among children (223 370 to 78 180), but also the average burden of each rotavirus AGE case (4.2 to 1.6 DALY/1000 cases). Approximately half the pathogen-specific DALY was due to mild AGE for norovirus and Giardia, outpatient AGE for Cryptosporidium, and fatal AGE for Salmonella (Figure 4). The combined DALY for the six pathogens studied was 25 952, of which 70% was attributable to Campylobacter (including 55% attributed to Campylobacter-associated IBS) and 12% to deaths following Campylobacter or Salmonella AGE. Ranking of the six gastrointestinal pathogens by different burden of disease metrics is shown in Table 4.

Table 2
Estimating the burden of acute gastroenteritis (AGE) in Australia, 2010—number of cases and deaths, illness duration, and years of life lost (YLL)

AGE (population)	Number of cases								Deaths		Illness duration			YLL
	Total		Mild		Outpatient		Hospitalized		(Number per 100 000cases)		Mild	Outpatient	Hospitalized	
	No. (% of all-cause)		No. (% of total)		No. (% of total)		No. (% of total)							
All-cause AGE	16 626 069	(100)	15 192 016	(91.4)	1 339 866	(8.1)	94 128	(0.6)	61[a]	(0.4)				14.1
Norovirus AGE	2 180 145	(13.1)	2 010 290	(92.2)	157 081	(7.2)	12 757	(0.6)	17	(0.8)	2.1 days	2.4 days	7.2 days	7.1
Rotavirus AGE														
All ages, no vaccine	592 745	(3.6)	502 808	(84.8)	60 396	(10.2)	29 521	(5.0)	20	(3.4)	4.9 days	7.1 days	7.7 days	31.9
<5 years, no vaccine	223 370	-	169 149	(75.7)	34 557	(15.5)	19 657	(8.8)	7	(3.0)	4.9 days	7.1 days	7.7 days	82.6
<5 years, vaccinated	78 180	-	61 367	(78.5)	12 095	(15.5)	4 718	(6.0)	0	(0.0)	4.9 days	7.1 days	7.7 days	-
Cryptosporidium AGE	195 495	(1.2)	168 107	(86.0)	24 105	(12.3)	3 283	(1.7)	0	(0.0)	4.0 days	12.5 days	21.4 days	-
Giardia AGE	614 740	(3.7)	556 642	(90.5)	56 981	(9.3)	1 117	(0.2)	0	(0.0)	5 days	15 days	33 days	-
Campylobacter AGE	774 003	(4.7)	621 676	(80.3)	140 047	(18.1)	12 228	(1.6)	52	(6.7)	3.5 days	9.7days	14.4 days	19.2
Salmonella	71 255	(0.4)	14 697	(20.6)	46 726	(65.6)	9 742	(13.7)	90	(126.3)	2.5 days	6 days	12 days	22.6

Sequelae (pathogen)	Total (% AGE cases)		Mild		Outpatient		Hospitalized		Deaths		All cases	YLL
IBS (Campylobacter)	68 112	(8.8)	-	-	-	-	-	-	0	(0.0)	5 years	-
IBS (Salmonella)	6 270	(8.8)	-	-	-	-	-	-	0	(0.0)	5 years	-
ReA (Campylobacter)	11 252	(1.5)	8 751	(77.8)	2 250	(20.0)	250	(2.2)	0	(0.0)	0.6 years	-
ReA (Salmonella)	2 505	(3.5)	1 592	(63.6)	763	(30.5)	149	(6.0)	0	(0.0)	0.6 years	-

	Total		Mild		Severe, <50 years		Severe, ≥50 years		Deaths		Acute (clinical) phase	Chronic phase	YLL
GBS (Campylobacter)	102	(0.01)	17	(16.7)	39	(39.0)	44	44.1	3	(0.4)	1 year		
37.1 years		14.2											

IBS, irritable bowel syndrome; ReA, reactive arthritis; GBS, Guillain–Barré syndrome.

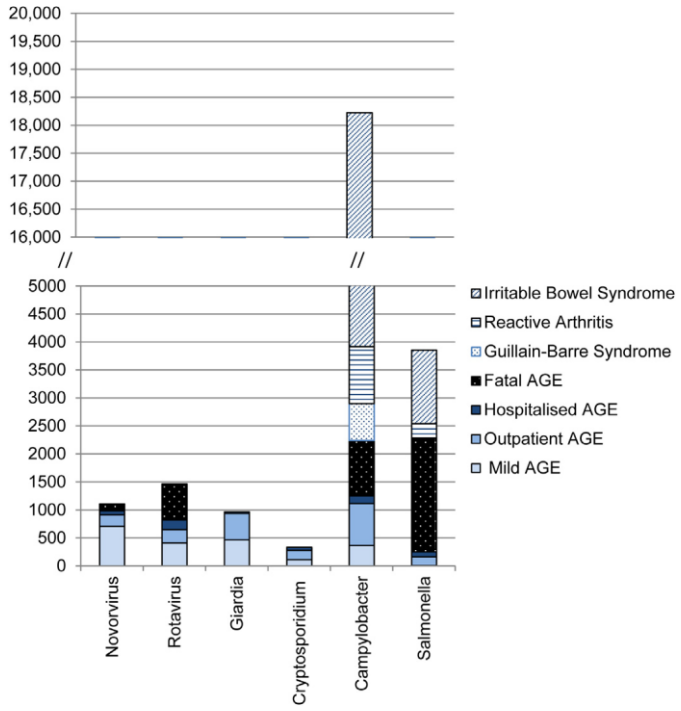


Figure 3. Disability adjusted life years (DALY) burden of six pathogens causing acute gastroenteritis (AGE), including contribution of different disease severity states and sequelae—Australia, 2010.

4. Discussion

We have documented the estimated disease burden in Australia 2010 attributable to six gastrointestinal pathogens using a number of metrics, including number of AGE cases, number of AGE fatalities, and DALYs. The pathogen with the greatest disease burden varied according to the metric used: norovirus caused the most cases (2 180 145), Salmonella the most fatalities (90), and Campylobacter with sequelae the most DALYs (18 222). Salmonella- and Campylobacter-associated sequelae, particularly Campylobacter-associated IBS, dominated the combined DALY estimates for the selected pathogens, while deaths associated with these two bacterial pathogens also had a significant impact. Therefore, preventing cases of Campylobacter and Salmonella would have a significant public health impact in Australia, and as food-borne transmission is significant for both,[4,6,53] optimizing food safety could significantly reduce the overall gastrointestinal disease burden. Additionally, these results support the need for further research into the pathogenesis, prevention, and management of post-infectious IBS to reduce the burden of AGE-associated disease in developed countries.

DALY models provide information that is lacking in estimates of disease cases and deaths. Using AGE case numbers to determine disease burden ignores differences in disease severity between pathogens. For example, although norovirus AGE cases are common, disease was often mild, fatalities were rare and occurred among the elderly, and illness duration was short, so the average DALY/case for norovirus was low. Using the number of deaths to demonstrate disease burden provides information about the most severe AGE cases, however information about morbidity is lacking. We estimated no deaths due to Giardia or Cryptosporidium, so their burden would be overlooked if only deaths were considered. In addition to number of AGE cases and deaths, DALY models incorporate information on different disease outcomes including sequelae, disease duration, disease severity (disability weights), and age at death. Furthermore, DALY/case estimates provide information about the severity of an average case of disease caused by each pathogen. Our disease models additionally demonstrate the contribution of different disease outcomes to the overall disease burden for each pathogen.

The six study pathogens were chosen as the most important in the three major pathogen groups (viral, protozoal, and bacterial) in high-income countries. Although the six study pathogens cause significant disease burden in developing countries, there are differences in AGE aetiology between high- and low-income countries. For example, in a prospective study of children in Africa and Asia, the four pathogens causing the most moderate-to-severe AGE cases were rotavirus, Cryptosporidium, enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-ETEC), and Shigella.[54] Therefore, the relative contribution of different pathogens to the overall AGE disease burden may differ substantially between high- and low-income countries. This highlights the need for country- or region-specific data when estimating pathogen-specific disease burden. Similarly, this study addresses the disease burden of study pathogens within the total Australian population and does not examine the burden among subpopulations. It would be interesting, but beyond the scope of the current study, to compare the burden of the study pathogens between indigenous and non-indigenous Australians; these results could be used to tailor public health interventions to the indigenous context. For

Table 3
Annual burden of selected pathogens causing acute gastroenteritis (AGE), Australia, 2010—number of cases and deaths, DALY, and DALY/case

Pathogen	Sequelae/population	AGE cases (Number per 1000 population)		AGE deaths (Number per million population)		DALY (Number per 100 000 population)		DALY/1000 cases Point estimate	DALY/1000 cases PERT distribution Mean	DALY/1000 cases PERT distribution 95% CrI
Campylobacter	Nil	774 003	(34.7)	52	(2.3)	2 242	(10.0)	2.9	3.0	2.0–4.2
	GBS, ReA					3 918	(17.5)	5.1	5.3	4.1–6.7
	GBS, ReA, IBS					18 222	(81.6)	23.5	25.9	10.7–43.6
Salmonella	Nil	71 255	(3.2)	90	(4.0)	2 285	(10.2)	32.1	34.9	13.8–57.4
	ReA					2 539	(11.4)	35.6	39.5	18.3–62.4
	ReA, IBS					3 856	(17.3)	54.1	59.8	32.2–88.0
Rotavirus	Nil									
	All, unvaccinated	592 745	(26.5)	20	(0.9)	1 465	(6.6)	2.5	2.2	1.8–2.5
	<5 years of age, unvaccinated	223 370	(152.9)	7	(4.5)	936	(64.1)	4.2	4.0	3.2–4.5
	<5 years of age, vaccinated	78 180	(53.5)	0	(0.0)	126	(8.6)	1.6	1.5	1.3–1.7
Norovirus	Nil	2 180 145	(97.6)	17	(0.8)	1 109	(5.0)	0.5	0.6	0.4–0.8
Giardia	Nil	614 740	(27.5)	0	(0.00)	967	(4.3)	1.6	1.7	1.1–2.8
Cryptosporidium	Nil	195 495	(8.8)	0	(0.0)	333	(1.5)	1.7	2.0	1.5–3.0

DALY, disability-adjusted life years; CrI, credible interval; GBS, Guillain–Barré syndrome; ReA, reactive arthritis; IBS, irritable bowel syndrome.

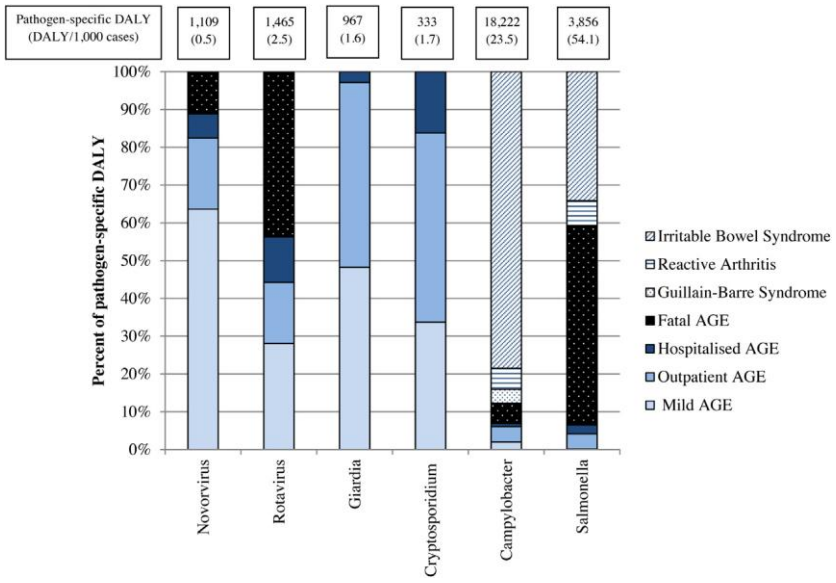


Figure 4. Relative contribution of disease severity states and sequelae to disability-adjusted life years (DALY) for six pathogens causing acute gastroenteritis (AGE)—Australia, 2010.

example, the burden of rotavirus disease in the pre-vaccine era was higher among indigenous compared to non-indigenous Australians and this gap has widened following vaccine introduction in 2007, possibly due to lower vaccine coverage among indigenous children and lower vaccine effectiveness against circulating rotavirus genotypes.[55]

Consistent with other studies that have failed to identify a pathogen for a majority of AGE cases, our six study pathogens accounted for 27% of the estimated number of all-cause infectious AGE cases in Australia in 2010. In a recent UK study, no pathogen was identified among 64% of mild AGE cases and 52% of outpatient AGE cases >5 years of age despite extensive testing.[20] Likewise, only 21% of AGE cases in the USA could be attributed to 24 known gastrointestinal pathogens.[56] Therefore, it is currently not possible to account for all AGE cases in pathogen-specific disease models.

The choice of AGE sequelae in disease models has the potential to dramatically impact DALY estimates. Based on our interpretation of available data, we incorporated GBS, ReA, and IBS into our Campylobacter disease model and ReA and IBS into our Salmonella disease model; however, other burden-of-disease studies have included different sequelae.[4,57,58] To facilitate comparison with other disease burden studies, we have clarified the contribution of each sequela to our DALY estimates and have provided results for Salmonella and Campylobacter with and without sequelae.

Comparing DALY results between studies is also affected by the inconsistent use of YLL discounting, disability weights, disease incidence, and duration estimates. For example, we used disability weights for AGE from the recently published GBD2010 study,[51] although the GBD2010 study defined AGE categories in terms of symptoms rather than healthcare-seeking behaviours as used in our study and most prior DALY studies of AGE.[4,9,58,59] Available data necessitated the use of healthcare-seeking behaviours rather than symptoms to classify mild, outpatient, and hospitalized AGE cases, however we believe that these criteria would roughly approximate the symptom-based categories of mild, moderate, and severe diarrhoea used in the GBD2010 study. The Burden of Disease and Injury in Australia 2003 study estimated the overall burden of diarrhoeal disease at 1858 DALYs,[59] much lower than our AGE DALY estimates. This is partly because they applied a discount rate of 3% to YLL estimates, did not include sequelae, and had different estimates for the proportion of cases requiring hospitalization and disease duration. Our DALY/1000 cases estimate for Salmonella was similar to a recent Dutch food-borne disease study (54.1 vs. 49), but our DALY/1000 cases estimate for Campylobacter was lower (23.5 vs. 41).[4] Conversely, our annual DALY/100 000 population estimate was higher for both Salmonella (17.3 vs. 7.7) and Campylobacter (81.6 vs. 20) than the Dutch study due to our higher estimated incidence of these diseases. Interestingly, the relative ranking of pathogens according to burden also differed between studies, with norovirus causing a greater DALY burden than Salmonella in Dutch and New Zealand food-borne disease studies, and Salmonella a greater quality-adjusted life years (QALY) loss than both Campylobacter and norovirus in a food-borne disease study in the USA.[57] Finally, our DALY/1000 cases estimate for rotavirus among unvaccinated children was much lower than a previous Australian estimate (4.2 vs. 13/1000 cases),[9] largely due to the reduction in estimated deaths when using data from Australia and other developed countries compared to estimates including developing countries with worse health outcomes. This highlights the benefits of using targeted, region-specific data sources.

Rotavirus vaccination has been available free of charge as part of Australia's National Immunisation Program since July 2007.[10] By the start of 2010, Australian children up to the age of 2.5 years would have been eligible for vaccination. Because data post-vaccination are limited, we presented our estimates for rotavirus burden among unvaccinated Australians but acknowledge this

Table 4
Ranking of gastrointestinal pathogens using different burden of disease metrics, Australia 2010[a]

Rank	No. AGE cases	No. deaths	DALY	DALY/case
1	Norovirus	Salmonella	Campylobacter	Salmonella
2	Campylobacter	Campylobacter	Salmonella	Campylobacter
3	Giardia	Rotavirus	Rotavirus	Rotavirus
4	Rotavirus	Norovirus	Norovirus	Cryptosporidium
5	Cryptosporidium	Giardia/ Cryptosporidium	Giardia	Giardia
6	Salmonella		Cryptosporidium	Norovirus

AGE, acute gastroenteritis; DALY, disability-adjusted life years.
[a] Rotavirus burden calculated using the non-vaccinated Australian population; however rotavirus vaccine was introduced for Australian infants in mid-2007.

overestimates the actual rotavirus burden in 2010 given vaccination reduces AGE cases, severity, and fatalities.[10] As further data become available, our rotavirus disease models could be used to quantify the reduction in DALY burden attributable to rotavirus vaccination in Australia.

Among our included pathogens, Salmonella stood out for having a high DALY/case. We estimated the incidence of Salmonella AGE to be 3.2/1000 person-years, which is similar to some previous estimates for Australasia and North America (2.5–6.9),[60–62] and our estimate of 71 255 Salmonella AGE cases in Australia in 2010 is in keeping with previous Australian estimates (49 843–92 000).[7,53] Our estimate that 65.6% of Salmonella AGE cases were outpatient cases exceeds studies from the USA and the Netherlands (12.3–15.4%),[49,62] however is similar to a UK study of food-borne disease (71.4%),[63] while our estimate that 13.7% of Salmonella AGE cases were hospitalized cases exceeds the other studies mentioned (1.1–3.6%), possibly due to our inclusion of half the non-admitted ED presentations in the hospitalized AGE category. Finally, although our case fatality rate for Salmonella (126/100 000 AGE cases) exceeds our estimates for the other pathogens studied (0–6.7/100 000), it is similar to recent estimates from Australasia and the Netherlands (114–152/100 000).[4,60]

The reliance on multiple datasets for our estimates is an acknowledged limitation. As highlighted by our Salmonella model, using multiple data sources to estimate numbers of AGE cases and deaths can result in apparent discrepancies within and between disease models. For fatal AGE cases we used different approaches as well as different data sources, resulting in our estimated number of fatal AGE cases caused by Campylobacter and Salmonella exceeding our estimated number of all-cause fatal AGE cases. NMD figures were used to estimate all-cause AGE mortality and these likely significantly underestimate deaths attributable to AGE due to under-diagnosis and under-reporting. Australian notification data have recently been used to estimate the number of food-borne Salmonella and Campylobacter AGE cases and these estimates were lower than ours.[64]

While an attempt has been made to include the most relevant high-quality data in the DALY/case models, inevitably the quality of input data varied across the models. We used results from the NGSII-2008 study to estimate the number of all-cause AGE in Australia.[65] Potential problems with the NGSII-2008 study include an unrepresentative sample of respondents (only those with a landline telephone were called, and of those contacted only 49% participated in the survey) and poor recall over a 4-week period. AGE rates estimated from retrospective surveys tend to be lower when the recall period is 4 weeks compared to 1 week,[20,66,67] while in a UK study, AGE rates calculated using a prospective cohort study design were lower than those obtained using a retrospective telephone survey design.[20] Although study design can impact estimated AGE rates, the NGSII-2008 study was designed to mirror the earlier national gastroenteritis survey and the estimated AGE rates were similar to international estimates.[2,68,69] Heterogeneity in data sources used could account for some of the apparent differences in pathogen-specific estimates presented in this study. However, we attempted to identify the most credible data source for each data point, which resulted in the use of different data sources within and between pathogen disease models. Differences in study design, including inconsistencies in laboratory techniques used to detect faecal pathogens, made pooling or meta-analysis of the results from different studies inappropriate. Monte Carlo simulations were performed to indicate the precision of the DALY/case point estimates.

In conclusion, we have estimated the burden of disease due to selected gastrointestinal pathogens using a number of metrics, including number of AGE cases, number of AGE fatalities, and DALYs. The pathogen with the greatest disease burden varied according to the metric used: norovirus caused the most cases, Salmonella the most fatalities, and Campylobacter with sequelae the greatest DALY burden. We believe DALYs provide the most meaningful measure of disease burden as they incorporate information about both morbidity and mortality. We have built disease models that can easily be updated as new data become available, including changes in case numbers and deaths due to public health interventions. These results can help prioritize and measure the impact of public health interventions and can be translated to other, similar, populations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.08.006.

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5.1.1 Supplementary material

The online supplementary material relating to this paper is included in Appendix One.

5.2 A Victorian cohort study to quantify sequelae among notified cases of campylobacteriosis, salmonellosis and cryptosporidiosis

One of the most striking findings of the paper above (5.1) was the impact of sequelae on DALY estimates for campylobacteriosis and salmonellosis. In the absence of Australian data, we used estimates of sequelae incidence and duration from international studies in our DALY calculations. A study published after ours estimated that in Australia in 2010 there were 70 GBS cases, 19,500 IBS cases, and 16,200 ReA cases as sequelae of bacterial foodborne AGE; each of these estimates had increased between 2000 and 2010.[137] Differences from our estimates indicate uncertainty in the burden of these conditions in Australia. The exact burden and contribution of sequelae to medical service utilisation, healthcare costs and reduced economic productivity in Australia is unknown. Additionally, the frequency and burden of these complications following parasitic and viral gastroenteritis have not been well studied.

Post-gastroenteritis sequelae are associated with a significant burden of illness.

Previous studies suggest between 3.7% and 36% of *Campylobacter* and *Salmonella* AGE cases develop PI-IBS.[138, 139] In the absence of specific local data, we estimated 8.8% of *Campylobacter* AGE cases developed PI-IBS, [140] and the inclusion of PI-IBS more than quadrupled our estimated *Campylobacter* DALY burden, with 88% of the total DALY burden then being attributable to sequelae. There is less evidence about the occurrence of IBS following protozoal infection; however, six years following a *Giardia* outbreak in Norway, 39% of laboratory-confirmed *Giardia* cases were diagnosed with IBS, 71% of which was attributed to the giardiasis.[141] No studies have estimated the likelihood of PI-IBS following cryptosporidiosis. Similarly, while international studies estimate ReA affects approximately 7% of notified *Campylobacter* cases and 4% of notified *Salmonella* cases,[142, 143] there are only case reports of ReA following cryptosporidiosis.[144-149] In addition to case reports of ReA triggered by giardiasis,[150-152] in a US study, 12% of 290 notified giardiasis cases reported

joint symptoms.[153] Approximately 30% of GBS is triggered by campylobacteriosis and it has been estimated that 30 per 100,000 notified campylobacteriosis cases develop GBS.[154] In the US, more than half the estimated economic costs associated with campylobacteriosis has been attributed to GBS.[155]

An aborted doctoral study of post-infectious sequelae to notified gastroenteritis.

Following the above study (5.1), I initiated a study involving primary data collection – the Victorian Infection Follow-Up Survey (VIFUS) – which I planned to include in my doctoral thesis. In 2014 VIFUS was launched to attempt to identify the proportion of notified campylobacteriosis, cryptosporidiosis, and salmonellosis cases that develop PI-IBS and ReA. At that time, giardiasis, rotavirus or norovirus (included in the paper above) were not notifiable in Victoria and therefore could not be included in VIFUS. Results would inform future burden-of-gastrointestinal-disease estimates and prioritisation of high-burden pathogens for public health intervention. This retrospective cohort study aimed to enrol Victorian residents notified between December 2012 and November 2013 with these gastroenteritis pathogens, along with varicella or pertussis (as a non-gastroenteritis group). This study was approved by the Monash University Human Research Ethics Committee (HREC), and the opt-out approach to recruitment was considered in detail by the Monash University HREC and Monash University researchers in the planning phases of this study. The Victorian Department of Health (DH) provided Monash University with funds to cover some costs of this study.

An initial letter was sent from the DH (signed by the Chief Health Officer) in March 2014 informing 8,708 potential participants of the study and providing the opportunity to opt-out of the study prior to their information being released to me at Monash University. Participants could opt-out by returning an 'opt-out slip' in the reply-paid envelope provided, or using the dedicated telephone and email contacts provided in the letter. Following this, a letter of

complaint was received by the Health Services Commissioner (with a copy sent to the Chief Health Officer) raising concerns that the opt-out approach used in this study was in breach of privacy legislation. The Acting Chief Health Officer requested an opinion from the DH legal team regarding the opt-out approach to consent to release personal information from the DH to Monash. The DH legal team advised that the DH not release the health information to Monash for the VIFUS project as to do so would breach the *Health Records Act 2001*. Based on this legal advice, the VIFUS study was terminated. A letter was sent to the study cohort informing them of this in July 2014.

The Health Records Act 2001 *and the Victorian Infection Follow-Up Survey (VIFUS)*.

The Act establishes the Health Privacy Principles with the purpose of protecting the privacy of an individual's health information "whilst also ensuring safe and effective service delivery, and the continued improvement of health services".[156] The Health Privacy Principles apply to all personal information collected in providing a health service and all health information, thereby incorporating notification data. The DH must comply with the *Health Records Act*. The DH legal team stated that consent to the disclosure of health information held by the DH to researchers for the VIFUS study is governed by the *Health Records Act*. Specifically, they expressed concern that the introductory letter sent from the DH did not explicitly state that if the potential participants do not return the 'opt-out' form, the DH would provide their health information to Monash. Further, the disclosure of the health information to Monash was not for a purpose relating to the primary purpose of the collection of health information under the *Public Health and Wellbeing Act 2008*. The *Health Records Act* allows disclosure of health information for a secondary purpose (i.e. other than the primary purpose of data collection), including research, under certain conditions. However, the DH legal team did not believe these conditions were met in the VIFUS study.

Opt-out consent for recruitment of patients to low-risk medical research. There are two possible approaches to recruiting patients to low-risk medical research: opt-in and opt-out. In the example of VIFUS, opt-in would require potential participants to actively signal willingness to participate in research by mail, email or telephone. In an opt-out model, personal and health information about the notified cases would be released to researchers and potential participants contacted about the research unless they signalled unwillingness to participate. The NHMRC support an opt-out approach to participant recruitment under certain conditions, including: the proposal is reviewed by an HREC; the research is of low risk to participants; the research is likely to be compromised if participation rate is lowered by the requirement for explicit consent; and prospective participants are provided with a mechanism to decline to participate.[157] In the ethics application, I identified the possibility that potential participants might be concerned about the DH sharing their contact details and details of the notified condition with researchers; this issue was considered by the Monash University HREC who approved the project. The opt-out approach was chosen in order to optimise response rate among potential participants, and justified on the grounds that release of information to Monash University researchers was low risk (researchers are bound to protect the privacy and confidentiality of the data) and involvement was low risk as participation was voluntary and required only completion of a short health-related questionnaire. There was no potential for serious events or emergencies to occur during the conduct of the research. Participants were invited to contact their general practitioner and/or myself (as an infectious diseases physician) if they had any concerns about their diagnosis or ongoing symptoms as a result of completing the study questionnaire.

It is well documented that an opt-in approach to recruitment results in lower response rates and participant bias.[158-160] For example, an RCT of opt-in versus opt-out recruitment for a study of patients with angina in London demonstrated that compared to an opt-out approach,

opt-in recruitment resulted in a lower response rate (38% opt-in arm vs. 50% opt-out arm) and a biased sample of healthier patients.[159] One hypothesis for the observed difference was that people willing to participate might find it burdensome to opt-in. The authors proposed the opt-out approach as the default recruitment strategy for studies with low risk to participants.

Discordant interpretation of legislation relevant to opt-out consent. In our cancelled study, the Monash University HREC and the data custodians (DH) came to different conclusions about the appropriateness of opt-out consent. Although HREC approval is required prior to the DH considering release of data for research, HREC approval does not guarantee data release. In our study the opt-out approach related to release of data to researchers in order for potential participants to be contacted for recruitment, rather than consent to the study per se. In another Australian study of road safety that used police crash databases to identify potential participants, the police department ethics review boards in Queensland and New South Wales came to different conclusions about release of data to researchers with respect to the *Privacy Act 1988*.[161] In New South Wales, the police department sent details of eligible persons directly to researchers without seeking participants' consent while in Queensland an opt-in approach was used – eligible persons received a letter from the police department and contacted researchers directly if they were interested in the study (with no release of personal data from the police department to researchers). The two approaches resulted in vastly different response rates – 54% in New South Wales vs. 16% in Queensland. Data collected from the Queensland arm of the study were excluded from the analysis because of inadequate response rate and concerns about a biased sample.[161] Similar to our experience, concerns raised by data custodians about the *Health Records Act* resulted in cancellation of an HREC-approved Victorian community-

based vaccine trial.[162] It is likely that the majority of studies cancelled for this reason are not represented in the published literature.

Lower participation rates associated with opt-in research has important implications for the validity of study findings, as well as sample size calculations, research costs and study feasibility. Legislation requiring opt-in consent (or interpretation of legislation as requiring opt-in consent) to release of information to medical researchers has significant implications for health research in Australia and internationally.[160-164] Although such legislation is designed to protect individual privacy and confidentiality of health records, its deleterious impact on health research needs to be carefully considered.

Chapter Six: Use of DALYs to set Health Based Targets

Declaration for thesis Chapter 6

Declaration by candidate

In the case of Chapter 6.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study concept; drafting manuscript; preparation of manuscript for submission	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Joanne O'Toole	Revision of manuscript from preliminary draft to submission	
Martha Sinclair	Revision of manuscript from preliminary draft to submission	
Karin Leder	Revision of manuscript from preliminary draft to submission	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 11th July, 2016
Main Supervisor's Signature	[redacted]	**Date** 11th July, 2016

Aim: To explore the implications of using DALYs to set health-based targets (HBTs), with reference to ongoing revisions of the *Australian Drinking Water Guidelines*.

Preface

Following the 1990 Global Burden of Disease (GBD) study, DALYs have been used widely to quantify the population health burden of diseases and to prioritise and evaluate the impact of specific public health interventions. This chapter comprises a published commentary on the novel use of DALYs to determine HBTs. This was published in the context of the release of the 2010 GBD study results. As with the more traditional use of DALYs, the main advantage of using DALYs as HBTs is the ability to account for differential disease severity, identify the most appropriate public health interventions, and measure the positive and negative outcomes of these interventions. Australia is currently considering adopting DALYs for setting HBTs for drinking water quality, as recommended by the WHO. If adopted, the DALY estimates for campylobacteriosis, cryptosporidiosis and rotavirus/norovirus from Chapter 5 will be used to specify the specific HBTs.

6.1 Using disability-adjusted life years to set health-based targets: A novel use of an established burden of disease metric

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Open

Original Article

Using disability-adjusted life years to set health-based targets: A novel use of an established burden of disease metric

Katherine Gibney*, Martha Sinclair, Joanne O'Toole, and Karin Leder

Department of Epidemiology and Preventive Medicine, The Alfred Centre, 99 Commercial Road, Melbourne VIC3004, Australia.
E-mail: katherine.gibney@monash.edu

*Corresponding author.

Abstract Following the 1990 Global Burden of Disease (GBD) study, Disability-Adjusted Life Years (DALYs) have been used widely to quantify the population health burden of diseases and to prioritise and evaluate the impact of specific public health interventions. In the context of the recent release of the 2010 GBD study, we explore the novel use of DALYS to determine health-based targets (HBTs). As with the more traditional use of DALYs, the main advantage of using DALYs as HBTs is the ability to account for differential disease severity, identify the most appropriate public health interventions, and measure the positive and negative outcomes of these interventions. Australia is currently considering adopting DALYs for setting HBTs for drinking water quality, as recommended by the WHO. Adoption of DALY HBTs could be relevant in other areas, including air quality, food safety, health care-associated infections, and surgical complications.
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Keywords: burden of illness; health-based targets; health policy; disability-adjusted life years; Australia; drinking water

The online version of this article is available Open Access

Following the 1990 Global Burden of Disease (GBD) study,[1] Disability-Adjusted Life Years (DALYs) have been widely used to quantify the population health burden of diseases and to prioritise and evaluate the impact of specific public health interventions. In the context of the recent release of the 2010 GBD study,[2] we explore the novel use of DALYS to determine health-based targets (HBTs).

DALYs measure the population impact of specific health conditions, accounting for both premature death and morbidity. One DALY equates to 1 lost year of 'healthy' life. The DALY metric quantifies the gap between a population's current health status and an ideal where everyone lives to advanced age, free from disease and disability.[3] DALYs are the sum of years of life lost (YLL) due to premature death and years lost due to disability (YLD) for incident cases of the particular health condition in a population ($DALY = YLL + YLD$). Calculation of YLL requires information on the number of people who died from the disease and their life expectancy at age of death. YLD incorporates the number of incident cases, symptom duration, and symptom severity (the 'disability weight' that ranges from 0 for perfect health to 1 for death). Differing health outcomes for a single health condition (that is, differing severity levels and disease sequelae) can be incorporated into the DALY model.

The DALY metric has been used for quantification and comparison of the burden of diseases in a population; comparison of disease burdens between countries, regions, and population groups; comparison of the impact of risk factors (for example, smoking and obesity) on disease burden; and prioritisation and evaluation of public health interventions.[4,5]

When DALYs are used to set HBTs, it is necessary to nominate a tolerable population DALY burden, or acceptable risk; calculate the average burden of a single case of disease (the DALY/case); and determine the tolerable number of disease cases (see Figure 1). As with the population-level DALY metric, calculation of the average DALY/case allows consideration of various disease outcomes. Waterborne

Step 1: Define the health-based target in terms of a tolerable population DALY burden (per person-year) for the reference condition (*disease A*)

Step 2: Determine the average burden of a single case of *disease A* (the DALY/case)

$$DALY/case_{Disease\ A} = DALY_{Disease\ A} / Number\ of\ cases_{Disease\ A}$$

Step 3: Calculate the tolerable number of *disease A* cases, based on the tolerable population DALY burden

$$Tolerable\ number\ of\ cases_{Disease\ A} = Tolerable\ DALY\ burden_{Disease\ A} / DALY\ per\ case_{Disease\ A}$$

Figure 1: Use of DALYs to set health-based targets.

gastrointestinal pathogens, for example, are chosen as reference pathogens when setting microbial HBTs for water quality.[6] Acute gastroenteritis has four possible courses – mild, moderate, or severe disease, and death. In addition, gastroenteritis caused by certain pathogens (for example, *Campylobacter*) can be followed by sequelae such as Guillain-Barré syndrome, reactive arthritis, and irritable bowel syndrome.[7] The contribution of these sequelae to the disease-specific DALY/case can exceed that of the acute gastroenteritis.[8] By considering the frequency and duration of different possible disease outcomes and the relevant disability weights, the average DALY/case can be calculated for each reference pathogen. Different pathogens have different average DALY/case impacts because of their unique morbidity and mortality characteristics.

The WHO Guidelines for Drinking Water Quality (GDWQ) define safe drinking water as 'not representing any significant risk to health over a lifetime of consumption'.[6,9] They promote the use of DALYs to determine HBTs, stating that provision of safe drinking water should involve: (i) setting HBTs; (ii) ensuring adequate and properly managed systems; and (iii) providing independent surveillance. The tolerable disease burden set in the GDWQ is 10^{-6} DALYs per person-year, meaning that each reference pathogen in drinking water should not cause the loss of more than 365 healthy days in a population of one million people in a year.[6] Reference pathogens are chosen to represent viruses, bacteria, and protozoa, based on criteria that include: being sufficiently well characterised in terms of dose-response, infectivity, and disease outcomes; occurrence in source waters and sensitivity to removal or inactivation by treatment processes; and having a high public health impact.[6,10] To determine the level of water treatment required to meet this HBT, DALY/case values for each reference pathogen and the tolerable number of water-related disease cases caused by that pathogen must first be defined. Quantitative microbial risk assessment (QMRA) is then applied to determine the likelihood of infection or illness following exposure to the reference pathogen in drinking water. Finally, pathogen surveillance data for source waters is combined with QMRA and DALY/case data to quantify the amount of source water treatment required to achieve adequate pathogen reduction to meet the HBT.

Although the WHO GDWQ first published in 2004 the recommendation for use of DALYs in setting HBTs for drinking water quality,[9] no country has adopted this approach in national drinking water or other

health-related guidelines, other than the Australian Guidelines for Water Recycling (AGWR).[11] The current Australian Drinking Water Guidelines provide quantitative (non-DALY) health-based guideline values for chemical and radiological water contaminants, but lack quantitative targets for microbial water quality.[12] In Australia, therefore, quantitative microbial HBTs are currently defined if highly treated sewage effluent, stormwater, or greywater is used to supplement drinking water supplies (covered in the AGWR), but not for drinking water drawn from conventional water sources.

An alternative HBT used in water safety guidelines by the US Environmental Protection Agency, Health Canada, the Netherlands, and New Zealand is the *annual infection risk* approach, with an accepted risk of one infection per 10 000 person-years. This target relates only to infection, not to the occurrence, severity, or outcome of symptomatic disease. Similar to the DALY/case approach, the annual infection risk approach identifies reference waterborne gastrointestinal pathogens, uses QMRA to determine the likelihood of infection following exposure, and applies surveillance data concentrations to quantify the required pathogen reduction.

When used for setting microbial HBTs, the DALY/case approach takes into consideration the potential public health impact of each pathogen, whereas the annual infection approach treats all pathogens as equally significant. In a study examining the disease burden attributable to foodborne pathogens in the Netherlands in 2009, the highest number of disease cases were attributed to norovirus, rotavirus, *Staphylococcus aureus*, and *Clostridium perfringens*; whereas the greatest population disease burden (DALYs) were attributed to *Toxoplasma gondii*, *Campylobacter*, rotavirus, norovirus, and *Salmonella*.[8] Differences were due to differential disease severity, age at death for fatal cases, and disease burden from sequelae related to these pathogens, resulted in *Campylobacter* causing a higher average disease burden per case (41 DALYs per 1000 cases) than rotavirus (4·9) or norovirus (2·4). Differences in impact-ranking of pathogens are even more pronounced if number of infections (rather than number of symptomatic cases) is compared with DALYs. The prevalence of asymptomatic norovirus infection has been reported at 12 per cent among healthy individuals in England.[13] Therefore, if norovirus were used as a reference pathogen to set HBTs using either an annual infection or DALY/case approach, more water treatment resources would be consumed to reduce the norovirus load to meet

the annual infection target (because of high numbers of asymptomatic and relatively mild cases) compared with the DALY/case approach (relatively low DALY/case for norovirus). When used to set water-related HBTs, the DALY/case approach might reduce requirements for unnecessary and costly water treatments.[6] An additional advantage of the DALY/case approach is that it can compare potential public health impacts posed by disparate health risks (for example, microbial, chemical, or radiological contamination of water supplies), along with health impacts and economic costs of proposed interventions.[6,14] Furthermore, the application of DALYs as HBTs is not limited to water guidelines; other potential areas include air quality, food safety, health care-associated infections, and surgical complications. Use of DALY HBTs for non-microbial health conditions, such as those associated with exposure to radiation or chemicals, is currently limited due to knowledge gaps.[6]

There are limitations to using DALYs in setting HBTs. First, this was not the intended use of the DALY metric, as it was developed to quantify the population burden of disease and injury.[15] Second, HBTs are often somewhat arbitrary and require a degree of value-judgement, which may be country- or situation-specific (for example, there is lack of consensus on the target of 10^{-6} DALYs per person-year included in the WHO GDWQ).[16] Similarly, disability weights used in different studies vary and revised disability weights from the 2010 GBD study were recently released.[2,17] Inherent uncertainties in DALY estimates are due to limited data on number, duration, and potential for sequelae following disease cases of each severity.[8] In addition, there are uncertainties in QMRA models and insufficient data regarding pathogen concentrations in source waters (necessary elements for implementation of DALY HBTs).[6,10] Use of HBTs requires selection of reference conditions and extrapolation of DALY/case estimates to other related conditions: for water guidelines, water treatment requirements for an entire class of pathogens (for example, viruses, bacteria, or protozoa) are based on DALY/case calculations for a single reference pathogen within each class, relying on the premise that water treatment options that control the reference pathogens are expected to control other important pathogens within each pathogen class.[10] Uncertainties regarding use of DALY HBTs also apply to other HBT approaches such as the annual infection approach, including the judgement-based nature of determining tolerable risk, QMRA uncertainty, and the use of reference pathogens to represent an entire pathogen class.

In conclusion, while DALYs were developed and have been widely used to compare diseases within and between populations and to prioritise and evaluate public health interventions, this metric can also be used to set meaningful HBTs. As with the more traditional use of DALYs, the main advantage of using DALYs as HBTs is the ability to account for differential disease severity and to prioritise and measure public health interventions more meaningfully. Australia is currently considering adopting DALYs for setting HBTs for drinking water quality,[18] as has been recommended by the WHO.[6] Adoption of DALY HBTs could also be relevant in other areas.

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About the Authors

Katherine Gibney, MBBS, MPH, FRACP, is an NHMRC Gustav Nossal Research Scholar in the Infectious Disease Epidemiology unit, Department of Epidemiology and Preventive Medicine at Monash University. Her research interests include use of health-based targets in regulation, communicable disease surveillance, arboviral diseases, and refugee and immigrant health.

Martha Sinclair, PhD, is a Senior Research Fellow in the Infectious Disease Epidemiology unit, Department of Epidemiology and Preventive Medicine at Monash University. (E-mail: Martha.Sinclair@monash.edu)

Joanne O'Toole, PhD, is an NHMRC Public Health Training Postdoctoral Fellow in the Infectious Disease Epidemiology unit, Department of Epidemiology and Preventive Medicine at Monash University. (E-mail: Joanne.OToole@monash.edu)

Karin Leder, MBBS, MPH, FRACP, PhD, is an Associate Professor and Head of the Infectious Disease Epidemiology unit in the Department of Epidemiology and Preventive Medicine at Monash University. (E-mail: Karin.Leder@monash.edu)

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6.2 Additional papers relating to health based targets for drinking water quality

The current debate around adopting HBTs for guidelines related to drinking water quality was the motivating factor behind the DALY estimates for potentially waterborne gastrointestinal pathogens in Chapter 5. In addition to the paper above (6.1), this public policy debate has resulted in two published articles, which I co-authored and which are included in Appendix Two:

- 0: Sinclair M, O'Toole J, **Gibney K**, Leder K. Evolution of regulatory targets for drinking water quality. *J Water Health*. 2015 Jun; 13(2):413-26. doi: 10.2166/wh.2014.242. PMID: 26042974

- 0: O'Toole J, Sinclair M, **Gibney K**, Leder K. Adoption of a microbial health-based target for Australian drinking water regulation. *J Water Health*. 2015 Sep; 13(3):662-70. doi: 10.2166/wh.2015.201. PMID: 26322752

Chapter Seven: Integrative discussion

This thesis provides an overview of public health surveillance and communicable disease epidemiology in Australia through analysis of surveillance data for all nationally notifiable diseases and estimation of burden of disease of six gastrointestinal pathogens. The longitudinal analyses of 21-years of NNDSS data in Chapters 2–4 represents a unique and comprehensive picture of the NNDSS and of the epidemiology of nationally notifiable diseases in Australia; while the burden of disease estimates in Chapter 5 are based on detailed pathogen-specific data on the incidence of disease and duration of symptoms at each severity level with inclusion of disease sequelae for the bacterial pathogens. The two approaches are complementary, and findings of Chapters 2–6 can be used by public health decision makers – both jurisdictional and national – to inform changes to public health surveillance and priorities for communicable disease control in Australia.

7.1 Key findings

- Australia has robust jurisdictional and national communicable disease surveillance systems. The NNDSS has expanded over its first 21 years in terms of number of nationally notifiable conditions, number of data fields, and number of notifications received. There has been a shift from receiving the majority of notifications from clinicians to automated (and increasingly electronic) notification by laboratories. There were significant interjurisdictional differences in the data completeness, data timeliness, and notification source, which limit comparison of notification data between jurisdictions.

- Completeness of Indigenous status reporting remains suboptimal both in Victoria and in the NNDSS. These data are essential to ensure surveillance usefully contributes to monitoring the gap in communicable disease burden between Indigenous and non-

Indigenous Australians. Collecting Indigenous status data is increasingly challenging in the setting of laboratory-only notifications.

- There was a significant increase in notification incidence over the first 21 years of NNDSS, driven by increases in sexually transmissible infections (STIs) and vaccine preventable diseases. Some of this is due to addition of conditions to NNDSS as well as more sensitive diagnostic tests, less invasive specimen requirements, and changing testing practices. Decreasing notification incidence for certain diseases indicates success of public health programs, such as immunisation (rubella, measles, *Haemophilus influenzae* type B) and eradication campaigns (e.g. donovanosis).

- There are significant socioeconomic and demographic inequities in notification incidence in Australia, particularly for Indigenous Australians and those living remotely. Although these inequities lessened over the 21-year study period for most disease groups, the differences remained high for blood-borne viral hepatitis among socioeconomically disadvantaged people. Of the eight most commonly notified conditions, gonococcal infection was the most geographically concentrated and the most over-represented among Indigenous Australians and in remote/very remote areas.

- A number of criteria can be used to prioritise diseases for public health intervention. Table 7:1 summarises the three highest priority diseases from analyses based on each of these criteria. Notification data can identify diseases with highest notification incidence, most rapidly changing epidemiology, and most unequal or inequitable distribution; each of these should be considered when prioritising diseases for action. Chlamydial and gonococcal infection, campylobacteriosis, and influenza were identified as high priority conditions following analysis of NNDSS data.

- Surveillance data underestimate disease incidence and therefore disease burden. Case ascertainment varies between population groups, introducing potential bias to surveillance data. When comparing burden between diseases, the choice of disease burden metric affects the ranking of pathogens. DALYs were considered the most useful disease burden metric for prioritising public health action as they take into account both morbidity and mortality. Disease sequelae dominated the DALY burden for campylobacteriosis, which had the highest DALY burden (Table 7.1).

Table 7:1: Priority infectious diseases for public health intervention identified using several criteria

Source	Criteria	Three priority diseases		
		Highest ranked	**2nd highest ranked**	**3rd highest ranked**
Surveillance data *Part A (Chapters 3 & 4)**	High notification incidence	**Chlamydial infection**	**Campylobacteriosis**	**Varicella zoster**
	Increasing notification incidence	**Chlamydial infection**	**Influenza**	**Pertussis**
	Unequal ± inequitable distribution			
	Children <5years†	**Cryptosporidiosis**	**Salmonellosis**	**Shigellosis**
	Older adults ≥65 years	**Listeriosis**	**Legionellosis**	**Pneumococcal disease**
	Geographic clustering‡	**Gonococcal infection**	**Hepatitis B**	**Influenza**
	Indigenous‡	**Gonococcal infection**	**Chlamydial infection**	**Influenza**
	Remote residence‡	**Gonococcal infection**	**Salmonellosis**	**Chlamydial infection**
	Socioeconomic disadvantage‡	**Hepatitis B**	**Gonococcal infection**	**Hepatitis C**
Burden of disease *Part B (Ch. 5)***	Incidence	**Norovirus**	**Campylobacteriosis**	**Giardiasis**
	Mortality or disease severity	**Salmonellosis**	**Campylobacteriosis**	**Rotavirus**
	Population burden (DALYs)	**Campylobacteriosis**	**Salmonellosis**	**Rotavirus**

*All nationally notifiable disease; **Six gastrointestinal pathogens only; †*Haemophilus influenzae* type B, measles and invasive meningococcal disease not listed as these are now uncommon following inclusion in funded childhood immunisation schedule; ‡Eight most commonly notified conditions analysed
Cells are colour coded according to pathogen group: STIs (orange); gastroenteritis (purple); vaccine preventable (green); blood-borne viral hepatitis (yellow)

7.2 Implications for policy, practice and research

Based on the research presented in this thesis and experience gained during my candidature, I make17 recommendations which are summarised in Table 7:2 and discussed below. Some of the detail in these recommendations is based on data and experience outside the information presented in this thesis; however the data indicating need for change or action in each of these areas is based on research presented in this thesis.

Table 7:2: Recommendations for policy, practice and research

	Recommendation
Surveillance *(Part A)*	1. Achieve consistency in public health surveillance across Australia
	2. Promote electronic notification, including electronic laboratory reporting
	3. Formalise and automate data linkages
	4. Improve completeness of Indigenous status reporting
	5. Incorporate emerging data of public health significance, particularly antimicrobial resistance (AMR) and whole genome sequencing (WGS)
	6. Adapt to changes in testing practices that impact surveillance
Disease burden (Part B)	7. Incorporate sequelae into DALY estimates of infectious disease burden
	8. Promote pathogen-specific DALY estimates for communicable diseases in Australia
	9. Use DALYs to set HBTs
Public health action *(Parts A & B)*	10. Use both surveillance data and DALY estimates to inform public health action
	11. Nationwide and targeted STI treatment and prevention programmes
	12. Nationwide food safety strategy with initial focus on chicken-meat and eggs
	13. Review immunisation schedules for influenza, varicella and pertussis
	14. Targeted programmes to diagnose, treat and prevent hepatitis B and C
Research *(Parts A & B)*	15. Clarify legislation to enable use of notification data for public health research
	16. Establish studies to determine DALY burden of post-infectious sequelae
	17. Quantify burden of disease averted by public health interventions

7.2.1 Surveillance

Achieve consistency in public health surveillance across Australia. National surveillance would be enhanced if there were uniformity in the surveillance practices between jurisdictions. This includes applying nationally agreed: notifiable disease list; case definitions; methods of case ascertainment, including laboratory practices; data fields; notification source, i.e. agreement on which diseases require clinician and laboratory notification vs. laboratory-only notification; and surveillance platform (i.e. the same electronic surveillance system used in jurisdictions and nationally).

It is striking that high incidence diseases, namely campylobacteriosis and varicella infection, are not notifiable in New South Wales, Australia's most populous jurisdiction. Ideally, diseases on the NNDL would all be notifiable in all Australian jurisdictions. All jurisdictional notifiable diseases lists contain diseases not included on the NNDL.[165] In some cases this reflects diseases that are endemic in parts but not all of Australia, for example melioidosis is notifiable in the Northern Territory, Queensland and Western Australia which reflects its distribution in the tropical north of Australia.[166] Periodic review of national and jurisdictional notifiable diseases lists using established criteria could ensure the highest priority diseases are included in an integrated national surveillance system.[55, 167, 168] There is an established process in Australia for adding a disease to the NNDL.[82] A recent analysis of diseases on the NNDL identified only hepatitis (not elsewhere classified) as not warranting inclusion, while recommending the addition of rotavirus and chikungunya.[169] However, this review did not refer to other conditions that might be priorities for national surveillance, such as methicillin resistant *Staphylococcus aureus* (MRSA).

A national integrated electronic surveillance system would require careful planning and agreement between public health agencies on multiple levels (national, jurisdictional, and sub-jurisdictional, such as local public health units), but would significantly enhance

surveillance at each of these levels. Currently in Australia, regular teleconferences and other communication between CDNA jurisdictional members provide a structure for detecting multijurisdictional outbreaks. Other public health networks, including OzFoodNet, also hold regular teleconferences to review notification data across jurisdictions. In my proposed nationally integrated system, the basic structure of communicable disease control would not change; states and territories would continue to be responsible for receiving notifications and the public health actions resulting from these notifications. A nationally integrated system, which includes the same electronic platform and user interface across jurisdictions, would promote consistent collection and storage of notification data and contribute to a less fragmented system of national surveillance. De-identified notification data could be viewed by other jurisdictions and national surveillance staff, which would aid detection of multijurisdictional events and nationally coordinated responses. One potential downside of such a nationally coordinated system is a loss of responsiveness if agreement from multiple stakeholders is required before changes and adaptations are made to the system. However, it is likely that a redesigned surveillance system would be accompanied by a rationalisation of committees involved in communicable disease control and hence more streamlined and integrated decision-making processes. Furthermore, jurisdictions might be reluctant to agree to a revised system in which they perceive a loss of autonomy of decision making regarding surveillance practices and responses. This should not be insurmountable, as several countries already have electronic communicable disease surveillance systems that are consistent between the national and sub-national jurisdictions, including China, Germany, Ireland, the Netherlands, and Sweden.[90, 98, 99, 101, 102]

Promote electronic notification, including electronic laboratory reporting. Some, but not all, Australian jurisdictions have capacity to receive electronic notifications from clinicians and electronic laboratory notifications.[76, 85] Sweden's integrated surveillance

system receives almost all notifications electronically, with shorter notification delays for electronic compared to paper notifications.[89, 99] The US CDC aim to receive 80% of laboratory reports to public health agencies electronically by 2016 to improve timeliness.[100] Electronic notification by clinicians and laboratories into a nationally integrated system has potential to improve data completeness and timeliness, as well as reducing workload and potential errors associated with manual data entry.

Formalise and automate data linkages to improve completeness of surveillance data and inform timely public health intervention. For example, linkages have potential to improve completeness of Indigenous status reporting,[67] vaccination status of cases via linkage with the Australian Childhood Immunisation Register (ACIR),[93] and information on disease severity through linkage with hospitalisation and mortality databases. A national surveillance objective in the US is that death reports are transmitted electronically to public health within one day of registration and nationally within 10 days of the event in order to support near real-time public health surveillance.[100] Timely linkage of mortality data with communicable disease notification data would provide important information on severe and emerging public health threats in Australia. Formalised linkage with laboratory testing data would inform interpretation of the role of increased testing in observed changes in notification incidence for conditions such as chlamydial and gonococcal infection (for which PCR testing is now widespread) and gastrointestinal infections (for which PCR testing is being increasingly used).[103, 170, 171]

Improve completeness of Indigenous status reporting in order to meet the National Surveillance Committee's target of 95% completeness for 18 priority notifiable diseases and 80% completeness for the remaining notifiable diseases.[30] This should contribute to better health for Indigenous Australians,[91] with more accurate quantification of the differential burden of notifiable diseases to inform development and evaluation of targeted policies.

Strategies include legislation of mandatory reporting of Indigenous status with notifications; documentation of Indigenous status on pathology request forms; a non-defaulting, mandatory data item on Indigenous status in electronic health records; and data linkages with other health-related data sources.[66, 67, 91-93]

Incorporate emerging data of public health significance, particularly surveillance for antibiotic resistance (AMR) and whole genome sequencing (WGS). Although it is likely much of these data would sit outside NNDSS, relevant data fields should be added to NNDSS and data linkages formalised to ensure this additional information is incorporated in timely public health responses to notifications. Australia's *First National Antimicrobial Resistance Strategy 2015–2019* includes the objective to develop "nationally coordinated One Health surveillance of antimicrobial resistance and antimicrobial usage".[172] Such a surveillance system should be carefully designed to ensure it complements, rather than duplicates, NNDSS. Relevant pathogens could be added to the NNDL and notification data for human cases stored in NNDSS. The role of WGS in public health is yet to be realised in Australia, although it could potentially provide data useful to outbreak investigations, disease transmission pathways, and AMR.[173] A Public Health Laboratory Network (PHLN) WGS expert advisory group expects all laboratories within the PHLN will eventually perform WGS in-house.[174] This group identified a lack of "robust, streamlined, simple to use bioinformatics pipelines" as a key limitation to the widespread utilisation of WGS in Australia.[174] The Doherty Institute in Melbourne contribute to the US-based Genome Trakr Network, a distributed network of laboratories that utilise WGS for pathogen identification. This network has demonstrated the utility of WGS in foodborne outbreak investigations, including salmonellosis and listeriosis outbreaks in the US. WGS is routinely used as part of Public Health England's specialist microbiology and epidemiology services, with particular utility in outbreak investigations and understanding patterns of AMR.[175]

Understand changes in testing practices that impact surveillance. Routinely collected laboratory data can inform interpretation of notification trends, as demonstrated by concurrent evaluation of chlamydial infection notifications, number of requested tests and test positivity rates.[176] Medicare Benefits Schedule (MBS) data could also be routinely utilised through data linkages to track testing practices for notifiable conditions.[103] However, this would currently miss tests undertaken in public health laboratories outside the federally funded MBS. Increased use of culture-independent diagnostic tests impacts the laboratory AMR surveillance necessary for national and regional treatment guidelines, requiring consideration of alternate approaches, such as sentinel surveillance or development of molecular testing for AMR detection.[177-179] Use of molecular point-of-care testing might lead to under-notification of cases;[180] if these were utilised in specific high-risk populations (e.g. in remote Indigenous communities), the excess burden of disease in these populations might be underappreciated (due to under-notification) and NNDSS might lose the ability to detect and monitor health inequities.

7.2.2 Burden of disease

Incorporate sequelae into DALY estimates of infectious disease burden to avoid underestimation of their burden. In our DALY estimates for campylobacteriosis, the inclusion of PI-IBS more than quadrupled our estimated DALY burden (5.1). For many conditions, this will require additional research to quantify the frequency of sequelae following infection (7.2.4).

Promote pathogen-specific DALY estimates for communicable diseases in Australia. This involves utilising a variety of existing data sources (e.g. surveillance data [combined with multiplication factors to account for under-notification], healthcare usage data [general practitioner, emergency department and hospitalisation data] and mortality data) along with

published studies. Estimates would be strengthened by further research studies to fill data gaps (7.2.4). These estimates will allow appropriate prioritisation of diseases for interventions based on a complete understanding of disease burden, rather than incomplete summary data, such as surveillance or mortality data.

Use of DALYs to set health based targets. The main advantage of using DALYs as HBTs is the ability to account for differential disease severity and to target and measure public health interventions more meaningfully. Australia is currently considering adopting DALYs for setting HBTs for drinking water quality, in line with WHO recommendations. Adoption of DALY HBTs could also be relevant in other areas, such as air-quality, food-safety, healthcare associated infections, and surgical complications.

7.2.3 Public health action

Results from this thesis have been used to identify priority infectious diseases for public health intervention (Table 7:1). Some current and potential preventive strategies for these high-priority infectious diseases are discussed below, however generating or evaluating an evidence-base for these interventions is beyond the scope of this thesis. It is essential that any intervention is evidence based and the impact and cost effectiveness of the intervention is properly evaluated as part of the implementation plan.

Use of both surveillance data and DALY estimates as information for public health action. Table 7:1 identifies the three highest priority conditions based on selected criteria. Notification data can be used to identify diseases with highest notification incidence, most rapidly increasing notification incidence, and most unequal or inequitable distribution. Information from each of these analyses is valuable and should be considered when using notification data to prioritise conditions for interventions. In addition, DALYs usefully

incorporate information on incidence, morbidity and mortality and can be used to set HBTs and monitor progress in disease prevention.

Nationwide and targeted STI treatment and prevention programmes. Chlamydial infection cases constituted one quarter of all NNDSS notifications, while gonococcal infection showed marked geographic clustering and strong association with Indigenous status, remote residence, and socioeconomic disadvantage. Syphilis, although less common, had increasing notification incidence over the study period (3.1). Australia needs both a nationwide STI programme (driven by chlamydial infection) and a targeted STI programme (driven by gonococcal infection) for high-risk communities, particularly Indigenous and remote-living Australians, and men who have sex with men. Potential national and targeted strategies are listed in Table 7:3. Many appropriate recommendations are already in place; however attention needs to focus on actioning these. Australia's *Third National Sexually Transmissible Infections Strategy* includes targets to reduce the incidence of chlamydial infection, gonococcal infection and infectious syphilis and eliminate congenital syphilis.[181]

Table 7:3: National and targeted strategies for diagnosis, treatment and prevention of sexually transmissible infections

National strategies	Additional strategies targeting high-risk groups
• Annual STI screening for all sexually active persons by urinary PCR for *N. gonorrhoeae* and *Chlamydia trachomatis*. Potentially limit to young women	• More regular STI screening of high-risk persons (e.g. six monthly) and inclusion of serology for syphilis ± HIV infection
• STI screen for pregnant women at first antenatal visit	• STI screening for pregnant women at first antenatal visit and repeat prior to delivery
• Re-test persons approximately three months after STI diagnosis/treatment to detect reinfection or relapse	• Annual community-wide test-and-treat days in high-incidence communities (age range dependant on local epidemiology)
• Partner notification and treatment	• Point of care STI testing to promote immediate treatment and contract tracing
• Free services, including testing, treatment, contact tracing, condoms	

Nationwide food safety strategy with initial focus on chicken meat and eggs.

Campylobacteriosis had the second highest notification incidence of all nationally notifiable conditions, with both campylobacteriosis and salmonellosis in the eight diseases most frequently notified to NNDSS. Salmonellosis disproportionately affected young children and remote living Australians and was more severe (higher DALY/case) than other common gastrointestinal pathogens. Sequelae to bacterial gastrointestinal pathogens are common, with IBS accounting for the majority of the DALY burden of campylobacteriosis.

Notification incidence of campylobacteriosis and salmonellosis in Australia are high by international standards. Among 17 OECD countries, Australia has the highest campylobacteriosis notification incidence and second highest salmonellosis notification incidence.[182] More rigorous food-safety regulations would reduce the burden of these pathogens, with 77% of campylobacteriosis and 75% salmonellosis cases in Australia attributed to contaminated food.[183] For sporadic cases of salmonellosis notified in South

Australia, 35% were attributed to chicken meat and 37% to eggs; for outbreak-related salmonellosis cases, 33% were attributed to chicken meat and 59% to eggs.[132] Among Australians aged ≥5 years, 29% of campylobacteriosis cases were attributed to consumption of chicken (>50,000 cases/year).[184]

In New Zealand, regulatory and industry interventions and activities to reduce *Campylobacter* contamination of poultry resulted in a 52% reduction in campylobacteriosis notifications and 13% drop in hospitalisations for GBS, with substantial cost savings.[185, 186] Enhanced human surveillance and source attribution work using molecular tools was undertaken, in conjunction with a coordinated suite of interventions targeting primary production, processing, retail, and the consumer.[186] Such coordinated interventions should be possible in Australia, although full cooperation of the food industry would be required and legislative changes might be required. The *2015 Nationwide workshops on Salmonella and eggs* was a positive step for galvanising action in this area; egg washing, vaccination of layer flocks, and inclusion of organic acids as dietary supplements for poultry were discussed as potential control strategies.[187]

Review immunisation schedules for influenza, varicella and pertussis. Analyses of surveillance data presented in this thesis demonstrate the success of Australia's National Immunisation Programme (NIP).[94] Notification incidence of rubella fell almost 100-fold, measles 30-fold, and *Haemophilus influenzae* type B 15-fold between the earliest and latest study period (1991–1997 vs. 2005–2011) (3.1). This is in addition to the significant reductions in notified vaccine preventable diseases documented in Australia in the pre-NNDSS era.[26]

Despite these successes, we have demonstrated that notification incidence of influenza and pertussis was increasing in Australia, while varicella (notifiable from 2006) had the third

highest notification incidence of all nationally notifiable diseases (3.1). The national approach to these three vaccine preventable diseases therefore needs review, and indeed recent changes to the NIP indicate responsiveness to this surveillance data. In 2015, seasonal influenza vaccine was funded for Indigenous children aged six months to <5 years.[188] To prevent latent reactivation of varicella zoster virus (shingles), the shingles vaccine will be provided free of charge to people aged 70 years with a catch-up program for people aged 71–79 years from November 2016, subject to vaccine supply.[94] This will coincide with the roll out of a national adult vaccination register. For pertussis, changes have been made to the childhood vaccination schedule in 2016, and vaccination for pregnant women ± new parents/carers of newborn infants (the cocoon strategy) has been funded in several jurisdictions starting with the Northern Territory in 2008.[189] The impact of each of these interventions must be carefully monitored and the need for future modifications assessed. Surveillance data is easily available for such analyses, while DALY measures would be useful to monitor the population impact of these changes given the differential severity of diseases in different population groups, for example the disproportionate severity of pertussis in infants <6 months of age and influenza in pregnant women.[190, 191]

Targeted programmes to diagnose, treat and prevent hepatitis B and C. The population attributable fraction (PAF) for socioeconomic disadvantage associated with hepatitis B and C was notable because it remained high throughout the 21-year study period (0). Hepatitis C is now the leading cause of liver transplantation in Australia, accounting for 31% of adult liver transplants in 2013.[192] The burden of chronic hepatitis B and C, namely chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC), is better measured using DALYs than surveillance data. The inequities in viral hepatitis incidence and prevalence observed in surveillance data are likely amplified in DALY estimates. Socioeconomic disadvantage has been associated with poorer five-year cancer survival in Australia.[110]

Socioeconomic disadvantage and residence in an area with a large Indigenous population were associated with poorer survival for persons with HCC in Queensland.[134]

The *Fourth National Hepatitis C Strategy 2014–2017* sets the targets of reducing the incidence of newly acquired hepatitis C infections by 50% and increasing the number of people on treatment.[193] However, the 2016 listing of new generation, direct acting antiviral medications on the Pharmaceutical Benefits Scheme (PBS) raises the possibility of eradication of hepatitis C from Australia.

The WHO recommends all infants are vaccinated against hepatitis B as soon as possible after birth.[194] Hepatitis B vaccine was nationally funded for adolescents in 1996 and infants in 2000.[195] Vaccination is the primary tool in eliminating hepatitis B transmission in Australia. Improving hepatitis B vaccination in childhood and coverage of priority populations are targets set in the *Second National Hepatitis B Strategy*, as are increasing the proportion of people with chronic hepatitis B who are diagnosed to 80% and who are receiving antiviral treatment to 15%.[196] More than 95% of new chronic hepatitis B infections in Australia are attributable to migration,[197] and mathematical modelling demonstrates that support for comprehensive hepatitis B vaccination programs in endemic countries with high levels of migration to Australia would be several times more cost effective at preventing chronic hepatitis B in Australia than vaccination of Australian infants.[198]

7.2.4 Research

Several research-related issues were identified during this thesis, including: appropriate use of notification data for research; generating data for DALY estimates; and using DALYs to estimate the benefits of historical public health interventions.

Clarify legislation to enable use of notification data for public health research. The interpretation by the Victorian Government's Department of Health legal team that the

Health Records Act 2001 precluded release of personal and health data of notified cases to researchers for the Victorian Infection Follow-Up Survey (VIFUS) had a significant impact on the contents of this thesis. However, this interpretation has wider implications in terms of the ability to use notification data for public health research in Australia. It is clear that there is some lack of clarity around this, with the Monash University HREC considering the issue of data release follow opt-out consent and approving the study. Use of opt-out consent has proven benefits in terms of levels of recruitment and avoidance of bias.[159] Public health surveillance systems can be used to identify potential research participants for population-level public health research into notifiable infectious diseases. It would be helpful for researchers if the legislation, or interpretation of legislation by the data custodians, was clarified to allow appropriate access to surveillance data for HREC-approved public health research.

Establish studies to determine DALY burden of post-infectious sequelae. Post-infectious sequelae often contribute more to the DALY or economic burden of the disease than the acute infection. Inclusion of IBS more than quadrupled our DALY estimate for campylobacteriosis in Australia (5.1). Internationally, a recent analysis of the global burden of dengue estimated that 90% of the disability burden (YLD) and 37% of the DALY burden was attributable to chronic fatigue.[199] There is also emerging evidence of significant sequelae associated with recent epidemics, including Zika and Ebola.[200, 201]

There is scarce Australian data regarding the burden of sequelae following infectious diseases, and international data is often also lacking. Prospectively following notified cases of selected infectious diseases to establish the frequency and impact of post-infectious sequelae would allow more complete understanding of the DALY burden of infectious diseases nationally and globally. This information would inform local, national and international

public health action, and could be used to estimate and measure the impact of public health interventions.

Quantify burden of disease averted through public health interventions, such as the National Immunisation Programme (NIP). Longitudinal analysis of surveillance data demonstrated success of public health interventions in reducing the notified incidence of several infectious diseases. Use of surveillance data to model the number of cases of disease and estimation of DALYs averted through public health interventions, such as the NIP, would highlight the importance of such measures and promote ongoing funding and public support for communicable disease control programmes in Australia. Project Tycho, which used US surveillance data to calculate the number of vaccine-preventable disease cases avoided through immunisation, is a good example of the power of such analyses. That study estimated that immunisation programmes prevented 103 million cases of childhood vaccine preventable diseases in the US (95% of those that would otherwise have occurred) from 1924 to 2011, including 26 million cases (99% of those that would otherwise have occurred) from 2002 to 2011.[106]

7.3 Limitations

This thesis has certain limitations. The surveillance system evaluations were based purely on available notification data and therefore did not cover the whole scope of the CDC's *Updated Guidelines for Evaluating Surveillance Systems*,[55] although most of the suggested framework was covered in Chapters 1 and 2. Despite this, the evaluations demonstrated both strengths and weaknesses of these systems and led to many of the recommendations of this thesis. The changes noted in the national and jurisdictional notifiable diseases lists, case definitions, diagnostic test availability, and testing practices influenced notification incidence and likely impacted epidemiologic analyses presented in Chapters 3 and 4. Some authors have sought to

use additional data, e.g. laboratory testing or MBS data, to quantify the impact of these changes on a disease caused by a single pathogen in a selected jurisdiction and time-period. However, this was beyond the scope of this thesis, which offered a 21-year overview of all nationally notifiable conditions. The findings of the analysis of Chapter 4, examining inequalities and inequities in notification incidence, could be affected by bias introduced by differential case ascertainment in different population groups. Furthermore, inadequate completeness of Indigenous status in most jurisdictions meant that analysis of notifications among Indigenous versus non-Indigenous Australians was limited to the Northern Territory, South Australia and Western Australia; missing data within these jurisdictions could also impact results, however this was at least partially addressed by the sensitivity analysis. There was evidence of a strong positive correlation between Indigenous status and remoteness (r_s=0.61) in the three jurisdictions analysed, indicating that Indigenous Australians were more likely to live remotely. While acknowledging this, we chose to keep both Indigenous status and remoteness in our sub-analysis as we felt both variables were important.

Our burden of disease analysis in Chapter 5 was based on existing data, both published and unpublished. Although we comprehensively reviewed available data and selected the most appropriate estimates based on pre-determined criteria, the precision of our estimates depends on the accuracy of these pre-existing data. We provided uncertainty analysis for the DALY/case estimates, but not number of cases, number of deaths or DALYs. The impact of sequelae was significant for bacterial enteric pathogens, prompting the planned VIFUS study aimed to determine the frequency, duration and severity of sequelae following notified campylobacteriosis, salmonellosis and cryptosporidiosis in Victoria. The decision by the Victorian Department of Health to terminate this study based on the use of opt-out consent in the recruitment process affected the contents of this thesis; there was neither the time nor funding to re-design and re-launch this study using opt-in consent.

7.4 Conclusion

This thesis provides a high-level longitudinal overview of the first 21 years of national infectious disease surveillance in Australia (Part A), as well as a more focussed and detailed analysis of six gastrointestinal pathogens in Australia, comparing pathogen-specific disease burden using several different metrics (Part B).

The major strength of Part A is the inclusion of all nationally notifiable diseases in the analyses, with a focus on the most frequently notified conditions. The availability of 21 years of continuous line-listed data allowed comprehensive longitudinal assessment of the national surveillance system as well as the epidemiology of nationally notifiable diseases in Australia. In addition to being the first time that such an analysis has been undertaken in Australia, this thesis is unique internationally for providing a comprehensive analysis of all nationally notifiable conditions for an entire country over more than two decades.

A number of recommendations regarding infectious disease surveillance were made, particularly the need for an integrated electronic system that is consistent between jurisdictions and the NNDSS, with formalised data linkages and renewed focus on complete reporting of Indigenous status for notified cases. There is a need to incorporate antimicrobial resistance and whole genome sequencing data to further modernise public health surveillance in Australia. Changes in surveillance and testing practices make interpretation of longitudinal surveillance data challenging, and incorporation of testing data through formal data linkages would be beneficial.

Our epidemiological overview identified the ten highest notification incidence conditions, which accounted for 88% of all notifications. Chlamydial infection stood out as the most frequently notified condition with the most rapidly increasing notification incidence. Campylobacter and varicella zoster were the next highest-incidence conditions, while

influenza and pertussis demonstrated marked increases in notification incidence over the study period. Socio-demographic analysis highlighted health inequities based on remoteness of residence and Indigenous status. These inequities were not uniform across all notifiable diseases; gonococcal infection was notable for its extremely strong association with remoteness and Indigenous status and marked geographic clustering, necessitating targeted public health interventions. Overall the observed health inequities lessened over the 21-year study period, except for the association between low socioeconomic status and blood-borne viral hepatitis (particularly hepatitis B), which remained unacceptably high. More needs to be done to address the health inequities highlighted in this thesis, particularly as Australia, which ranks second on the United Nation's Human Development Index, is one of the most privileged countries in the world.[112]

The strength of Part B of the thesis was the detailed analysis of disease burden for six common gastrointestinal pathogens. The use of several methods to determine disease burden (incidence, number of deaths, DALYs, and DALYs/case) demonstrated that the choice of metric influences the ranking of pathogens. It also demonstrated the benefits of DALYs, which incorporate data on morbidity associated with the acute infection and post-infectious sequelae as well as mortality. Inclusion of sequelae, particularly IBS, increased the DALY burden of campylobacteriosis more than four-fold. Of the pathogens examined, the highest DALY burden was associated with campylobacteriosis followed by salmonellosis. Prevention of these pathogens should be the focus of food-safety interventions, with initial focus on chicken meat and eggs. The benefits of using DALYs to set HBTs were discussed, with the potential application of the DALY/case estimates from this thesis in upcoming revisions of the *Australian Drinking Water Guidelines*. Future research should focus on generating DALY estimates for other infectious diseases of public health significance in Australia (particularly STIs); collecting primary data on the frequency, duration and severity of sequelae to

infectious diseases; and quantifying the historical and future impact of public health interventions in Australia in terms of cases, deaths or DALYs averted, to highlight the ongoing need for public health programmes, such as the National Immunisation Programme.

The findings of this thesis contribute to our understanding of public health surveillance and the epidemiology of infectious diseases in Australia. The analyses presented in this thesis have enabled prioritisation of conditions for public health interventions based on notification incidence, changing epidemiology, health inequities, and DALY burden. Based on these criteria a number of priority conditions were identified and potential interventions discussed. The methods and results of this work have potential to contribute to a reduction in the burden of infectious diseases in Australia through improvements to the jurisdictional and national public health surveillance systems, identification of priority conditions for intervention, and provision of baseline measurements that can be repeated to assess the impact of these disease control strategies.

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Appendix 1. Online supplementary material for Chapter 5.1

The following supplementary material is available on the *Int J Infect Dis* website.

Gibney KB, O'Toole J, Sinclair M, Leder K. Disease burden of selected gastrointestinal pathogens in Australia, 2010. Int J Infect Dis. Supplementary Material.

Single input values were used to obtain the point estimate for the number of cases, DALY and DALY/case estimates. These single input values were considered the 'most likely' values, based on assessment of the quality of the study from which the values were derived and generalizability of results to the Australian population. In addition, Monte Carlo analyses (10,000 iterations) using PERT distributions was used to calculate 95% credible intervals (95%CrI) for DALY/case estimates. For the Monte Caro analyses the 'most likely' value included in the primary disease models was included as the mode value in the PERT distribution. Data extracted from additional studies were included in the PERT distributions as minimum or maximum values. These values were considered plausible alternatives to the single input 'most likely' values included in the primary disease models, again based on assessment of the quality of the study and generalizability to the Australian population. Where the 'most likely' value was also found to be higher or lower than the plausible alternatives, this value was included in the PERT distribution as the maximum or minimum values respectively, as well as the mode. Minimum, mode, and maximum values used in the PERT distributions, along with the data sources and approaches to calculate these, are included in this Appendix.

Supplementary Table S5.1: Estimated number of norovirus-AGE cases and deaths—Australia, 2010: input data for PERT distributions

Severity Total cases	Calculated number	Sources / Calculation
Minimum	1,023,258	Norovirus incidence in England (Phillips 2010)[202] applied to the 2010 Australian population by age-group
Most likely	2,180,145	NGSII-2008 AGE rate[203] X ABS 2010 population X norovirus-fraction for community AGE in Sensor[204] (by age-group)
Maximum	2,732,394	NGSII-2008 AGE rate[203] X ABS 2010 population X norovirus-fraction for community AGE in IID2[205] (age < or ≥5 years)
Moderate		
Minimum	61,959	GP AGE encounters (BEACH/Medicare) x age-specific norovirus fraction (NIVEL)[206] PLUS 0.5 x ED AGE visits (AIWH/ States) x age-standardised norovirus fraction (NIVEL)
Most likely /Maximum	157,081	GP AGE encounters (BEACH/Medicare) x age-specific norovirus-fraction (IID2)[205] PLUS 0.5 x ED AGE visits (AIWH/ States) x age-standardised norovirus-fraction (IID2)
Severe		
Minimum	9,632	AGE hospitalisation rate (AIWH) X age-specific norovirus-fraction (Lopman 2011)[207] PLUS 0.5 x ED AGE visits (AIWH/ States) X age-standardised norovirus-fraction (Lopman 2011)
Most likely	12,757	AGE hospitalisation rate (AIWH) X norovirus-fraction in adults (Jansen 2008), 5–15yo (Lorrot 2011) and <5yo (Patel 2008) PLUS 0.5 x ED AGE visits (AIWH/ States) X age-standardised norovirus-fraction (Jansen / Lorrot / Patel)[208-210]
Maximum	13,651	AGE hospitalisation rate (AIWH) X age-specific norovirus-fraction (Lau 2004)[211] PLUS 0.5 x ED AGE visits (AIWH/ States) X age-standardised norovirus-fraction (Lau 2004)
Fatal		
Minimum	1	AIHW 1997–2007: death records with norovirus as underlying (n=7) or associated (n=6) cause – likely underestimate
Most likely	17	Population case-fatality rate of notified norovirus deaths in Germany, 2001–09 (Bernard 2014)[212] applied to the 2010 Australian population
Maximum	20	Average annual number of deaths reported during norovirus outbreaks in long-term care facilities, 2002–08 (Kirk 2010)[213]

Supplementary Table S5.2: Estimated number rotavirus AGE cases and deaths—Australia, 2010: input data for PERT distributions

Severity	Total population, not vaccinated		<5 years of age, not vaccinated	
Total cases	**Calculated number**	**Sources / Calculation**	**Calculated number**	**Sources / Calculation**
Minimum /Most likely	592,745	NGSII-2008 AGE rate[203] X ABS 2010 population X rotavirus fraction in Sensor[204] (all by age-group)	223,370	NGSII-2008 AGE rate[203] X ABS 2010 population X rotavirus fraction in Sensor[204] (all by age-group)
Maximum	663,034	NGSII-2008 AGE rate[203] X ABS 2010 population X rotavirus fraction for community AGE in IID2[205] (age < or ≥5 years)	230,319	NGSII-2008 AGE rate[203] X ABS 2010 population X rotavirus fraction for community AGE in IID2[205]
Moderate				
Minimum/ Most likely	60,396	GP AGE encounters (BEACH/Medicare) x age-specific rotavirus fraction (NIVEL)[206] PLUS 0.5 x ED AGE visits (AIWH/ States) x overall rotavirus fraction (NIVEL)	34,557	As for total population but limited to <5yo age group
Maximum	80,996	GP AGE encounters (BEACH/Medicare) x age-specific rotavirus fraction (IID2)[205] PLUS 0.5 x ED AGE visits (AIWH/ States) x overall rotavirus fraction (IID2)	77,674	GP encounters for AGE (BEACH / Medicare) by rotavirus-fraction for GP visits (Galati)[214] PLUS 0.5 x ED encounters for AGE (AIWH/States) x rotavirus-fraction for ED visits (Galati)
Severe				
Minimum	22,596	AGE hospitalisations (AIWH/ABS) X rotavirus fraction in ≥15 years (Loosli) and children <15 (Barnes 1998) PLUS 0.5 x ED AGE visits (AIWH/ States) by average rotavirus-fraction (from Barnes / Loosli)[215, 216]	13,328	**[**AGE hospitalisations (AIWH / ABS) PLUS 0.5 x ED AGE visits (AIWH/ States)**]** MULTIPLIED BY rotavirus fraction (Widdowson 2007)[217]
Most likely/ Maximum	29,343	AGE hospitalisations (AIWH / ABS) X rotavirus-fraction in adults ≥18 years (Jansen 2008), children 5–17 years (Lopman 2011) and children <5 years (Carlin 1998) PLUS 0.5 x ED AGE visits (AIWH/ States) X average rotavirus-fraction (Jansen/Lopman/Carlin)[207, 208, 218]	19,657	As above, rotavirus fraction (Barnes 1998)[215]
Fatal				
Minimum	1	AIHW 1997-2007: death records with rotavirus as underlying cause – likely underestimate	0.5	Based on Australian death records with rotavirus as underlying cause from 1990–2003 (Brotherton 2007) [219] – likely underestimate
Most likely/ Maximum	20	Population mortality for rotavirus in Germany (0.09/100,000/year) (Werber 2013)[220]	6.6	Population mortality for rotavirus in Germany (0.45/100,000/year) (Werber 2013)[220]

Supplementary Table S5.3: Estimated number *Cryptosporidium*-AGE cases and deaths—Australia, 2010: input data for PERT distributions

Severity	Calculated number	Sources / Calculation
Total		
Minimum	60,022	NGSII-2008 AGE rate [203] X ABS 2010 population X *Cryptosporidium*-fraction in IID2 [205] (age < or ≥5 years)
Most likely	195,495	NGSII-2008 AGE rate [203] X ABS 2010 population X *Cryptosporidium*-fraction in Sensor [204] (all by age-group)
Maximum	265,702	Estimated under-diagnosis factor for cryptosporidiosis (Scallan 2011[221]) applied to average age-specific rate of cryptosporidiosis notifications (NNDSS 2001–2010) multiplied by 2010 Australian population
Moderate		
Minimum	18,744	GP AGE encounters (BEACH/Medicare) x age-specific *Cryptosporidium* fraction (IID2)[205] PLUS 0.5 x ED AGE visits (AIWH/States) x overall *Cryptosporidium* fraction (IID2)
Most likely/ Maximum	24,105	GP AGE encounters (BEACH/Medicare) x age-specific *Cryptosporidium* fraction (NIVEL)[206] PLUS 0.5 x ED AGE visits (AIWH/ States) x overall *Cryptosporidium* fraction (NIVEL)
Severe		
Minimum	2,770	AGE hospitalisations (AIWH/ABS) by *Cryptosporidium* fraction in children (Essers 2000) and adults (Jansen 2008) PLUS 0.5 x ED AGE visits (AIWH/ States) by average *Cryptosporidium*-fraction (from Essers / Jansen)[208, 222]
Most likely	3,283	AGE hospitalisations (AIWH / ABS) x age-specific *Cryptosporidium*-fraction (Tzipori 1983)[223] PLUS 0.5 x ED AGE visits (AIWH/ States) by average *Cryptosporidium*-fraction (Tzipori 1983)
Maximum	5,020	AGE hospitalisations (AIWH / ABS) x age-specific *Cryptosporidium*-fraction (Thomson 1987)[224] PLUS 0.5 x ED AGE visits (AIWH/States) by average *Cryptosporidium*-fraction (Thomson 1987)
Fatal		
Minimum / Most likely	0	AIHW 1997–2007: death records with *Cryptosporidium* as underlying or associated cause – likely underestimate (0 reports of *Cryptosporidium* as underlying cause of death, <3 reports of *Cryptosporidium* as associated cause of death)
Maximum	5	Average *Cryptosporidium*-fraction for AGE hospitalisations (Tzipori)[223] X estimated number gastroenteritis deaths in Australia in 2010 (AIWH underlying or associated cause A01–A09, 1997–2008) – likely overestimate

Supplementary Table S5.4: Estimated number *Giardia* AGE cases—Australia, 2010: input data for PERT distributions

Severity Total	Calculated number	Calculation	Giardia fraction
Minimum	75,301	NGSII-2008 AGE rate applied to ABS 2010 population then multiplied by Giardia-fraction for community AGE	IID[225]
Most likely /Maximum	614,740		Sensor[204]
Moderate		**Calculation**	**Giardia fraction**
Minimum	13,783	GP AGE encounters (BEACH/Medicare) x giardia fraction PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) x giardia fraction	IID2 (1.0%)[205]
Most likely	56,981		Hilmarsdottir 2012 (3.9%)[226]
Maximum	72,462		Nivel (5.4%)[206]
Severe			**Giardia fraction**
Minimum / Most likely	1,117	AGE hospitalisations (AIWH / ABS) x giardia fraction PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) x giardia fraction	Children – Essers 2000 (1.3%)[222] Adults – Jansen 2008 (1.0%) [208]
Maximum	3,054		Goldsmid 1980 (3.3%)[227]
Fatal		**Sources / Calculation**	
Minimum / Most likely	0	AIHW 1997–2007: <3 death records with A07 'other protozoal disease' as underlying cause and 10 with A07 'other protozoal disease' as associated cause over the 11 year period – possible underestimate	
Maximum	16	CFR for domestically acquired foodborne giardiasis in US (0.003%) from Scallan 2011[221] and applied this to the base estimate of giardiasis cases	

Supplementary Table S5.5: Estimated number of *Campylobacter*-AGE and sequelae cases and deaths—Australia, 2010: input data for PERT distributions

Category **Total AGE**	Calculated number	Sources / Calculation
Minimum	259,192	Applied the multiplication-factor of 10 (for under-diagnosis and under-reporting, Hall 2008)[36] to estimated *Campylobacter* notifications in 2010 (the average rate of notifications from 2001–2010 applied to the 2010 population)
Most likely/ Maximum	774,003	NGSII-2008 AGE rate[203] applied to ABS 2010 population then multiplied by *Campylobacter*-fraction for community AGE in IID2[205] (age < or ≥5 years)
Moderate AGE		
Minimum	79,099	Proportion of *Campylobacter* cases who sought outpatient medical care (proportion hospitalised subtracted from proportion who sought medical care in Unicomb 2009)[228] applied to 'minimum' model estimate for total *Campylobacter* cases
Most likely	140,047	GP AGE encounters (BEACH/Medicare) x age-specific *Campylobacter*-fraction (NIVEL)[206] PLUS 0.5 x ED AGE visits (AIWH/ States) x age-standardised *Campylobacter*-fraction (NIVEL)
Maximum	177,155	GP AGE encounters (BEACH/Medicare) x age-specific *Campylobacter*-fraction (IID2)[205] PLUS 0.5 x ED AGE visits (AIWH/ States) x age-standardised *Campylobacter*-fraction (IID2)
Severe AGE		
Minimum	8,191	AGE hospitalisations (AIWH / ABS) X *Campylobacter*-fraction in adults (Svenungsson 2000) and children (Elliott 1996) PLUS 0.5 x ED AGE visits (AIWH/ States) X age-standardised *Campylobacter*-fraction (Svenungsson / Elliott)[229, 230]
Most likely	12,228	AGE hospitalisations (AIWH / ABS) X *Campylobacter*-fraction in adults (Jansen 2008) and children (Barnes 1998) PLUS 0.5 x ED AGE visits (AIWH/ States) X age-standardised *Campylobacter*-fraction (Jansen / Barnes)[208, 215]
Maximum	17,656	Proportion of *Campylobacter* cases who were hospitalised reported by Unicomb 2009[228] applied to 'minimum' estimate for total *Campylobacter* cases
Fatal AGE		
Minimum	2	AIHW 1997–2007: death records with *Campylobacter* (A04.5) as underlying (n=12) or associated (n=7) cause – likely underestimate
Most likely	52	Case fatality ratio (0.2%) applied to estimated 2010 *Campylobacter* notifications (NNDSS 2001–2010) (Scallan 2011) [221]
Maximum	82	Standardised mortality ratio for <1 and 1–2 months following *Campylobacter* infection (Ternhag 2005)[231] applied to average mortality rates (2000–10, ABS) by age-group to determine expected number of deaths among notified *Campylobacter* cases
GBS cases		
Minimum	79	Incidence of GBS following notified *Campylobacter* AGE (McCarthy 2001)[154] X estimate of 2010 *Campylobacter* notifications X multiplication factor of 10 to account for under-diagnosis (Hall 2008[36])
Most likely	102	Campylobacter fraction (Poropatich 2010)[232] applied to incidence-based Australian estimate of GBS (Hankey 1987)[233]
Maximum	112	Campylobacter fraction (Poropatich 2010)[232] applied to GBS incidence based on a systematic review of 63 papers (McGrogan 2009)[234]
GBS Deaths		
Minimum	2	Case fatality rate for GBS (van der Meche 1992)[235] applied to 'most likely' estimate of *Campylobacter*-associated GBS cases (Poropatich / Hankey)[232, 233]
Most likely	3	Campylobacter fraction (Poropatich 2010)[232] applied to average number of deaths/year with GBS listed as underlying cause (AIHW 1997–2007)
Maximum	7	Campylobacter fraction (Poropatich 2010)[232] applied to average number of deaths/year with GBS listed as underlying or associated cause (AIHW 1997–2007)
ReA cases		
Minimum	4,568	Midpoint of range of ReA fraction presented in a systematic review (Pope 2007)[236] applied to the base-model estimate of moderate + severe *Campylobacter* AGE
Most likely	11,252	ReA fraction (Hannu 2002)[142] applied to the base-model estimate of moderate + severe *Campylobacter* AGE
Maximum	23,765	ReA fraction (Locht 2002)[237] applied to the base-model estimate of moderate + severe *Campylobacter* AGE
IBS cases		
Minimum	4,644	Standardised IBS ratio in the year following culture-confirmed *Campylobacter* infection (Ternhag 2008)[238] X incidence IBS in general population (Lock 2004)[239] X base-model estimate of all *Campylobacter* AGE cases
Most likely	68,112	IBS fraction (8.8% - Haagsma 2010)[140] applied to the base-model estimate of all *Campylobacter* AGE cases
Maximum	177,712	IBS fraction for children (Thabane 2010)[240] and adults (Marshall 2006)[241] from Canada's Walkerton Health Study applied to the base-model estimate of all AGE cases

Supplementary Table S5.6: Estimated number of *Salmonella* AGE and sequelae cases and deaths — Australia, 2010: input data for PERT distributions

Category	Calculated number	Sources / Calculation
Total AGE		
Minimum	43,272	OzFoodNet NGSII-2008 AGE rate X ABS 2010 population X *Salmonella* -fraction for community AGE in IID2[205] (age < or ≥5 years)
Most likely/ Maximum	71,255	OzFoodNet NGSII-2008 AGE rate applied to ABS 2010 population (age-weighted) then multiplied by *Salmonella* -fraction for community AGE in Sensor (0.4%)[203, 204]
Moderate AGE		
Minimum	10,641	GP AGE encounters (BEACH/Medicare) x age-specific *Salmonella*-fraction (IID2)[205] PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) x age-standardised *Salmonella*-fraction (IID2)
Most likely	46,726	GP AGE encounters (BEACH/Medicare) x age-specific *Salmonella* -fraction (NIVEL)[206] PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) x age-standardised *Salmonella* -fraction (NIVEL)
Maximum	66,665	GP AGE encounters (BEACH/Medicare) x age-specific *Salmonella* -fraction (Hilmarsdottir 2011)[226] PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) x age-standardised *Salmonella* -fraction (Hilmarsdottir)
Severe cases		
Minimum	4,919	Applied hospitalisation rate to notified *Salmonella* cases (Scallan 2011)[221]
Most likely /Maximum	9,742	AGE hospitalisations (AIWH / ABS) X *Salmonella*-fraction in adults (Jansen 2008) and children (Barnes 1998) PLUS 0.5 x ED AGE visits (AIWH/NPHED/States) X age-standardised *Salmonella*-fraction (Jansen / Barnes)[208, 215]
Fatal AGE		
Minimum	6	Average age-adjusted *Salmonella*-fraction for AGE hospitalisations (Jansen 2008/ Barnes 1998)[208, 215] applied to estimated number AGE deaths in Australia in 2010 (AIHW underlying cause A01–A09, 1997–2008)
Most likely	90	Case fatality ratio (1%) applied to estimated 2010 *Salmonella* notifications (NNDSS 2001–2010) (Scallan 2011) [221]
Maximum	182	Excess deaths among notified *Salmonella* cases (Helms 2003[242], 2%) applied to estimated *Salmonella* notifications in Australia in 2010
ReA cases		
Minimum/ Most likely	2,505	ReA fraction (Tuompo 2013)[143] applied to moderate + severe *Salmonella* AGE cases (4.4%)
Maximum	8,244	ReA fraction (Lee 2005)[243] applied to moderate + severe *Salmonella* AGE cases (14.6%)
IBS cases		
Minimum	242	Standardised IBS ratio in the year following culture-confirmed *Salmonella* (1.7) infection (Ternhag 2008)[238] X incidence IBS in general population (0.2%, Lock 2004)[239] X all *Salmonella* AGE cases
Most likely	6,270	IBS fraction (8.8% - Haagsma 2010)[140] applied to all *Salmonella* AGE cases
Maximum	16,068	IBS fraction for children (13.2%, Thabane 2010)[240] and adults (26.4%, Marshall 2006)[241] from Canada's Walkerton Health Study applied to all *Salmonella* AGE cases

Supplementary Table S5.7: Duration of AGE for selected pathogens—Australia, 2010: input data for PERT distributions

Pathogen	Severity	Duration (days)	Sources
Norovirus			
Mild	Minimum	1.0	Atmar 2008 [244]
	Most likely	2.1	Unpublished data, Water Quality Study [245]
	Maximum	5.0	Rockx 2002 [246]
Moderate	Minimum	2.3	Unpublished data, Water Quality Study [245]
	Most likely	2.4	Unpublished data, OzFoodNet National Outbreak Register [247]
	Maximum	5.8	IID [225]
Severe	Minimum	4	Colomba 2007 [248]
	Most likely / maximum	7.2	Kemmeren 2006 [249]
Rotavirus	**Mild**		
Mild	Minimum	2.5	Unpublished data, Water Quality Study [245]
	Most likely	4.9	Kemmeren 2006 [249]
	Maximum	5.5	Ford-Jones 2000 [250]
Moderate	Minimum	3.7	Unpublished data, OzFoodNet National Outbreak Register [247]
	Most likely	7.1	Kemmeren 2006 [249]
	Maximum	7.5	Stein 2010 [251]
Severe	Minimum	6.0	DeWit 2000 [252]
	Most likely	7.7	Kemmeren 2006 [249]
	Maximum	8.3	Lacroix 2010 [253]
Cryptosporidium			
Mild	Minimum / most likely	4.0	Unpublished data, Water Quality Study [245]
	Maximum	5.0	Tangermann 1991 [254]
Moderate	Minimum	9.0	MacKenzie 1994 [255]
	Most likely	12.5	Unpublished data, Water Quality Study [245]
	Maximum	26.0	Boehmer 2009 [256]
Severe	Minimum	8.2	UK Public Health Laboratory Service Study Group 1990 [257]
	Most likely	21.4	Unpublished data from Australian *Cryptosporidium* case-control studies [258]
	Maximum	23.4	Corso 2003[259]
Giardia			
Mild	Minimum	2	Unpublished data, Water Quality Study [245]
	Most likely / maximum	5	Nash 1987 [260]
Moderate	Minimum	4	Unpublished data, Water Quality Study [245]
	Most likely	15	Homan 2001 [261]
	Maximum	35	Rimhanen-Finne 2010 [262]
Severe	Minimum	13	Sum duration moderate-severe disease (10 days, López 1980 [263]) and average length hospital stay for giardiasis (3 days, AIHW 1998–99 to 2007–08)
	Most likely / maximum	33	As above, using Nygård 2006 [264] (30 days) and AIHW 1998–99 to 2007–08
Campylobacter			
Mild	Minimum / most likely	3.5	Kemmeren 2006 [249]
	Maximum	5.1	Havelaar 2000 [265]
Moderate	Minimum	2.2	Unpublished data, Water Quality Study [245]
	Most likely / maximum	9.7	Kemmeren 2006 [249]
Severe	Minimum	7.1	Unpublished data from Australian *Campylobacter* case-control studies [266, 267]
	Most likely / maximum	14.4	Kemmeren 2006 [249]
Salmonella			
Mild	Minimum / most likely	2.5	Unpublished data, Water Quality Study [245]
	Maximum	5.6	Kemmeren 2006 [249]
Moderate	Minimum	4.0	Unpublished data, Water Quality Study [245]
	Most likely	6	IID [225]
	Maximum	10.6	Kemmeren 2006 [249]
Severe	Minimum	11	Sum duration moderate-severe disease (Munnoch 2009 [268]) and average length hospital stay for Salmonella AGE (4 days, AIHW 1998–99 to 2007–08)
	Most likely	12	As above, using McPherson 2006[269] and AIHW 1998–99 to 2007–08
	Maximum	16.1	Kemmeren 2006 [249]

Appendix 2. Co-authored publications related to Chapter 6

Appendix 2.1: Sinclair M, O'Toole J, Gibney K, Leder K. Evolution of regulatory targets for drinking water quality. ***J Water Health***. 2015 Jun;13(2):413-26. doi: 0.2166/wh.2014.242.

Evolution of regulatory targets for drinking water quality

Martha Sinclair, Joanne O'Toole, Katherine Gibney and Karin Leder

ABSTRACT

The last century has been marked by major advances in the understanding of microbial disease risks from water supplies and significant changes in expectations of drinking water safety. The focus of drinking water quality regulation has moved progressively from simple prevention of detectable waterborne outbreaks towards adoption of health-based targets that aim to reduce infection and disease to a level well below detection limits at the community level. This review outlines the changes in understanding of community disease and waterborne risks that prompted development of these targets, and also describes their underlying assumptions and current context. Issues regarding the appropriateness of selected target values, and how continuing changes in knowledge and practice may influence their evolution, are also discussed.

Key words | disability adjusted life years (DALY), health-based targets, water safety

Martha Sinclair (corresponding author)
Joanne O'Toole
Katherine Gibney
Karin Leder
Department of Epidemiology and Preventive Medicine,
Monash University,
The Alfred Centre,
99 Commercial Road,
Melbourne,
VIC 3004,
Australia
E-mail: *martha.sinclair@monash.edu*

INTRODUCTION

In the 160 years since demonstration of the linkage between faecal contamination of water and human disease, our understanding of microbial disease risks and expectations of drinking water safety have changed markedly. From the initial focus on prevention of waterborne outbreaks, water quality regulations have moved towards adoption of health-based targets to limit infection and disease at the community level. This transition represents a change of several orders of magnitude in disease incidence, and as more countries begin to incorporate health-based targets into national regulations and guidelines, it is timely to examine the origins and current context of these targets.

We begin by outlining how current disease surveillance systems operate, the relationship between detected outbreaks and disease patterns in the community, and how understanding of the infection process has changed over recent decades. We then summarise the role of traditional microbial water quality indicators in reducing levels of waterborne disease in the first half of the 20th century, the subsequent emergence of viral and protozoal pathogens as significant causes of waterborne outbreaks, and increasing recognition of the need for a new approach to address these risks. The origins of the two most widely used health-based targets (the US Environmental Protection Agency (USEPA) annual infection risk and the World Health Organization (WHO) annual disability adjusted life years (DALY) burden) are outlined, and we examine the data and assumptions that underpin them. Finally, we discuss the context of current health-based water quality targets in relation to broader public health considerations, and how they may require further adaptation in the future.

DETECTION OF WATERBORNE DISEASE

Surveillance systems and waterborne disease

The predominant illness caused by waterborne pathogens is gastroenteritis, characterised primarily by diarrhoea and often accompanied by other symptoms including vomiting, abdominal cramps, nausea, or fever. Gastroenteritis remains a major cause of morbidity and mortality in the developing world, especially among young children. In developed nations, the health impacts are much less severe, but gastroenteritis remains a relatively common illness in the community, with estimated incidence rates varying from 0.1

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to 3.5 episodes per person per year (Roy *et al.* 2006). This illness may be caused by a wide range of enteric pathogens, all of which can be acquired by multiple routes of infection including person-to-person transmission, contaminated food, drinking water, and recreational water. The source of infection for an individual case of disease cannot usually be determined except in the context of an outbreak investigation.

Surveillance for gastroenteritis pathogens and other infectious diseases relies predominantly on laboratory identification of individual pathogens through the healthcare system and reporting of these cases of infection to health agencies. The pathogens for which reporting is mandated are specified by the regulations of the relevant government agency. Routine monitoring of these data for evidence of disease outbreaks may consist simply of noting case numbers, and scanning for temporal or geographical clustering, which then triggers further investigation. For selected pathogens, a more active level of surveillance may be implemented by contacting the affected individuals and collecting information about recent exposures (e.g. food, water, and international travel) to seek evidence of a shared source. Routine surveillance systems detect only a small fraction of the pathogen infections that occur in the community, because they require: firstly, that the infected person experiences symptoms that are sufficiently severe to cause them to seek medical care; secondly, that the physician obtains an appropriate clinical specimen from the patient and orders relevant pathology tests; thirdly, that a positive test result is obtained by the laboratory; and finally, that the appropriate authority is notified of the positive result. The diminishing number of events at each stage of this process is typically depicted as a 'reporting pyramid' (Figure 1) (CDC 2014a).

The healthcare system may capture the number of cases in the upper portion of the pyramid (from seeking medical attention upwards), but the causative pathogen can only be identified among the subgroup of cases for whom an appropriate pathology test is ordered. Even when such a test is performed, the pathogen responsible for the illness may not be detected due to limitations in test sensitivity, and not all positive tests are reported to surveillance systems even when reporting is mandated. The lower levels of the pyramid may be investigated using epidemiological studies

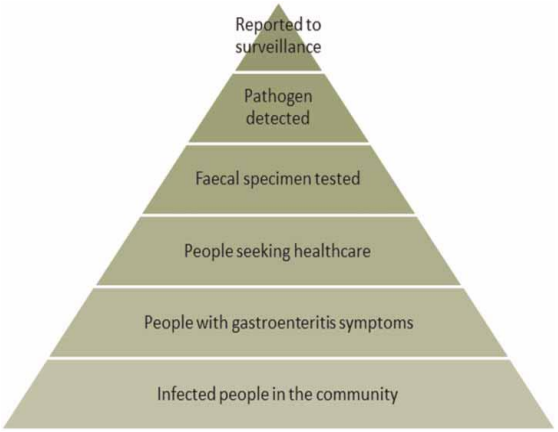

Figure 1 | Reporting pyramid for gastroenteritis.

comparing the number of cases identified by normal clinical practice with disease incidence at a community level. Direct enumeration of the number of asymptomatic or mild infections in the community is particularly difficult as it requires obtaining and analysing faecal specimens from people who are either not ill or not sufficiently ill to seek healthcare. Routine surveillance systems are limited to pathogens for which laboratory tests are available and widely used, meaning that some important and common gastroenteritis pathogens (notably norovirus) are much less likely to be detected. Most surveillance systems also contain a provision for reporting of suspected foodborne or waterborne disease even where the pathogen is unknown.

The ratio between the number of cases notified to surveillance systems and the number of symptomatic cases in the community varies between pathogens according to symptom severity, and the nature of the healthcare and surveillance systems. A recent epidemiological study in the UK found that the overall ratio between identified enteric pathogen cases reported to the national surveillance system and symptomatic cases of gastroenteritis in the community was one reported pathogen per 147 community cases (Tam *et al.* 2012a). Another study in Canada estimated an average ratio of 313 community cases of infectious gastrointestinal illness for every case reported to the provincial surveillance system (Majowicz *et al.* 2005), while comparison of the total number of gastrointestinal pathogens reported to Australia's national surveillance system (NCDC 2002) and a national survey of gastroenteritis in 2002 (Hall *et al.* 2006) suggested a ratio of about 500 community cases to one notified

pathogen. Even in research studies where an extensive range of pathogen tests are carried out on faecal specimens, a large proportion (commonly 50–60%) of community gastroenteritis cases do not have a pathogen identified (de Wit *et al.* 2001; Hellard *et al.* 2001; Tam *et al.* 2012b). Such cases may be attributable to known pathogens that are present but unable to be detected due to limitations in test methods, pathogens that are as yet undiscovered, or non-infectious causes of gastroenteritis.

Outbreaks and endemic disease

A disease outbreak is generally defined as a significant increase in the number of cases of a specific disease in a localised area over a short period of time. This definition is flexible, and individual jurisdictions may apply various criteria or algorithms to detect unusual spatial and/or temporal clustering of pathogen reports, which trigger further investigation. The characteristics of the pathogen and the nature of the illness influence the likelihood of detecting an outbreak, with unusual pathogen species/serotypes or rare/severe symptoms (e.g. bloody diarrhoea or illness requiring hospitalisation) more likely to trigger an investigation. Sometimes, an outbreak may be recognised as a cluster of gastroenteritis cases even before any attempt is made to identify a pathogen, particularly when the cases have an identifiable relationship, which is linked to the common exposure (e.g. attendees at a social event and residents in a healthcare facility). Identification of the source of an outbreak (e.g. contaminated water or food) may rely only on epidemiological evidence (significantly higher rate of illness in those with a particular exposure compared to those without the exposure) or may be supplemented by detection of pathogens or other evidence of contamination in the suspect transmission vehicle. The ability to recognise outbreaks and identify their source and causation is constrained by the human and technical resources available to public health agencies for such investigations.

Although the definition of an outbreak requires identification of as few as two cases associated with a common exposure source, consideration of the reporting pyramid suggests that somewhere between 50 and 150 gastroenteritis cases are probably required at the community level before an outbreak would be detected by routine surveillance systems. Once an outbreak is recognised, active case finding through contact with physicians and hospitals, local organisations, or media publicity will lead to identification of gastroenteritis cases at steps further down the pyramid. Most of these will be classified as outbreak cases only on the basis of symptoms and exposure to the suspect source during the relevant time period, with laboratory confirmation of pathogen infection usually being performed in only a minority of cases.

Cases linked to recognised gastroenteritis outbreaks make up only a small fraction of all reported enteric pathogen infection cases, and it is acknowledged that many outbreaks may pass undetected due to the low sensitivity of surveillance systems. Most cases of gastroenteritis in the community, however, probably do not arise from simultaneous exposure of a group of people to a common infection source, but are acquired independently by separate individuals at different times. Some pathogen infections are present continuously in a population at a low but fairly stable rate (endemic disease) while others appear intermittently (sporadic disease). The relationship between detected outbreaks, undetected outbreaks, and rates of endemic disease in the community is illustrated in Figure 2 (Frost *et al.* 1996). For obvious reasons, detected outbreaks are often said to represent the 'tip of the iceberg', while the vast bulk of disease cases exist well below the threshold of detection by routine surveillance.

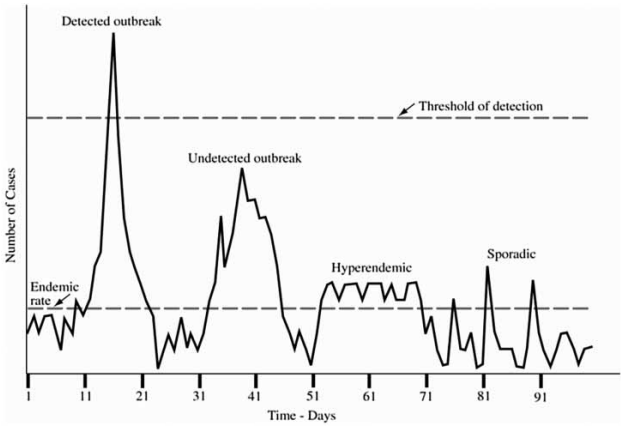

Figure 2 | Limits to outbreak detection (Frost *et al.* 1996). Republished with permission of American Water Works Association, from *J. AWWA* 88 (9) (September 1996). Copyright ©1996 American Water Works Association; permission conveyed through Copyright Clearance Center, Inc.

Characterising the infection process

Understanding of the relationship between enteric pathogen exposure and infection was developed initially through investigation of foodborne disease outbreaks and later by experimental studies in animals, cell culture systems, and human subjects. The term 'minimum (or minimal) infectious dose' (MID) is often used in early publications, but the meaning of this term has always been imprecise (Ward & Akin 1984). The MID is commonly defined as 'the smallest number of pathogens capable of causing an infection', but this description lacks any quantitative measure of the exposed population (i.e. does it mean the dose required to infect one subject among 10 exposed, or perhaps one among 100 or even one among 1,000,000?). The term also conveys the implication that there exists a dose threshold for any given pathogen, below which infection does not occur. An early review of the minimum infective doses of human enteric viruses suggested that the MID should be defined as the dose required to infect 5% of subjects (ID_5) or even 1% of subjects (ID_1), but noted that the low number of human subjects (or tissue culture replicates) in experimental studies meant that the ID_{50} was usually reported as the MID (Plotkin & Katz 1965). Similarly, a review of data on the infectious dose for *Salmonella* infection found that the lowest dose tested in human studies was 10^3 cells, and even when no infections were observed at this dose, the small number of subjects meant that the true infection risk could have been as high as 23% (Blaser & Newman 1982). Furthermore, examination of available data from *Salmonella* outbreaks suggested infection and illness had sometimes resulted from doses as low as 17–30 organisms. Another virus review in 1984 found little had changed, and the ID_{50} remained the most frequently quoted statistic for describing the MID (Ward & Akin 1984). Use of the ID_{50} provides a benchmark to enable comparisons between different studies and between strains of pathogens, but clearly does not correspond to the popular perception of what is meant by the term 'MID'.

Another question related to the concept of the MID is whether pathogenic microorganisms act cooperatively to establish infection (consistent with existence of a dose threshold), or whether each organism acts independently. Experimental work on *Salmonella* infections performed in the 1950s provided strong support for the independent action model (Meynell 1957; Meynell & Stocker 1957), but the assumption of cooperative action prevailed in the literature well into the 1980s despite accumulation of data from other bacterial genera, which also supported the independent action hypothesis (Rubin 1987). The mathematical modelling methods used to describe dose–response relationships for microbial pathogens subsequently evolved into the formal discipline of Quantitative Microbial Risk Assessment (QMRA) (Haas *et al.* 1999), utilising a four-step conceptual framework analogous to that previously developed for assessment of health risks from chemical exposures (NAS 1983). The current body of evidence from QMRA studies of experimental and outbreak data strongly supports the independent action (single-organism) hypothesis for pathogen infection (Haas *et al.* 1999).

Given appropriate input data on human exposure (infectious pathogen concentrations in water, volume of water ingested daily), the pathogen dose–response relationship (likelihood of infection for a given pathogen dose), and susceptibility (percentage of the exposed population not immune to the pathogen), QMRA permits an estimate to be made of infection risks for a human population consuming pathogen-contaminated drinking water. If information is available on the proportion of infected people who develop symptoms, the number of cases of illness can also be estimated.

The first applications of this approach to estimation of disease risks from exposure to waterborne pathogens focussed on recreational water quality (Fuhs 1974; Dudley *et al.* 1976). Later, as concern grew about the possibility that treated drinking water might still contain low concentrations of infectious pathogens (see below), the technique was widely used to model risks from drinking water supplies (Regli *et al.* 1991; Rose & Gerba 1991).

WATER QUALITY AND DISEASE

Indicator organisms and waterborne disease risks

The link between faecal pollution of drinking water and transmission of diseases such as cholera was first proposed in the 1850s, but it was not until three decades later that

the 'germ theory' of disease was widely accepted and effective measures to reduce the incidence of infectious diseases began to be implemented in developed nations (Hrudey & Hrudey 2004). Although it was possible at that time to detect and identify some waterborne pathogens, the diversity of pathogens, the complexity of test methods, and the intermittent presence of individual species in water made direct testing for pathogens impractical for routine water quality testing. Instead, methods were developed to monitor the more abundant non-pathogenic species of faecal bacteria and use these as 'indicators' to assess levels of faecal pollution in water supplies (Gleeson & Gray 1997).

The bacterium *Escherichia coli* (at that time called *Bacillus coli*) was known to be one of the most numerous bacterial species in human faeces, but the lack of a simple one-step test for this organism led to the widespread adoption of the total coliform group as the routine microbial indicator in the early decades of the 20th century (Allen & Geldreich 1978). During this period, the frequency of waterborne outbreaks in developed nations fell markedly as basic water disinfection and treatment methods (chlorination and sand filtration) were progressively implemented, together with improved living conditions, sanitation, and better protection of source waters from human waste. The use of coliform indicator bacteria played a key role in reducing the risk of outbreaks by providing a means to assess faecal pollution in source waters, and evaluate the efficacy of disinfection and water treatment processes. Over time, tests for thermotolerant coliforms were added to monitoring programmes to provide a more focussed measure of faecal contamination, and then in the 1990s, defined substrate technology tests that permitted rapid detection and enumeration of both *E. coli* and total coliforms were widely adopted (Edberg *et al.* 1988).

During the 1970s and 1980s, there was an apparent increase in the number of drinking water-related outbreaks reported in both the USA and the UK (Craun 1978; Hunter 1997). It was also noted that the proportion of waterborne outbreaks attributable to bacterial pathogens appeared to be decreasing, while the proportion attributable to *Giardia lamblia* and enteric viruses was increasing. Indeed, *Giardia* had become most commonly identified cause of outbreaks associated with surface water supplies in the USA, accounting for more than half of outbreaks between 1971 and 1985 where a causative agent was identified (Craun 1988). It is not clear whether this apparent increase in the number of outbreaks reflected a real change in incidence, or whether it was at least partially attributable to more effective disease surveillance systems. Concurrent improvements in detection methods for viral and protozoal pathogens in both clinical and environmental samples permitted the identification of causative agents for outbreaks that in previous times would have been classified as having unknown aetiology. Underlying factors such as absent, interrupted, or inadequate water treatment and disinfection could be identified as the cause in many outbreaks (Craun 1988), but several virus outbreaks were documented in the USA and other countries in water supplies where coliform bacteria were not detected, and free chlorine residuals were maintained throughout the outbreak period (Hejkal *et al.* 1982; Bosch *et al.* 1991). Only a few years later, the recognition of several waterborne outbreaks caused by *Cryptosporidium* heralded the emergence of another significant pathogen with even higher levels of chlorine resistance than enteric viruses (D'Antonio *et al.* 1985; Hayes *et al.* 1989; Rush *et al.* 1990).

In parallel with the apparent upwards trend in reported waterborne outbreaks, evidence had been accumulating that culturable human viruses could be detected at low concentrations in apparently well operated, fully treated water supplies that complied with relevant water quality standards (Payment 1981; Keswick *et al.* 1984). These developments brought into question the prevailing belief that the absence of coliform bacteria was a reliable marker of 'safe' drinking water. There was growing knowledge that the persistence of viral and protozoal pathogens in the environment and their responses to water treatment and disinfection processes were significantly different from those of bacterial pathogens, and therefore, elimination of coliforms from treated water was not a guarantee that all classes of pathogen had been effectively removed. Many attempts have since been made to identify indicator organisms for protozoal and viral pathogens that could serve with the same utility as *E. coli* does for bacterial enteric pathogens. Candidate organisms have included faecal streptococci and enterococci, sulphite-reducing *Clostridium* species and several types of bacteriophage, but none has gained widespread

acceptance for routine use in monitoring drinking water quality (Ashbolt *et al.* 2001).

The question of endemic waterborne disease

Early reports of infectious viruses in treated drinking water provoked debate about whether such low concentrations (generally averaging one tissue culture infectious virus dose per several 100 l of water) should be considered a public health risk (Plotkin & Katz 1965). The prevailing idea of an 'MID' for pathogens led many to conclude that such low exposures would be unable to initiate infections, but as QMRA techniques developed and the single-organism concept became more widely accepted, this view changed. It was predicted that even with very low pathogen concentrations, the large size of exposed populations and repeated daily exposures could potentially result in many cases of infection and illness arising annually from water supplies that had previously been considered 'safe'.

These predictions prompted a number of epidemiological studies that attempted to detect evidence of endemic waterborne disease from drinking water supplies, including several studies undertaken as part of a research programme instituted by the Centers for Disease Control and Prevention and the USEPA (CDC 2014b). The body of evidence on endemic waterborne disease was summarised in a Supplement to the *Journal of Water and Health* in 2006. Observational studies of various designs that assessed illness rates or markers of infection in communities with differing water supplies or significant changes in water treatment gave mixed results, with some supporting the idea of significant waterborne disease transmission, while others did not (Craun & Calderon 2006). In addition, several randomised intervention trials have compared self-reported gastroenteritis rates in groups of people randomly allocated to drink tap water with or without additional point-of-use treatment to remove (presumed) residual pathogens. Studies of this design provide the strongest level of evidence for human disease, because they are able to control for underlying differences in non-water sources of gastrointestinal disease, which may influence the results of observational studies. The intervention trials have shown variable results, with some finding evidence that the intervention significantly reduced rates of disease (Payment *et al.* 1991, 1997; Borchardt *et al.* 2012) while others did not (Hellard *et al.* 2001; Colford *et al.* 2005). This may reflect different risk levels in the different water supplies being examined or different susceptibility to infection in the target population groups, but also may be at least partially attributable to limitations in some study designs (i.e. lack of blinding to water treatment allocation). Information from five such studies conducted before 2006 was used to construct an estimate of the fraction of gastroenteritis attributable to public drinking water supplies in the USA (Colford *et al.* 2006). A number of different scenarios were explored in regard to levels of risk from surface or groundwater sources, and effects of source water contamination, inadequate water treatment, or contamination in the distribution system. This analysis produced a median estimate that 12% of gastroenteritis among the immunocompetent population in the USA could be attributable to community drinking water systems. However, due to lack of specific information, many of the assumptions were necessarily arbitrary in nature. Another estimate by USEPA researchers using similar information produced a slightly lower figure of 8.5% for waterborne illness from community drinking water systems (Messner *et al.* 2006).

Although epidemiological studies can measure actual disease rates in a community, the size of the population that can be included (and consequently the statistical power of the study to detect differences between exposure groups) is limited by resource and logistical constraints. Increases in statistical power require a disproportionately large increase in sample size, and it has been calculated that a randomised trial capable of detecting 100 additional cases of gastroenteritis annually in a population of 10,000 (corresponding to roughly a 1% increase in gastroenteritis incidence) would require enrolment of around 416,000 people (Eisenberg *et al.* 2006). Randomised studies of this size are not feasible, and the most stringent resolution yet achieved by this type of study was around 10% of the overall gastroenteritis rate (Colford *et al.* 2005). Therefore, the potential existence of lower rates of waterborne disease in communities can only be addressed using QMRA for specific pathogens or modelling using information from the few randomised studies available.

HEALTH-BASED TARGETS

Alternative approaches to health-based targets

Recognition of the limited utility of traditional indicator organisms to assess risks from non-bacterial pathogens and the inability of epidemiological studies to detect small differences in illness rates led regulatory authorities to develop QMRA based approaches to assess drinking water safety and set regulatory targets. These targets have been formulated to set upper limits on the adverse health effects that may be suffered by consumer populations as a result of microbial contamination of drinking water. Internationally, two main approaches have been used to define microbial safety targets for water as follows:

1. USEPA annual infection risk target: the USEPA used QMRA to develop water treatment requirements for *G. lamblia* and enteric viruses in the Surface Water Treatment Rule (SWTR) (USEPA 1989). Subsequent changes to the rule have been aimed at enhancing pathogen removal capability for poor quality source waters and reducing risks of *Cryptosporidium* infection. The specified treatment requirements are consistent with limiting waterborne pathogen infections to a rate of one per 10,000 people per year, although this target figure has not been officially adopted into USEPA policy (Regli *et al.* 1999).
2. WHO DALY target: the WHO adopted a tolerable risk level expressed in terms of DALY in the 3rd edition of the drinking-water guidelines (WHO 2004). The DALY is a summary measure of the health impact of a disease that incorporates both fatal and non-fatal (mortality and morbidity) outcomes. One DALY can be thought of as one lost year of 'healthy' life. WHO has set the health-based target for microbial drinking water quality at 1 DALY per million persons per year.

The USEPA infection risk target and the WHO DALY target rely on the same data and models for QMRA calculations to predict infection risks from pathogens in drinking water. In theory, this process could be carried out for many pathogens, but in practice, the limitations of data on dose–response relationships, occurrence of pathogens in water, and their removal by water treatment processes mean that modelling is limited to a relatively small group of 'reference pathogens'. These comprise representatives of the three major pathogens categories (viruses, bacteria, and protozoa) selected on the basis of demonstrated waterborne transmission, relatively high infectivity and severity of illness, as well as having sufficient data available to perform QMRA. The DALY approach then uses additional clinical and epidemiological information on the severity and duration of symptoms and risks of fatal outcomes to compute the health burden. The infection risk approach results in water treatment requirements corresponding to equal risks of infection for each category of pathogen, while the DALY approach aims to achieve water quality that would produce an equal health burden for each category of pathogen.

Selection of target values

In the SWTR, the USEPA expresses the belief that public water supplies should provide a much greater level of protection than simply that necessary to avoid outbreaks (citing estimated infection rates of 50 in 10,000 people or greater in reported *Giardia* outbreaks in the USA), and states that 'providing treatment to ensure less than one case of microbiologically caused illness per year per 10,000 people is a reasonable goal'. The one in 10,000 annual risk target is also described as 'comparable to other acceptable microbiological risk levels' (Regli *et al.* 1991). This reference in turn cites the transcript of an expert panel discussion at the 1987 Calgary *Giardia* Conference (Regli *et al.* 1988). The expert panel canvassed different waterborne risk estimates (reported *Giardia* outbreaks, estimated symptomatic *Giardia* cases in the community, and gastroenteritis from recreational water use) as well as possible targets from QMRA modelling. These estimates ranged over several orders of magnitude, and the expert panel did not attempt to develop a consensus position on a suitable target for drinking water regulation.

Another line of reasoning in support of the one in 10,000 annual infection risk figure has also been presented (Macler & Regli 1993). These authors calculated that an annual infection risk of one in 10,000 for *Giardia* would be equivalent to approximately a one in 10 cumulative risk of waterborne infection over a 70-year lifetime. This

was derived from a study that estimated the total number of 'clinically significant infections' for a range of pathogens in the USA in 1985 and the proportion attributable to various sources (food, water, zoonotic transmission, etc.) (Bennett *et al.* 1987). *Giardia* was estimated to cause a total of 120,000 cases of illness annually, with 60% being attributable to waterborne transmission. This pathogen was believed to be responsible for 8% of all waterborne infections, and there was a mean average 10% lifetime risk of microbial infection from drinking water (Macler & Regli 1993). The 95% upper-bound risk for this estimate was approximately one, and assuming the risk of death from waterborne illness in the USA is 0.1% of all cases (Bennett *et al.* 1987), this would give an estimated lifetime risk of death from waterborne infection of one in 1,000. Alternatively, if one assumes that only 10% of infections result in significant illness, and uses the mean lifetime risk of infection (rather than the upper-bound estimate), then the risk of death from waterborne infection would be about one in 100,000 over a lifetime. These figures are in the same range as lifetime risks of cancer that are considered by the USEPA to be acceptable for chemical contaminants in water (two in 100,000 to two in 10,000,000 theoretical upper-bound), thus providing similarity in tolerable risk levels for fatality for chemical and microbial contaminants.

This calculation is potentially open to question however, as the fatality rate estimated by Bennett *et al.* (1987) was based on cases of 'clinically significant infections' estimated by the Centers for Disease Control and Prevention. No definition is given for the term 'clinically significant infection', and it is not clear what proportion of community illness is encompassed by this term. A comparison of the overall enteric illness rate (0.11 illness cases per person per year) in the 1985 study (Bennett *et al.* 1987) with a more recent estimate (0.79 illness cases per person per year) in 1997 (Mead *et al.* 1999) suggests that the earlier study significantly underestimated the endemic disease rate. The estimated fatality rates in the two studies are also markedly different; 0.04% for all enteric cases and 0.10% for waterborne cases in the 1985 study, versus 0.003% for all enteric cases in the 1997 estimate. This disparity may be partially explained by changes in the relative prevalence of different pathogens and advances in clinical treatment in the intervening period, as well as the inclusion of all endemic cases in the denominator of the more recent study.

The 1987 Bennett *et al.* study has been cited by a number of authors (LeChevallier & Buckley 2007) as the source of the one in 10,000 annual waterborne disease target figure. In this interpretation, this is described as the rate of waterborne infections already tolerated in the USA in 1987 (cited as 25,000 cases of waterborne disease in a population of about 250 million). However, the number actually stated in the monograph is 940,000 annual cases of waterborne disease, or about 38 cases per 10,000 people per year. This was derived by multiplying the estimated waterborne fraction for several individual enteric pathogens by the estimated total number of cases of each pathogen. It is not evident how the numerical estimates given in the Bennett publication (either collectively or individually) could have been subsequently interpreted to derive a rate of one in 10,000 per person per year for waterborne disease rather than this higher figure.

The DALY was developed by Harvard University for the World Bank to provide a consistent framework to quantify and compare the health burden of a wide range of diseases and injuries on populations (World Bank 1993). This measure was developed as an alternative approach to simply using the number of deaths (mortality) or illnesses (morbidity) to rank the effects of diseases on populations. The DALY integrates disease impacts including premature death, degree of disability caused by an illness, and the length of time lived with disability into a single measure, which can be used to compare the importance of different diseases, injuries, and risk factors as part of health decision-making and planning processes. The DALY was used by the WHO in the first Global Burden of Disease Study in 1990 (Murray & Lopez 1997) and has become an established metric to quantify and compare the population health burden of diseases between countries, regions, and population groups. The DALY has also been widely used for priority setting and evaluating the impacts of specific public health interventions on reducing disease burdens (WHO 2009). However, its use to set a fixed regulatory target for a specific route of pathogen exposure (drinking water) is a novel application (Gibney *et al.* 2013).

The concept of applying a health-based target using the DALY metric to drinking water quality was discussed in a

2003 background document (Havelaar & Melse 2003; WHO 2004) in the lead-up to formulation of the 3rd edition of the WHO Guidelines for Drinking-water Quality. This 2003 report presents estimates of the DALY burden for several microbial pathogens that may be transmitted by drinking water, and for cancers potentially caused by two chemical contaminants (naturally occurring arsenic and bromate generated by ozone disinfection). In discussing selection of an appropriate 'reference level of risk' (health target), a lifetime excess risk of one excess cancer death per million people is mentioned as 'a widely used threshold for environmental cancer risk assessment'. In relation to translating this fatality risk to DALYs, the authors note that the average number of life years lost per cancer death in the Netherlands (for all types of cancer) is 13.8 years. Therefore, counting only mortality and disregarding any contribution of morbidity to the health burden, an equivalent target of 13.8 DALYs per million people over a lifetime of exposure (70 years), or about 0.2×10^{-6} DALYs per person per year, can be derived on this basis, although the calculation is not presented in this publication.

The level of cancer risk used in the above example, however, is 10-fold lower than that conventionally adopted by the WHO for exposures to genotoxic carcinogens. Accordingly, in the 3rd edition of the WHO guidelines (WHO 2004), the target for microbial risk was selected by analogy to the reference level of a 10^{-5} lifetime excess cancer risk (one excess case of cancer per 100,000 population ingesting drinking water containing the carcinogen at the guideline value over a lifetime). This is an upper-bound estimate for cancer risk, approximating the 95 percentile limit. The specific cancer cited as an example is renal cell cancer, which may arise from exposure to bromate in drinking water. A figure of 11.4 DALYs per cancer case is said to be derived from a publication comparing microbial and cancer risks (Havelaar *et al.* 2000), but this number does not actually appear in this reference, rather a median value of 10 DALYs per cancer case is given in the text. However, using a value of 11.4 DALYs per cancer case and a tolerable cancer risk of 10^{-5} per 70 year life span produces an estimate of 1.6×10^{-6} DALYs per person per year, and this is then rounded down to 1.0×10^{-6} DALY per person per year. As the DALY impact of illness varies from one pathogen to another, adoption of a uniform DALY target for each of the three categories of waterborne pathogen results in different rates of illness (and thus different rates of infection) being tolerated for each category. The WHO guidelines also note that appropriate target values should be based on local circumstances, and that setting a stringent target for water quality may have little effect on the overall disease burden if high rates of pathogen transmission occur by other routes of exposure. Health targets in the range of one DALY per 100,000 to one DALY per 10,000 people per year may be suitable as an initial target in such circumstances.

Are the current target levels appropriate?

The setting of a target level for the safety of drinking water (or any other potential hazard to which humans are exposed) recognises that a level of zero risk cannot be achieved, and therefore, some low level of risk must be acknowledged as being 'tolerable' or 'acceptable'. In a background publication for the 2003 WHO Guidelines for Drinking-water Quality, various approaches that may be used to derive tolerable risk levels for regulatory purposes were discussed (Hunter & Fewtrell 2001). These include:

- the risk falls below an arbitrary defined probability;
- the risk falls below some level that is already tolerated;
- the risk falls below an arbitrary defined attributable fraction of total disease burden in the community;
- the cost of reducing the risk would exceed the costs saved;
- the cost of reducing the risk would exceed the costs saved when the 'costs of suffering' are also factored in;
- the opportunity costs would be better spent on other, more pressing, public health problems;
- public health professionals say it is acceptable;
- the general public say it is acceptable (or more likely, do not say it is not); and
- politicians say it is acceptable.

In the case of cancer risks from chemical drinking water, the established guideline levels for both the USEPA and WHO may be viewed as being 'below an arbitrarily defined probability'. The USEPA uses a target range of one in 10,000 to one in 1,000,000 (10^{-4}–10^{-6}) for carcinogens in drinking water (Cotruvo 1988), while the WHO sets

guideline values for genotoxic carcinogens that are consistent with an upper-bound estimate of an excess lifetime cancer risk of one in 100,000 (10^{-5}) (WHO 1993). Cancer risks in this range are considered to be negligible, and not to require further regulatory consideration. To place these risks in context, the current lifetime risk of a person being diagnosed with cancer is of the order of 300,000–400,000 in 1,000,000 (American Cancer Society 2014; Cancer Research UK 2014).

Both the USEPA and WHO microbial health-based targets can be related at least approximately to current regulatory targets for carcinogenic chemicals in water, and just as the target levels for carcinogens correspond to risk levels several orders of magnitude lower than the cancer risks that already exist in the population, so too the target levels for waterborne microbial risk are much lower than the rates of gastroenteritis already experienced in the community. Well operated water supplies in developed nations are likely to have waterborne illness levels below those that can be measured by routine surveillance systems or even by targeted epidemiological studies, and thus, any health gains from improvements to meet the health-based targets can only be inferred by QMRA modelling and not demonstrated by changes in illness rates or health service utilisation.

The stringency of the USEPA target has been questioned on the basis that it was formulated at a time when the magnitude of endemic gastroenteritis was not fully appreciated (Haas 1996), and the WHO target has also been criticised more recently as being overprotective and unlikely to provide quantifiable health benefits despite the potential for considerable public expenditure on water treatment (Mara 2011). If a current level of community gastroenteritis of one episode per person per year is assumed, then the USEPA target would restrict waterborne illness to less than 0.01% of all gastroenteritis (assuming all drinking water supplies operate at the target level), while the WHO target permits a slightly higher level. While one would not argue that current levels of community gastroenteritis should be considered tolerable, it is legitimate to question whether the balance between waterborne gastroenteritis risks and risks from all other sources implied by these targets is appropriate in terms of regulatory effort, public expenditure, and achievable health benefits.

Implications of changes in knowledge or practice

The scientific and clinical data that underpin both the USEPA target and the WHO target represent the best information available at the time each target was formulated. However, as knowledge increases and clinical practice changes, it may become necessary to revise these targets or reconsider how they are constructed. Both targets may be affected by changes in the data available for use in QMRA for the reference pathogens. For example, QMRA for *Cryptosporidium* was initially limited to human dose–response data for a single strain of *Cryptosporidium parvum* (the IOWA strain) (DuPont *et al.* 1995). In subsequent years, more human feeding trials have been performed and data are now available from two additional *C. parvum* strains (Okhuysen *et al.* 1999) and one *C. hominis* strain (Chappell *et al.* 2006). These studies showed a range of ID_{50} values for *C. parvum* isolates from 9 to 1,042 oocysts, illustrating the high variability between strains. In this situation, it is unclear whether the QMRA model used for target setting should be revised to use the 'worst' strain (most highly infective) in order to provide maximum protection, or perhaps a strain from the middle of the infectivity range. Perhaps, the model should remain unaltered, given the high degree of health protection already built in to the current target level. Alternatively, the additional knowledge could be incorporated by deriving a dose–response curve for a mixture of strains.

The basis of the WHO DALY target may also be affected by changes in clinical practice or increasing knowledge about the health impacts of infections. Rotavirus was selected as the reference virus because of its relatively high clinical impact in terms of severe illness and mortality rate in young children. However, an effective rotavirus vaccine has been available since the mid-2000s, and is being progressively incorporated into childhood vaccination programmes worldwide. This has resulted in a significant decline in both morbidity and mortality for rotavirus, which in turn has reduced the rotavirus DALY burden (Gibney *et al.* 2014). Should the DALY value for rotavirus used in derivation of the WHO target be revised (and water treatment requirements therefore relaxed) in view of this change? Or should the current target be retained as being representative of a 'plausible worst case' viral pathogen, which may emerge in the future?

Another area of knowledge that may have a significant impact on the DALY values for enteric pathogens is the accumulating evidence of clinical sequelae (long-term effects after the initial infection), which develop in some patients after an episode of gastroenteritis. The current WHO DALY calculation for *Campylobacter* infection includes the recognised sequelae of reactive arthritis and Guillain–Barré syndrome, and these illnesses accounted for 39% of the calculated average health burden for cases of symptomatic *Campylobacter* infection (WHO 2011). Recent research indicates that *Campylobacter* infection is also associated with irritable bowel syndrome (IBS), and the health burden for an average case would increase more than four-fold if this illness is also included in DALY calculations (Gibney *et al.* 2014). Evidence for other enteric pathogens is less extensive, but there are indications that IBS may also occur after *Giardia* infections (Wensaas *et al.* 2012) and viral infections (Zanini *et al.* 2012). If IBS is included in calculations of health burden while retaining the one DALY per million people per year target, then pathogen removal requirements for water supplies would increase correspondingly. This would also have the effect of reducing the tolerable level of waterborne disease as a proportion of all gastroenteritis in the community. On the other hand, progressive improvements in the treatment of acute gastroenteritis or sequelae may counterbalance these factors by reducing morbidity and mortality and thus reduce the average health impact for some or all pathogens.

DISCUSSION

The concept of endemic disease from drinking water had not been explicitly considered by health regulatory agencies prior to the 1980s, and thinking about water safety centred on outbreak prevention. However, developments in detection methods for viral and protozoal pathogens, together with evidence from some waterborne outbreaks, gradually led to acceptance of the concept that pathogens in drinking water considered 'safe' by then-current standards could be contributing to the 'background' or endemic rate of gastroenteritis in the community. The development of QMRA techniques permitted estimation of the number of infections that might be caused by exposure to very low concentrations of pathogens in treated drinking water.

Subsequently, the USEPA developed an annual infection risk target to limit the risks of endemic waterborne illness, and the WHO later developed a target based on the health burden of waterborne infections. Both targets can be roughly equated to health targets for carcinogenic chemical contaminants for the corresponding regulations or guidelines. As is the case for chemical contaminants, the disease levels incorporated in these targets are far below the levels that actually occur in the community, and therefore, the health benefits associated with achieving the target for water supplies that are already well operated can only be modelled and not measured.

Whether to adopt an infection risk or a DALY health target for water-related exposures, as well as which numerical values to choose, are decisions for individual jurisdictions to make based on economic, environmental, social, and cultural conditions. Knowledge of the origins for the numbers currently suggested as target values helps to understand the limitations of each quantitative choice and sheds light on the data assumptions that have been incorporated in developing these figures. Understanding the origin of the infection and DALY health targets for water-related exposures and the estimated magnitude of waterborne disease to the overall level of gastroenteritis in the community helps to determine the relevance and applicability of target values to individual settings. Consideration also needs to be given to how increasing scientific knowledge and changes in disease impacts may influence chosen target values. The information provided in this paper provides a context for decision-making about health-based target selection and highlights more generally the relative and judgemental nature of defining tolerable risk.

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Adoption of a microbial health-based target for Australian drinking water regulation

Joanne O'Toole, Martha Sinclair, Katherine Gibney and Karin Leder

ABSTRACT

The health-based targets of 1 in 10,000 for infection and 10^{-6} disability adjusted life years (DALYs) per person per year are increasingly being considered, or have already been adopted, to define microbial safety targets for water. The aim of this paper is to convey information about how these two targets compare by converting each of the target values to a common metric. The metric chosen for viral (rotavirus and norovirus) and protozoan (*Cryptosporidium*) reference pathogens is the estimated maximum number of annual drinking water-associated cases of acute diarrhoeal disease tolerated. For the reference bacterial pathogen *Campylobacter*, sequelae to acute diarrhoeal illness have also been considered in estimating the tolerable number of cases for the DALY target. Also investigated is whether non-compliance with targets would be detected as a waterborne disease outbreak by the health surveillance system in an extreme hypothetical situation whereby all tolerable cases per annum occurred as a single event. The paper highlights that verification of compliance with targets cannot be demonstrated by the absence of reported drinking water-associated outbreaks alone and concludes that introduction of a quantitative health-based outcome for drinking water in Australia would help improve water quality management by providing a common goal directly linked to health outcomes.

Key words | DALY, health-based targets, water safety

Joanne O'Toole (corresponding author)
Martha Sinclair
Katherine Gibney
Karin Leder
Department of Epidemiology and Preventive Medicine,
School of Public Health and Preventive Medicine,
Monash University,
99 Commercial Road,
Victoria 3004,
Melbourne,
Australia
E-mail: *joanne.otoole@monash.edu*

INTRODUCTION

Currently, Australia is considering adoption of a microbial health-based target for its drinking water supplies. The target being considered is 10^{-6} disability adjusted life years (DALYs) per person per year, the same target as defined in the World Health Organization guidelines for drinking water quality (WHO GDWQ) (WHO 2011) and already adopted in Australian guidelines for water recycling (AGWR) (NRMMC/EPHC/AHMC 2006). To date, only Canada has adopted this target to set drinking water treatment goals (Health Canada 2013). The alternative microbial health-based target, which underpins the USEPA drinking water standards, is 1 infection per 10,000 people per year (Macler & Regli 1993) and is the basis of drinking water regulation in the Netherlands (Anonymous 2001, 2005) and New Zealand (Ministry of Health 2008).

As a consequence of the proposed extension of using the 10^{-6} DALY target for drinking water regulation in Australia, questions have arisen about the implications of its adoption and the applicability of the alternative target of 1 infection per 10,000 people per year. Although currently there is no prescribed microbial health outcome target for drinking water regulation in Australia (NHMRC 2004), some larger urban water authorities have nevertheless adopted 1 infection per 10,000 people per year as their operational target for drinking water treatment. Adoption of this target has often occurred under the guise of industry best practice, sometimes without full understanding of the underpinnings of the target itself. Wide familiarity with the 10^{-6} DALY target might be expected because it has been embedded in recycled water guidelines since 2006, but deliberate supplementation of drinking water with recycled water from sewage effluent has not yet occurred in Australia, so implementation of the target has been limited to non-potable recycled water applications. Hence, many water authorities

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are newly considering the relevance of the numerical value for drinking water drawn from conventional sources, some of which contain partially or secondary treated wastewater and thus, effectively represent situations of unintended indirect potable reuse.

As part of the process of considering incorporation of a health-based target in Australian drinking water guidelines, a research study was funded to quantify the average burden of single cases of diarrhoeal disease (DALY per case) associated with selected reference pathogens (designated human-infectious species from each of bacterial, viral and protozoan classes) *Campylobacter*, rotavirus, norovirus and *Cryptosporidium*, using Australian epidemiological and clinical data (Gibney *et al.* 2014). Accordingly, it is now possible to compare the estimated maximum tolerable number of cases of diarrhoeal disease transmitted by drinking water for each target using Australian data for these reference micro-organisms.

The aim of this paper is to convey information about how the two health-based targets compare by converting each of the health-based target values to a common metric. The metric chosen for rotavirus, norovirus and *Cryptosporidium* is the estimated tolerable maximum number of annual drinking water-associated cases of acute diarrhoeal disease. While this metric allows for a valid direct comparison of target values in relation to these reference micro-organisms, where acute diarrhoeal disease is generally the only/most significant disease end point, this is not the case for *Campylobacter*. This is because an estimated high burden of disease is associated with sequelae such as Guillian–Barré syndrome (GBS), reactive arthritis (ReA) and post-infectious irritable bowel syndrome (PI-IBS), which can develop following the diarrhoeal illness. Accordingly, for *Campylobacter* we present three different values for the DALY target for comparison purposes: estimated tolerable maximum number of cases of acute diarrhoeal disease; estimated maximum number of cases of acute diarrhoeal disease inclusive of the related disease burden (db) of GBS and ReA; and, finally, the estimated maximum number of cases of acute diarrhoeal disease incorporating the estimated related db of GBS, ReA, as well as PI-IBS.

Acknowledging that both the infection and DALY health-based targets are expressed as annual targets, we then use the estimated maximum number of annual drinking water-associated cases tolerated by each target to investigate a hypothetical situation whereby drinking water-associated cases are not spread throughout the whole year but occur as a single event per water supply. By 'loading' all of the tolerable drinking water-associated cases per water supply onto a single event, such as might occur as a consequence of a short duration drinking water contamination event (whether resulting from source water contamination and inadequate water treatment or from distribution system contamination) we can explore whether non-compliance with either of these targets would be detected by the health surveillance system as a waterborne disease outbreak in this most extreme hypothetical situation.

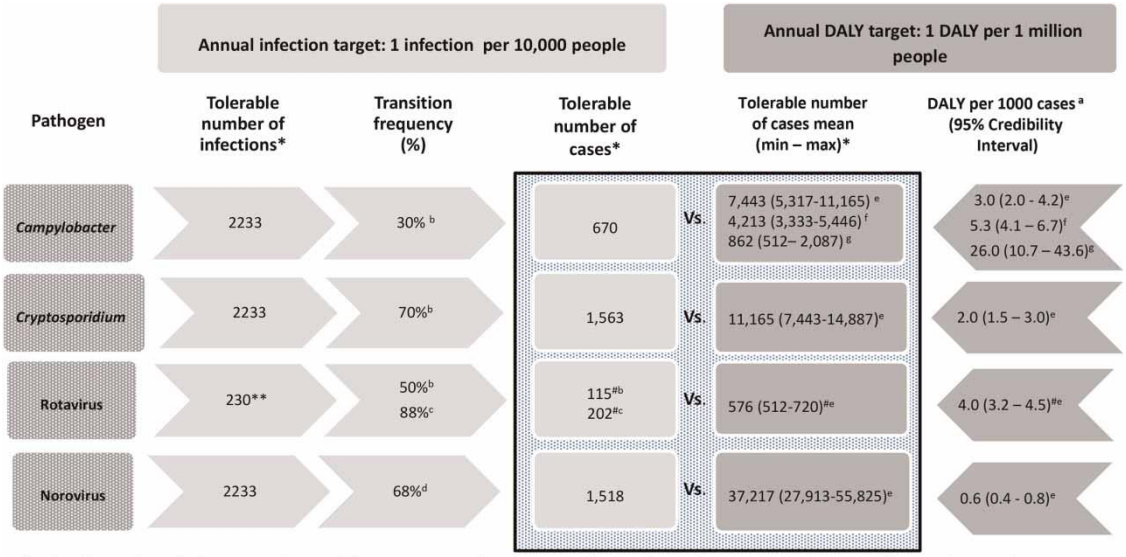
Such an exploration is valuable when communicating the implication of adoption of a health-based target for drinking water, whether an infection or DALY target, to water managers. This is because it allows for enhanced understanding of the relationship between infection and DALY target values and more loosely defined or 'de facto' health-based targets such as 'non-detection of drinking water-associated outbreaks of diarrhoeal disease by the routine health surveillance systems'. Both infection and DALY targets in combination with quantitative microbial risk assessment (QMRA) processes can be used to estimate the amount of water treatment that is required to meet target values, but this is impossible to perform or verify with more loosely defined health-based targets because of their lack of sensitivity and/or specificity. Furthermore, while water managers have familiarity with the need to collect data about the concentration of pathogens in source waters for input to QMRA processes and also appreciate the importance of maintaining operational controls of water treatment processes (e.g., maintenance of chlorine residuals) to meet health targets, these considerations are separate to the process of selecting a health target to implement. The analysis presented here serves to elaborate on the connection between health target selection and implementation. It also highlights the reasoning which underlies drinking water treatment and control, which is to reduce the number of cases of drinking water-associated diarrhoeal disease to an agreed on, predetermined, acceptable level.

While this evaluation uses Australian data it is also relevant to other jurisdictions contemplating adoption of the WHO drinking water DALY target and those interested in exploring the relationship between an infection and DALY health-based target. Data for other jurisdictions can be directly compared with Australian data and computations adjusted accordingly.

COMPARING THE MAXIMUM TOLERABLE NUMBER OF CASES OF DRINKING WATER-ASSOCIATED DIARRHOEAL DISEASE THAT EACH TARGET PERMITS

For the 1 infection per 10,000 people per year target, to convert the maximum tolerable number of infections to numbers of cases of diarrhoeal disease, information about the proportion of infected persons that develop disease is required. For the DALY target, information required to estimate the maximum tolerable number of cases is a 'DALY per case'. The 'DALY per case' is the average burden of a single case of disease and it is different for each microorganism, reflecting the severity and duration of disease outcomes and whether or not the disease comprises acute effects only, or a combination of acute and longer-term effects.

The relationship between the infection and DALY targets and the estimated maximum tolerable number of cases of diarrhoeal disease associated with consumption of drinking water for each target is shown in Figure 1. Transition percentages from infection of susceptible persons to disease states used for *Campylobacter* (30%) and *Cryptosporidium* (70%) are the same as those used in WHO (2011) and in AGWR (NRMMC/EPHC/AHMC 2006) guidelines, with these values originating from studies conducted in the Netherlands (Havelaar *et al.* 2000) and USA (Okhuysen *et al.* 1998), respectively. For rotavirus, the transition percentage in WHO GDWQ (50%) differs from that used in AGWR (88%), with the latter attributed (Havelaar & Melse 2003) to a hospital study in the early 1980s pertaining to children less than 36 months old (original reference source not specified but believed to be Schaap *et al.* (1985), as cited in Koopmans & Van Asperen (1999)). A value of 50% for transition frequency, as used in WHO GDWQ, is consistent with transition frequency values used by others (Gerba *et al.* 1996). Both 50–88% transition frequencies have been used



* Tolerable number of infections and cases of illness per annum based on Australian total population 2010 = 22,330,000; ** Australian population < 5 year old in 2010 = 2,303,000 (10.3% of total population); [a] Gibney et al., 2014; [b] Transition proportions from infection to disease in susceptible individuals (WHO Guidelines for Drinking Water Quality 2011); [c] Transition proportions from infection to disease in susceptible individuals (Australian Guidelines for Water Recycling 2006); # Rotavirus values for unvaccinated children < 5 years old; [d] Norovirus transition proportion from infection to disease in susceptible individuals (Teunis et al., 2008); [e] disease burden of acute gastroenteritis (AGE); [f] disease burden of AGE plus reactive arthritis (ReA) and Guillian-Barré Syndrome (GBS); [g] disease burden of AGE plus ReA; GBS and post-infectious irritable bowel syndrome

Figure 1 | Comparison of health targets maximum tolerable number of cases per year in Australia.

to estimate the maximum number of cases tolerated by the infection target shown in Figure 1. DALY per case values are given for the three reference pathogens used in the WHO and AGWR guidelines (*Campylobacter*, rotavirus, *Cryptosporidium*) and norovirus based on Australian data (Gibney *et al.* 2014). Of note is that for rotavirus only, the estimation of the maximum number of cases tolerated by each target pertains to the Australian 2010 under 5-year-old population because this is the section of the population primarily affected by this virus and subsequent immunity is conferred to those that have been infected (NRMMC/EPHC/AHMC 2006). The DALY per case value presented and used for rotavirus calculations in Figure 1 was determined using 2010 data and is for an unvaccinated under 5-year-old population despite rotavirus vaccination having been available free of charge to all Australian infants born after 1 May 2007 (Gibney *et al.* 2014). As vaccine uptake becomes close to universal for this age group in Australia, DALY per case values will decrease, potentially resulting in an increase in the tolerable maximum number of cases of viral gastroenteritis. Calculations for norovirus (a candidate reference virus but not used in either AGWR or WHO GDWQ) were also included because clinical data about norovirus were available and although causing less severe disease than rotavirus, norovirus is the most prevalent cause of viral gastroenteritis in Australia. Indeed, a recent systematic review showed that norovirus contributes substantially to the global burden of acute gastroenteritis (AGE) across all settings and age groups, causing an estimated 18% (95% confidence interval 17–20) of all cases of gastroenteritis (Ahmed *et al.* 2014). The norovirus transition percentage (68%) used to 'convert' maximum tolerable number of infections to estimated maximum tolerable number of cases of diarrhoea associated with consumption of drinking water is based on work by Teunis *et al.* (2008), and is consistent with results (67% of infected persons developing viral gastroenteritis) obtained in a more recent study (Atmar *et al.* 2014).

As shown in Figure 1, the 10^{-6} DALY per person per year target is more lenient than the target of 1 infection per 10,000 people per year for all micro-organisms, except in the case of *Campylobacter* when PI-IBS is included and 95% credibility interval (CrI) of the DALY per case estimate is factored into calculations. The estimated tolerable total number of cases for the DALY target is 862 with a 95% CrI of 512–2,087 cases when the db of ReA, GBS and PI-IBS are included, compared with the infection target with an estimated maximum tolerable number of cases of 670.

WATER TREATMENT

Required pathogen percentage removal and/or inactivation for adequate water treatment for the infection target is calculated according to the difference between the maximum numbers of infections tolerated by the health target and the estimated number of infections predicted to arise from consumption of untreated drinking water. Similarly, for the DALY target, the difference between the maximum db tolerated by the health target and the estimated burden of disease per annum estimated using QMRA determines the water treatment requirements. Differences are calculated separately for each class of pathogen (i.e., bacteria, viruses and protozoa) because of their differential responses to water treatment and disinfection processes. Determination of the water treatment train to meet the relevant health target is based upon the predominating pollution sources in the catchment and the treatment processes best suited for their removal and/or inactivation.

Reference pathogens are selected as plausibly representing human-infectious pathogens that are the most prevalent, most difficult to remove by water treatment and most virulent waterborne agents in their class. In determining water treatment requirements for reference pathogens, all other members of the class can be assumed to also be adequately controlled. Selection of reference pathogens is also governed by other considerations such as the availability of relevant data. For example, the AGWR acknowledges that there is no single virus that represents an ideal reference pathogen for this class and uses an amalgam of dose–response data for rotaviruses and occurrence data for adenovirus. This decision is justified by rotaviruses having the highest pathogenicity of candidate viruses, the availability of Australian cell culture data for adenovirus in sewage and, because adenovirus appear more resistant to disinfection than other viral agents (NRMMC/EPHC/AHMC 2006). Similar rationale for rotavirus selection as a reference virus, but for drinking water, is presented in WHO GDWQ with enteroviruses, not adenoviruses, preferred to provide

source water occurrence data based on there being a routine culture-based analysis for measuring infective particles and their high concentration in waters contaminated by human waste (WHO 2011). Norovirus was not included in AGWR as a reference pathogen based on there being no dose–response model at the time of guideline formulation, as well as the lack of availability of a routine culture-based method measuring infective particles. This situation has since changed with the availability of 50% human-infectious dose for norovirus (Teunis *et al.* 2008; Atmar *et al.* 2014), now allowing for an estimate of the number of resultant infections/db of this viral pathogen for a given source water quality for comparison with the target value. However, there is still no routine culture-based method for quantifying norovirus infectious units in source water. This limitation is referred to in the WHO GDWQ as a barrier to selection of norovirus as a reference viral pathogen, necessitating the use of another human-infectious virus candidate for the estimation of their concentration in source waters (WHO 2011).

Numbers of infections arising from consumption of untreated drinking water are obtained by independently applying QMRA processes to the water supply in question, which requires information about the concentration of reference pathogens in source water, volume and frequency of exposure to drinking water, numbers of each pathogen required to initiate infection (dose–response) and the proportion of the population that is susceptible to infection. To convert the number of infections arising from consumption of untreated drinking water to DALYs for comparison with a DALY target value, additional information is required: transition percentage from infection to disease state and estimates of DALY per case estimates for each reference pathogen.

Because a higher number of cases of diarrhoeal illness is tolerated when the DALY rather than the infection target is applied for *Campylobacter,* rotavirus, norovirus and *Cryptosporidium*, calculated water treatment log 10 pathogen removal/inactivation requirements to achieve target compliance with the DALY target are less stringent than for the infection target (with the possible exception of *Campylobacter* when PI-IBS is included in the DALY per case estimate of db). However, this does not have a practical impact on water treatment requirements. In contrast to viruses and protozoa, bacterial pathogens as represented by the reference pathogen *Campylobacter* do not drive water treatment requirements due to their lesser persistence and the greater ease with which they are removed/inactivated. Accordingly, Australian water supplies currently using the target value of 1 infection per 10,000 people per year to set their operational targets for drinking water treatment and complying with it will, as a matter of course, also comply with the 10^{-6} DALY per person per year health-based target.

Achievement of the selected health-based target depends not only on the design capability of the drinking water treatment system, but on ensuring the reliability of the day-to-day performance of the system. Thus, water safety plans, operational controls and process monitoring assume a crucial role in ensuring that the required levels of overall system performance are consistently achieved. In addition, it is essential to maintain and manage the water distribution system effectively to prevent recontamination of treated water.

The role of health-based targets in drinking water regulation is to limit the number of cases of drinking water-associated illness to predetermined acceptable levels. While it is important to prevent peak contamination events to avert waterborne outbreaks, it is also important to ensure that water treatment and distribution system protection is continuously effective to limit the number of sporadic cases during baseline (normal) conditions (i.e., endemic disease). This is because per annum, endemic disease may represent a greater proportion of drinking water-associated disease than outbreaks and, accordingly, a higher db. In countries such as Australia with a low level of endemic diarrhoeal disease, even specially designed high-quality epidemiological trials have limited ability to detect drinking water-associated cases of diarrhoea (Sinclair *et al.* in press). Routine disease surveillance systems are even less sensitive and, at best, will only detect a proportion of drinking water-associated outbreaks.

HEALTH TARGETS EXPRESSED AS A PROPORTION OF PATHOGEN-SPECIFIC GASTROENTERITIS CASES

Table 1 shows the tolerable number of cases per year for each health target expressed as a proportion (%) of total

Table 1 | Target (tolerable cases) as a proportion of total AGE cases

Reference pathogen	Total estimated number AGE Australia (Gibney *et al.* 2014)	Number of tolerable AGE cases for infection target expressed as % of estimated number of AGE cases in column 2	Number of tolerable AGE cases for DALY target expressed as % (95% CrI) of estimated number of AGE cases in column 2
Campylobacter	774,003	0.09%	0.96% (0.69–1.44%)[a]
Campylobacter (burden of disease of GBS and ReA included)	774,003	0.09%	0.54% (0.43–0.70%)[b]
Campylobacter (burden of disease of GBS, ReA and PI-IBS included)	774,003	0.09%	0.11% (0.07–0.27%)[c]
Cryptosporidium	195,495	0.80%	5.71% (3.81–7.61%)[a]
Rotavirus	172,739[d]	0.07%[e] (0.012%[f])	0.31% (0.25–0.61%)[a]
Norovirus	2,180,145	0.07%	1.71% (1.28–2.56%)[a]

[a]Calculations consider db for AGE only.
[b]Calculations incorporate db for GBS and ReA.
[c]Calculations incorporate db for GBS, ReA and PI-IBS.
[d]Total GE cases among <5-year-olds in 2010.
[e]Number of tolerable AGE cases based on 50% transition from infection to disease (WHO 2011).
[f]Number of tolerable AGE cases based on 88% transition from infection to disease (NRMMC/EPHC/AHMC 2006).

cases of gastroenteritis estimated for each of these four pathogens annually in Australia. These results show that the infection target of 1 infection per 10,000 people per year allows for less than 1% of estimated diarrheal disease per annum for each pathogen to be attributable to consumption of drinking water. The 10^{-6} DALY per person per year target allows for up to approximately 6% of diarrhoeal disease caused by *Cryptosporidium* to be associated with consumption of drinking water and approximately 2% for norovirus. The DALY target for drinking water-associated *Campylobacter* disease represents less than 1% of the estimated total annual cases of *Campylobacter*-associated diarrhoeal disease. For rotavirus, the DALY target represents approximately 0.3% of the estimated total annual cases of diarrhoeal disease in the unvaccinated under 5-year-old population.

These calculations represent the waterborne proportion of gastroenteritis for each pathogen that would be predicted if the entire Australian population consumed drinking water which barely complied with the relevant health-based target. The current level of waterborne disease in Australia is unknown, and although few disease outbreaks from public drinking water supplies have been recorded, the limitations of health surveillance systems mean that the occurrence of unrecognised outbreaks in some small water supplies remains a possibility even if the estimated maximum annual number of cases occurred as a single event.

COMPLIANCE WITH HEALTH-BASED TARGETS AT AN INDIVIDUAL WATER SUPPLY LEVEL

Figure 1 gives the estimated maximum tolerable number of diarrhoeal cases per year associated with drinking water consumption for the whole of Australia to meet each of the two targets. Table 1 shows the small percentage of the total that they represent. When disease transmission through a single source such as drinking water occurs at levels similar to or below the background level of disease transmission from all sources, the limits of health surveillance to detect drinking water-associated cases have been reached. If it is assumed that a water treatment failure could lead to the maximum tolerable number of cases per annum occurring at one time, the number of cases representing non-compliance with the health target for a population of 1,000 is extremely small (e.g., two cases of waterborne norovirus would constitute non-compliance with the 10^{-6} DALY target). When this is considered against the 'background' rate of illness for this pathogen (which can be calculated as 98 cases per year or an average of two cases

per week if spread evenly over the year in a population of 1,000) it is evident that such an event is unlikely to be recognised either by local health professionals or by the much less sensitive routine surveillance systems for infectious disease. Even in a population of 1,000,000, and again making the assumption that all cases occur simultaneously, 2,000 cases of norovirus gastroenteritis (representing non-compliance with the 10^{-6} DALY target) might not be recognised as being drinking water associated, depending upon the severity of diarrhoea and the proportion of affected people seeking medical care, variation in incubation periods, geographical spread of cases and/or the presence of any concomitant non-drinking water outbreaks.

Accordingly, the absence of waterborne outbreaks of gastroenteritis alone does not assure target compliance, particularly for water supplies serving small populations when single or few excess cases per year represent non-compliance with the target. Thus, assurance must be additionally achieved by using a multi-barrier approach to water supply management and using QMRA as a means of appropriately directing efforts to reduce pathogen risks throughout the water supply system.

The ability of individual Australian water authorities to comply with a 10^{-6} DALY per person per year microbial target will vary. For smaller water authorities, more stringent operational controls and possibly additional water treatment processes to those currently implemented may be required. Larger water authorities already using a target value of 1 infection per 10,000 people per year to set their operational targets for drinking water treatment and with a multi-barrier approach to water supply management will achieve compliance with the 10^{-6} DALY per person per year target. Others, using alternative but nonetheless rigorous operational targets but ones not specifically linked to a quantitative health-based end point, are also likely to comply with, or at least approach compliance with, a 10^{-6} DALY per person per year microbial target. Smaller water authorities are likely to have more difficulty demonstrating compliance with the target, associated with insufficient water quality monitoring data for input to QMRA processes. Default ranges in pathogen levels for source waters and treatment performance currently available (despite problems or shortcomings) are being further developed, and provide a means to determine required water treatment processes using QMRA for target compliance where collection of relevant data for individual water supplies is not feasible.

While the best available data have been used here to estimate the maximum tolerable number of cases for each target, derived numbers should be regarded as approximations because of the inherent variability and uncertainty of input data. Nevertheless, they allow the relative magnitude of case numbers and proportions of total gastroenteritis for the two target values to be compared and provide valuable information. Also, while 95% credibility limits are given for the DALY per case estimates, reflecting the variability in clinical input data used for their determination, the infection and DALY target values themselves are expressed as single maximum values (1 infection per 10,000 persons per year and 10^{-6} DALY per person per year, respectively). Furthermore, transition percentages from infection to disease states for the selected reference pathogens from the literature likewise are point estimates, allowing the maximum tolerable number of cases for the infection target to be expressed only as a single (estimated) number.

This discussion should not be construed as advocating the adoption of a particular microbial health-based target because of its stringency or leniency. Rather, it highlights the principle behind health-based target adoption and shows the infection target to be more stringent than the DALY target. It also serves to highlight that adoption of the 10^{-6} DALY per person per year target for drinking water in Australia will not preclude water authorities that currently use the infection target as their 'working target' from continuing to surpass the DALY target if this is already the case, or from future adoption of water management practices that reduce microbial risks even further than is required for target compliance.

While issues such as data shortfalls (e.g., dose–response data for a range of relevant pathogens; pathogen concentration in source waters; proportion of the population susceptible to infection) for QMRA or the QMRA process itself are important for determining appropriate water treatment, they are common to both the infection and DALY targets. Also they are somewhat separate to the principle of adopting a quantitative health-based target for drinking water, so have not been elaborated on here. When using

the infection target, infection is the end point of computations with the value obtained using QMRA directly compared with the target value of 1 infection per 10,000 people per year to determine water treatment requirements. When using the DALY health-based target, further computations are required before a comparison of QMRA values and the target value can be made. These include sequential conversion of the estimated number of infections based on concentrations of pathogens in source water to number of symptomatic cases, followed by conversion to burden of disease per pathogen expressed as total DALYs per annum using DALY per case estimates. We have used the estimated maximum number of annual drinking water-associated cases of acute diarrhoeal disease tolerated by each of the infection and DALY targets (including sequelae for *Campylobacter*) as the metric for comparison, even though this represents an additional 'conversion' step for the infection target, not usually performed. However, in doing this we have used the same transition percentages (from infection of susceptible persons to disease states) as used in the QMRA process when converting the estimated number of infections associated with consumption of untreated drinking water to estimated case number and then, to estimated DALYs.

CONCLUSION

Introducing a quantitative health-based outcome target for drinking water in Australia would be an improvement in terms of water quality management. While verification of compliance with a target of either 1 infection per 10,000 people per year or 10^{-6} DALY per person per year cannot be demonstrated by the absence of reported drinking water-associated outbreaks alone (particularly for water supplies serving small populations where the maximum estimated number of tolerable cases per annum in absolute terms is very low), introduction of a quantitative target provides a common goal directly linked to health outcomes for all drinking water supplies. Available evidence suggests that the 10^{-6} DALY per person per year microbial target will be met by larger, well-resourced urban water authorities in Australia who are already using and complying with the infection target. Also, some smaller water supplies will already be meeting the infection and/or the DALY target based on high microbial quality of their source water and good water treatment and operational practices. Others, based on poor source water quality and/or limited funds to determine and/or install and operate appropriate water treatment processes, may not be able to immediately meet DALY target values but may achieve this through incremental staged improvements in water supply treatment and operation.

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