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Short Report

How much does tuberculosis cost? An Australian healthcare perspective analysis

EC Chan, A Nolan, JT Denholm

Abstract

Tuberculosis (TB) remains a disease of high morbidity in Australia, with implications for both public health and the individual. Cost analyses is relevant for programmatic evaluation of TB. There is minimal published TB cost data in the Australian setting. Patients with drug sensitive active pulmonary TB (DS-PTB) and latent TB (LTBI) were enrolled in a single tertiary referral centre to evaluate healthcare provider costs. The median cost of treating drug susceptible pulmonary TB in this case series was 11,538 AUD. Approximately 50% of total costs is derived from inpatient hospitalisation bed days. In comparison, the average cost of managing latent TB was 582 AUD per completed course. We find the median provider cost of our DS-PTB treatment group comparable to costs from other regions globally with similar economic profiles. A program designed to detect and treat LTBI to prevent subsequent disease may be cost effective in appropriately selected patients and warrants further study.

Keywords: Tuberculosis, TB, Healthcare cost, Management, Latent tuberculosis

Background

Despite significant advances in tuberculosis (TB) worldwide, globally it remains a disease of high morbidity and mortality[1-2]. In Australia TB incidence is low but has not declined in recent years, and it continues to have an important impact on affected individuals, families and healthcare systems[3]. While outcome assessment is critical for programmatic management of TB, economic evaluation is equally important, including assessment of population-level interventions to treat and prevent disease, with unavoidable pressures within most healthcare systems to optimise the allocation of limited resources.

ABBREVIATIONS

AUD	Australian dollars
DS-PTB	Drug sensitive pulmonary tuberculosis
HREC	Human research ethics committee
LTBI	Latent tuberculosis infection
MBS	Medicare Benefits Scheme
MDR TB	Multidrug resistant tuberculosis
PTB	Pulmonary tuberculosis
TB	Tuberculosis
VTP	Victorian Tuberculosis Program

Recent meta-analyses provide a global perspective of TB management costs[4-5]. While data regarding TB management in developing world settings are readily available, less data has been produced in Australia with the most recent published estimates of management cost now two decades old[6]. Timely and locally specific information is required to inform current healthcare practices, and guide effective and efficient programmatic management. This paper therefore seeks to provide an accurate and contemporaneous cost evaluation of managing TB in an Australian setting.

Methods

The aims of this study were to calculate healthcare system-level costs for the treatment of cases of pulmonary TB (PTB) and latent TB (LTBI) in an Australian setting.

Ten patients with drug sensitive (DS) PTB were sequentially included in this retrospective record review. All patients received care at the Royal Melbourne Hospital, a single tertiary referral centre providing both inpatient and outpatient management care of TB. Patients were eligible for inclusion if they had completed treatment in the previous 12 months. There were no specific exclusion criteria. A single case of multidrug resistant (MDR) TB within the same enrolment time period was included to broadly illustrate the differences in cost. Finally, a prospectively collected

consecutive series of 100 patients commencing LTBI therapy at the same institution had their management costs reviewed[7].

All costs were calculated in Australian Dollars (AUD). Costs were calculated from first presentation to the hospital for investigation of suspected pulmonary TB, until completion of treatment care. Costs were calculated from the perspective of the healthcare system, defined as provider costs. The 2014 Medicare Benefits Scheme (MBS) item numbers were used to provide fee structures for diagnostic investigations. Hospitalisation costs were taken from previously published Australian costing studies, reporting a cost per bed day of 562 AUD for general medical admissions, and 3,021 AUD per Intensive Care Unit bed day[8-9]. Direct pharmaceutical costs for TB therapy were provided by the Victorian Tuberculosis Program (VTP).

In addition to direct medical costs, all individuals diagnosed with TB in Victoria have public health management conducted by the VTP. This individualised VTP service encompasses contact tracing, adherence, and psychological support. Entries from electronic case notes were used to review the public health activities associated with each case, in order to attribute a cost figure. Aggregated VTP ancillary costs, including administrative and transport expenses, were averaged over a three-year period (2012-2014) and distributed evenly across all patients diagnosed with TB. As some variation was anticipated between individual cases, median costs are presented.

This report was approved by Melbourne Health human research ethics committee (HREC) as a quality-assurance project, (QA2012219). VTP data was incorporated as a programmatic audit, and as such, no additional ethics approval was required under the rules of our institution.

Results

The age of patients who completed standard therapy for DS-PTB ranged between 21 and 71, with a median age of 35. Other patient characteristics are shown in table 1.

The median cost of treating DS-PTB in this case series was 11,538 AUD [range 5,820 – 170,119]. It was noted that one outlier case cost AUD 170,119. Eight out of ten cases cost less than AUD 17,000. Median provider subset costs and the relative percentage of the total cost are listed in Table 2. Hospital admission is the single largest component of provider costs. Community-based VTP services account for around less than 15% of the total cost.

The total cost of managing a single multidrug resistant TB patient was calculated to be 258,089 AUD. Of the 100 consecutive latent TB patients enrolled for treatment, 93 successfully completed their treatment course, with an average completed treatment cost of 582 AUD (Table 2).

Discussion

This report has considered costs in managing TB at a healthcare system level in contemporary, metropolitan Australia. For drug sensitive pulmonary TB cases, approximately 50% of cost was derived from inpatient hospitalisation bed days. Efforts to reduce the duration of hospital stay would correspondingly reduce associated costs. This however, must be counterbalanced against potential harms, such as increasing the risk of community TB transmission. In our experience, outreach nursing support programs, such as one provided by the VTP are an invaluable resource. Further work should be done to ascertain the cost-effectiveness of such programs.

Cost of MDR TB management in an Australian setting has not previously been estimated. We

Table 1: Characteristics of patients in this study managed for drug-sensitive pulmonary TB, and latent TB infection

Demographics and clinical characteristics	DS pulmonary TB (median and range)	Latent TB (median and range)
n	10	100
Age, years	35 (21-71)	29 (16-72)
Male (%)	6 (60%)	58 (58%)
Australian born (%)	1 (10%)	14 (14%)
Bronchoscopic evaluation (%)	3 (30%)	NA
Duration of hospitalisation (days)	8.5 (0-226)	NA
Duration of anti-TB therapy (months)	6 (6-9)	9 (1-9)
Number of outpatient medical reviews	11 (4-15)	4 (1-6)

Table 2: Representation of the breakdown of provider costs by subset for latent TB (n=100), pulmonary TB (n=10), and MDR TB (n=1).

Provider subset cost	Latent TB		Active pulmonary TB		Multidrug resistant TB	
	AUD	%	AUD	%	AUD%	total
Diagnostic	141	24	1,408	12	6,250	2.4
Inpatient hospitalisation	-	-	4,777	43	129,822	50.3
Outpatient clinics	313	54	831	5	2,486	1.0
Medications	128	22	840	7	112,813	43.7
VTP outreach service	-	-	1,640	12	5,124	2.0
VTP ancillary costs	-	-	1,594	14	1,594	0.6
Total		**582**		**11,538**		**258,089**

As median values were used for active pulmonary TB, the sum of costs and percentages do not add up to 100%.

provide a brief snapshot here by examining the cost of managing one patient. Although MDR-TB accounts for less than 3% of active TB cases diagnosed in Australia, the disproportionate cost simply highlights how such cases may impact on local healthcare systems[10]. Typically, 85-90% of diagnosed TB cases in Australia occur in individuals born overseas[3]. Our report found that the cost of LTBI treatment was approximately 1/20th of DS-PTB, suggesting that a program designed to detect and pre-emptively treat LTBI to prevent subsequent disease may be cost effective in appropriately selected patients. Further cost-effectiveness analyses of specific strategies targeting LTBI in our local context is currently underway.

The median cost of our DS-PTB treatment group is consistent with results from a recent meta-analysis of TB management costs globally[4]. Our study only examined cases of pulmonary TB, which perhaps factored in our lower overall cost. In general, the lower median cost from our report suggests a cost-effective TB program in Victoria, Australia. It is difficult to reconcile our findings with historic cost analysis conducted locally[6]. Aside from methodological differences that may have underestimated costs previously, comparisons made on the basis of real-dollar terms over two decades is less likely to be reliable. One case in our cohort had pulmonary TB complicated by development of a brochoesophageal fistula. This necessitated multiple endoscopic surgeries and a prolonged inpatient hospitalisation spanning 226 days. This was the principle factor in the inordinate total cost attributable to this case.

Our report is strengthened by inclusion of detailed individual-level costs and consideration of both public health and clinical management expense. In this low-incidence setting with limited drug resistance, we are limited by small patient numbers, and a focus on adult cases. We noted that most of our PTB cohort had similar durations of hospitalisation, medication treatment, type and frequency of investigations, and number of ambulatory care visits. Hence a larger sample size may not yield substantially different cost findings.

Finally, it should be remembered that the financial burden of TB is not borne merely by healthcare systems but also by the individual. Although TB is treated without charge in Australia, regardless of residency status, patients may have some direct costs (ie. transport costs) and more significantly, indirect and opportunity costs such as loss of capacity to work. These intangible patient costs are challenging to standardise and attribute in monetary terms. However, they form an important component of the true cost of TB and future evaluation of patient-level costs should be a priority.

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Short Report

Prevention of perinatal hepatitis B virus transmission: are we following guidelines?

Peter G Markey, Helena A White, Alexander T Matthews, Charles R Strebor, Vicki Krause

Abstract

It is recommended that infants born to women with hepatitis B infection should have serological review following completion of a four dose vaccination schedule. A review was undertaken on 102 neonates who received hepatitis B immunoglobulin to ascertain the proportion that were fully immunised and then followed up. Of the 66 infants for whom data were available, 65 (98.5%) had appropriately received four doses of hepatitis B vaccine in infancy and a further child had received three doses. Only 19/66 (29%; 95%CI: 18-41%) infants had documented follow-up serology results, one of whom was infected and one of whom was immune through clearance of infection. All children who had no serology documented were traced and offered testing in primary care. Our results demonstrate that although adherence to the vaccination schedule in this group of infants was good, mechanisms for ensuring that infants receive serology testing need to be strengthened.

Keywords: Hepatitis B, Hepatitis B immunoglobulin, Immunity, Vaccination, Vertical infectious disease transmission

Background

Chronic hepatitis B virus (HBV) infection affects over 230 000 Australians, disproportionately affecting Aboriginal and Torres Strait Islander populations.[1] It is associated with adverse health outcomes including progressive liver disease, cirrhosis, and hepatocellular carcinoma. Globally, vertical transmission of HBV is the predominant mode of spread in high prevalence areas and strategies to decrease transmission include administration of hepatitis B immunoglobulin (HBIg) at birth, infant vaccination and the recent introduction of antenatal anti-virals for highly viraemic mothers.[2] In Australia, infants born to HBV-infected mothers are recommended to have testing three months after completion of a four dose vaccination schedule (birth, 2, 4 and 6 months of age) to demonstrate immunity and exclude infection.[3,4] We performed an audit to evaluate vaccination and follow-up serology in infants born to HBV-infected mothers in the Northern Territory (NT).

Methods

Following registration with the NT Department of Health and Menzies School of Health Research Quality Assurance Audit Register, we extracted details of all neonates who had received HBIg within eight days of birth between December 2008 and December 2011, from the NT Immunisation Register. HBV serology results for the mothers of these infants was checked by interrogating laboratory records, the NT Notifiable Diseases System and other departmental electronic health records. HBV immunisation records and serology for infants of confirmed HBsAg-positive mothers were retrieved. Infants who had not been followed up and who were still living in the NT were traced, and offered testing after discussion with their primary care physicians, but the results of these tests were not recorded as part of the audit

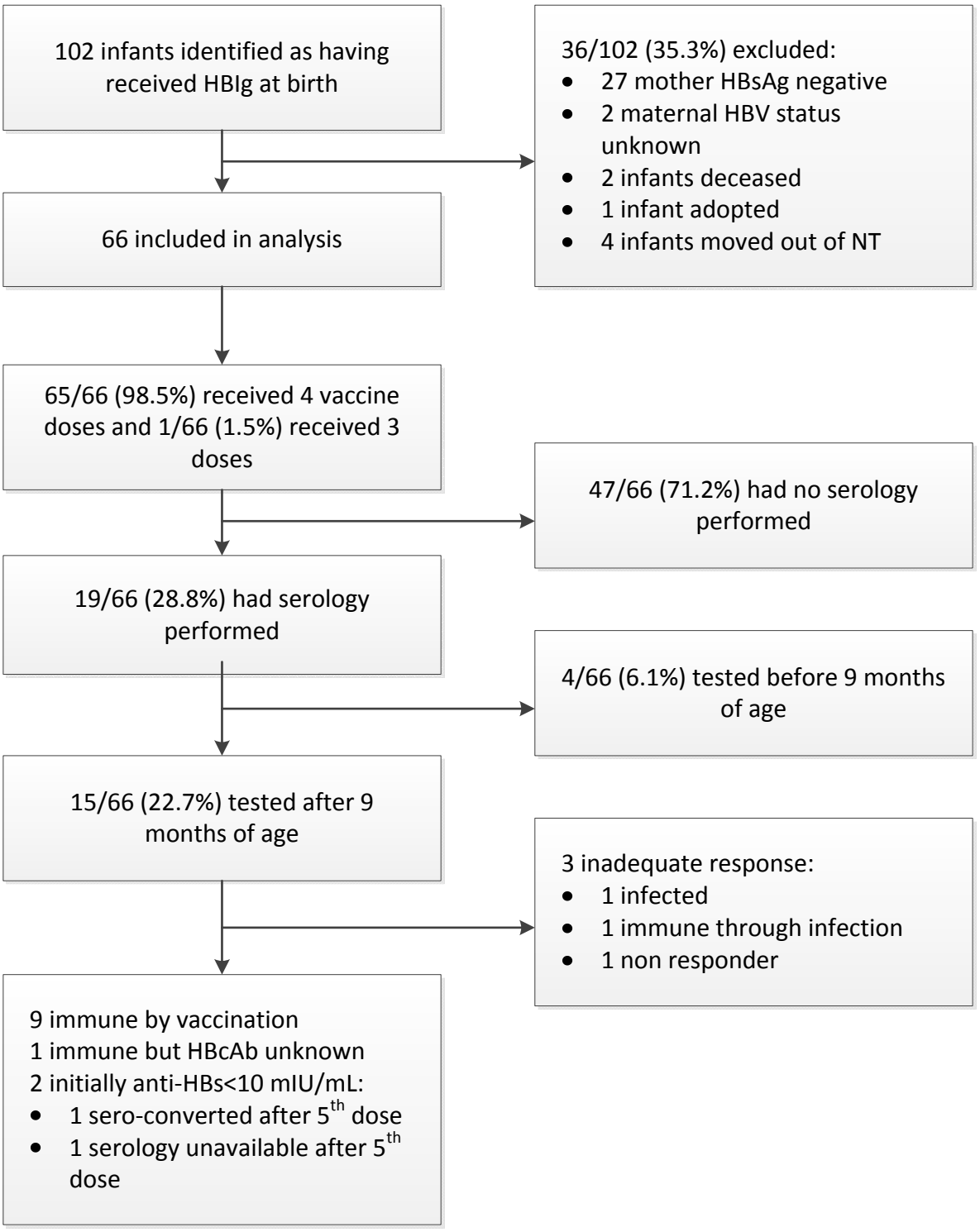
Results

Of 102 infants identified as having received HBIg, 36 were excluded from further analysis (Figure 1) including 27 whose mothers were subsequently found to be HBsAg negative. Of the 66 remaining infants, 46 (69.7%) were Aboriginal.

The recommended four-dose childhood HBV vaccination schedule[3] was completed by 65 of the 66 (98.5%) infants included in analysis (Figure 1). The remaining child received three vaccines only.

Only 19/66 (28.8%; 95%CI: 18-41%) children had been serologically tested. Serology results performed at least 3 months after the fourth vaccination, in line with guidelines, were found in 15/66 (22.7%; 95%CI: 13-35%) infants and a further 4/66 (6.1%) infants were tested before 9 months of age. While serology results indicated

Figure 1: Flow chart of infants included with exclusion criteria



immunity in these 4 infants, the serology could have been confounded by the administration of HBIg at birth.[3]

Of the 15 infants who were tested at least 3 months after the fourth vaccination, one was infected with HBV and one was immune through previous infection (HBsAg negative, anti-HBc positive, anti-HBs >10 mIU/mL). Nine infants were immune through vaccination and a further infant was immune (HBsAg negative, anti-HBs >10 mIU/ml), but anti-HBc had not been performed and so it was unclear whether immunity resulted from vaccination or infection. Three infants were uninfected, but had anti-HBs levels of <10 mIU/mL. One of these infants had received a total of six vaccines and was thought to be a non-responder to vaccination, with undetectable anti-HBs. The second infant, tested 39 months after the fourth vaccine, received an extra dose of vaccine with a resultant anti-HBs level of 109 mIU/mL. The third infant was tested 30 months after the fourth vaccine, then received an extra dose but follow-up serology has not yet been completed. Follow up serology was performed more often in the Aboriginal infants but not significantly so (15/46 (30.4%) compared with 4/20 (20%); x^2=1.08;p=0.30).

Discussion

HBV infection among young women in Australia is declining thanks to universal immunisation introduced in the 1990s[5,6] but in the NT, HBV is over-represented among the Indigenous population, especially those living in rural communities.[6] Our results demonstrate that increased commitment is still required from health services, to ensure that infants born to infected mothers are fully vaccinated and tested at the appropriate age. Documented vaccination and serology testing rates in this group vary widely across the world[7-9] and challenges including poor understanding of English, reduced health literacy, high rates of mobility and reduced health service accessibility may apply equally to Australian Indigenous communities as well as to other ethnic communities with high HBV prevalence.

There were three cases of concern, all Indigenous, in whom the immune response was inadequate; comprising two infants who contracted infection, and one who was a vaccine non-responder. The effectiveness of hepatitis B vaccination in the Indigenous population is the subject of ongoing research in the NT.

Novel initiatives such as dried blood spot testing may make testing of young children easier due to their ease of utilisation and avoidance of the need for peripheral venous sampling.[10] Chronic disease care plans and recall systems such as those implemented through the Northern Territory Immunisation Register, and sent monthly to primary care services, can be utilised to ensure that follow-up is arranged in a timely fashion. Outside of the NT, follow-up plans will need to be adapted to integrate with local early childhood services. Whichever strategies are employed, it is imperative that families are given all possible opportunities across primary and secondary care services, to access vaccination and serology testing, irrespective of geographical location. Infant infection is a potentially devastating consequence of inaction.

Albeit beyond our initial objectives, our data also revealed an overuse of HBIg. More than a quarter of our infant cohort received HBIg despite their mother's most recent serology demonstrating they were not infected with HBV. This highlights the need for ongoing education among healthcare staff regarding serology interpretation and sharing of maternal records across healthcare settings.

Conclusion

A birth dose of HBIg and hepatitis B vaccination of those infants born to mothers with hepatitis B infection has significantly diminished the chance of vertical transmission. However monitoring the effectiveness of this intervention is essential, not only for the health of the infant but also to ensure that the program is achieving the expected results.

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Other

National Tuberculosis Advisory Committee Guideline: Management of Tuberculosis Risk in Healthcare Workers in Australia

Justin Waring and the National Tuberculosis Advisory Committee

Introduction

Tuberculosis (TB) is uncommon in Australia and not commonly managed by most healthcare workers (HCWs). However, even in a low incidence setting, occasional exposure of HCWs is inevitable and transmission of TB to HCWs leading to disease does occur. In addition, HCWs may have been recruited to Australia from countries with high TB incidence. These HCWs are more likely to be infected with TB before arrival and subsequently develop active disease while working in health settings in Australia. In 2001, there were 20 TB notifications in HCWs in Australia, of which 10 were born overseas, whereas in 2013, 70 of 77 notified cases (91%) were people born overseas.[1, 2]

Managing the risk of TB in HCWs is multifaceted. A combination of staff education, awareness, early diagnosis, appropriate use of personal protective equipment (PPE), environmental controls and screening procedures is required to minimise the risk of transmission to HCWs and from HCWs to patients. Prevention of nosocomial transmission from HCWs is particularly important in patients that are more vulnerable, for example children and the immunocompromised. This document aims to describe the components that are considered essential for all healthcare facilities in Australia to minimise this risk. It is not intended to be operational, and reference should be made to specific state and territory TB Control Program policies for this detail. Each facility should develop its own policy for the management of TB risk in HCWs according to this jurisdictional policy and the facility specific factors that determine risk, but it should include at least the following components.

Components

1. Pre-employment Screening

Healthcare facilities are responsible for providing assessment and screening services including a test for latent tuberculosis infection (LTBI), chest x-ray and appropriate referral processes for the interpretation and follow-up of such test results in partnership with jurisdictional TB control programs. Assessment and screening must be undertaken by clinicians trained in TB. Screening should include students undertaking placement at a healthcare facility, locums and agency staff.

The rationale for pre-employment screening determines who is tested and the action taken from results. The rationale is threefold:

a. obtaining a baseline test result in case of future testing after exposure at work;
b. identifying LTBI in HCWs that warrants preventive therapy; and
c. identifying active TB in HCWs.

Pre-employment screening involves a risk assessment in all HCWs. There are two elements of this risk assessment:

a. An estimate of the probability of future TB exposure.
   This is determined by the historical incidence of TB in the facility and the specific work place of the HCW.
b. The pre-test risk of LTBI.

   This can be broadly categorised as high or low based on risk factors for LTBI. Specifically a new employee has a "high" risk for LTBI if:

   i. born, or worked for more than 3 months, in a country with higher TB incidence. This is arbitrarily set at an incidence rate of greater than 40 per 100,000*; or
   ii. known past history of contact with TB

* TB incidence rates by country can be obtained from http://www.who.int/tb/country/data/profiles/en/. It is noted that 40/100,000 is a lower threshold than that adopted in some settings, but considered appropriate here because of the higher risk of exposure in HCWs as compared to the general population.

(work or personal).

Based on this risk assessment some HCWs should have a test for LTBI. Note, all HCWs should be screened (i.e. undergo the above risk assessment), but only some of these HCWs should be required to have a diagnostic test. The HCWs that are tested, in general, are those that may come into contact with TB (establishing a baseline) and those with a high pre-test risk for LTBI (preventive therapy may be recommended). Within these parameters the extent of testing and the action taken for a positive result varies between jurisdictions, and reference should be made to specific state and territory TB control program policies for guidance on this. For further The National Tuberculosis Advisory Committee (NTAC) guidance on LTBI treatment in Australia, refer to the "National Position Statement for the Management of Latent Tuberculosis Infection". It is important that screening test results are formally recorded and permanently retained for future reference.

HCWs requiring a screening test for LTBI can have a tuberculin skin test (TST) or an interferon gamma release assay (IGRA, such as the QuantiFERON-TB Gold assay, Cellestis/Qiagen, Carnegie, Australia). IGRAs offer the advantages of improved specificity in a low prevalence setting, a lack of a booster effect with repeated testing and the convenience of a blood test. However, problems with interpretation of results near the cut-off and what determines a conversion, as well as the expense of the test, are disadvantages of IGRAs. For HCWs that undergo routine recurrent testing (see Component 3 below) the choice of test remains controversial. [3] High rates of conversions and reversions have been reported leading to more costly follow-up of screen-positive subjects. [4, 5] These conversions and reversions tend to occur more frequently when the initial IGRA result is close to the cut-off (0.35 IU/ml). NTAC recommends that either a TST or an IGRA are suitable as a single screening test, apart from when a HCW is likely to undergo serial testing. In these HCWs the preferred test is a TST and the role of IGRAs should be limited to supplementary testing to improve specificity. [6]

When a HCW does not undertake a screening test, the reason for this should be recorded and the HCW should be counselled about prompt presentation with symptoms suggestive of active TB. This may occur because the screening is not warranted e.g. a history of active TB or documentation of a prior positive screening test. Alternatively, HCWs that do not consent to a screening test that is recommended should be advised of the potential risks involved and should acknowledge in writing their non-participation.

Pre-employment screening for active TB should be considered in HCWs with a high pre-test risk for LTBI, especially if a pre-employment test for LTBI is positive. This includes a symptom screen and chest x-ray.

HCWs with a positive pre-employment screening test for LTBI should be considered for preventive therapy, in consultation with a physician with expertise in TB medicine. For further NTAC guidance on LTBI treatment in Australia, refer to the "National Position Statement for the Management of Latent Tuberculosis Infection". HCWs who do not take preventive therapy may also be considered for follow up surveillance for active TB, especially if they have recently arrived from a country with high TB incidence (see definition above). This is to detect TB reactivation early, and usually involves periodic symptom screening and a chest x-ray for 2 years.

Prospective HCWs that are identified in pre-employment screening to be immunocompromised should have their work position carefully assessed and, if necessary, modified to avoid potential exposure to TB.

2. Post Exposure Contact Tracing

Contact tracing amongst HCWs that are exposed to TB through the course of their work should be undertaken according to usual contact tracing principles and practices. In particular, reference should be made to the Series of National Guidelines (SoNG) for the Public Health Management of TB and relevant state or territory TB control program policies. [7]

The extent of post exposure testing of HCWs, in general, depends on the degree to which the index case was isolated (i.e. whether in a single room and the ventilation characteristics of the room) , the estimated level of infectiousness of the index case and the amount of contact that the HCW has with the index case.

Post exposure testing for LTBI should use the same test for LTBI (TST or IGRA) as was used for the pre-employment screening test. Reference to the pre-employment or "baseline" result aids interpretation of the post exposure result by more clearly determining if conversion, and therefore new infection, has occurred.

In contact tracing of HCWs there are a number of special considerations including:

a. anxiety and unfounded fears are just as common even though HCWs may be better educated in respect to TB, so clear and

prompt communication is essential;
b. publicity and media attention are possible and should be prepared for, including informing senior health executives; and
c. maintaining the confidentiality of the identity and medical record of the index case and HCWs affected is essential.

3. Routine Recurrent Screening

The pre-employment screening test for LTBI can be repeated at pre-determined routine intervals that are not dictated by episodes of exposure. The aim of this recurrent or serial testing is to detect conversion that would have otherwise been unrecognised. In addition to being of potential benefit to the HCW, the results act as a surveillance of undetected transmission of TB that may be occurring in the health facility.

Recurrent screening is not recommended for all HCWs. It should be considered in a HCW with a negative pre-employment test who works in an area of high potential risk of exposure to TB. These occupations will be specified at a jurisdictional level, but may include workers in TB clinics, respiratory and infectious disease departments, mycobacterial laboratories, bronchoscopy and induced sputum suites, and mortuaries.

Serial testing should use the same test for LTBI used at baseline screening (TST or IGRA) so that conversion, indicating recent infection, can be appropriately recognised. The previously mentioned concerns around the definition of conversion in an IGRA should be borne in mind. A positive result, indicating conversion, should prompt a recommendation of preventive therapy. If a HCW declines preventive therapy after a serial LTBI test is positive, the follow up periodic clinical review and chest x-ray described in Component 1 above is more strongly indicated, because of the higher risk of reactivation after recent infection.

HCWs who work in these high risk areas and have a positive preemployment screening test can be considered for chest x-ray and clinical review. The interval period for recurrent screening is usually, but arbitrarily, set at one year.

4. Active TB in HCWs

HCWs diagnosed with active TB are managed as for other cases of active TB. However, special considerations include:

a. informed consent should be obtained from the HCW before information about the diagnosis is disclosed to the employer; and
b. if pulmonary TB is diagnosed, the HCW should be excluded from work until the treating physician has determined that adequate treatment has been taken to ensure the HCW is no longer infectious.

In respect to this, additional caution may be required if the HCW works with vulnerable patients e.g. the immunocompromised or children.

5. Surveillance

Monitoring of recurrent screening test conversions (see Component 3) and the incidence of active TB in HCWs in a healthcare facility can be important indicators of TB transmission risk and adequacy of infection control practice. In a HCW with active TB, identifying nosocomial transmission (HCW to patient or vice-a-versa) by analysis of genetic typing of the TB isolates (e.g. VNTR/MIRU typing) is particularly important, and if it occurs should be reported to the jurisdictional TB Control Program.

6. BCG Vaccination

BCG vaccination is not routinely recommended for HCWs in Australia. [8,9] BCG vaccination can occasionally be considered in HCWs that are at high risk of exposure to multi-drug resistant TB (MDR-TB) e.g. mycobacterial laboratory workers, those going to work in high MDR-TB prevalence settings.

7. Education

In healthcare settings with a low TB incidence, such as in Australia, experience with TB is often limited, but an enhanced awareness of the risks of infection transmission and sentinel symptoms is important. A program of regular education of HCWs is intended to ensure early detection of cases, appropriate infection control practices and early presentation for diagnosis if the HCW has symptoms suspicious of TB. Emphasis should be on the fact that the most effective way to control TB is early detection and commencement of treatment.

Healthcare Facility Protection of HCWs

Management of patients with TB

Management of the risk presented to HCWs by patients with TB is outlined in the NTAC *Infection Control Guidelines for the Management of Patients with Suspected or Confirmed Pulmonary Tuberculosis in Healthcare Settings*. [10] Each health-

care facility should write and periodically review a TB Infection Control Policy with reference to these guidelines and local jurisdictional policy, and ensure that all HCWs are updated on current policy. These guidelines include recommendations for airborne infection control precautions, engineering controls for infection control and the use of personal protective equipment. In addition, facilities that are likely to have patients presenting with TB should have protocols to ensure the rapid detection, isolation and treatment of patients with infectious TB.

Management of TB transmission risk in the laboratory

Infection control practices aimed at preventing transmission to HCWs working in mycobacterial laboratories are described in the NTAC *Guidelines for Australian Mycobacteriology Laboratories.* [11]

Jurisdictional Contacts

Specific state and territory TB control programs should be contacted to obtain operational policies regarding management of TB risk in HCWs.

Australian Capital Territory

Department of Respiratory and Sleep Medicine
Canberra Hospital & Health Service
Yamba Drive, Garran, Australian Capital Territory 2605
T: 02 6244 2066
Policy: *Occupational Assessment, Screening and Vaccination.*

New South Wales

NSW TB Program
Health Protection NSW
T: 02 9391 9277
Policy: Occupational Assessment, Screening and Vaccination Against Specified Infectious Diseases (http://www.health.nsw.gov.au/Infectious/tuberculosis/Pages/Policies.aspx).

Northern Territory

TB Chest Clinic
Centre of Disease Control
Department of Health, Northern Territory
T: 08 89228044
F: 08 89228310
Policy: Guidelines for the Control of Tuberculosis in the Northern Territory

Queensland

Communicable Diseases and Infection Management Unit
Communicable Diseases Branch
Department of Health, Queensland
T: 07 33289724
Policy: Health Service Directive – Tuberculosis Control Protocol for the Control of Tuberculosis (https://www.health.qld.gov.au/directives/docs/ptl/qh-hsdptl-040-1.pdf)

South Australia

South Australia Tuberculosis Service
275 North Terrace, Adelaide, South Australia, 5000
T: 08 8222 4867
Policy: *Control of Tuberculosis in South Australian Health Services Directive*

Tasmania

Director Workplace Health and Wellbeing
Tasmanian Health Service - Southern Region
Ground Floor, 56 Collins Street, Hobart, Tasmania, 7000
T: 03 6166 6883
F: 03 6166 7516
or
Communicable Disease Prevention Unit
Public Health Services, Department of Health and Human Services
GPO Box 125, 25 Argyle Street, Hobart, Tasmania, 7001
T: 03 6166 0702
F: 03 6222 7744
Tasmanian Health Organisation – South Policy: *Immunisation Protocol for Health Care Workers (HR-58)*

Tasmanian Health Organisation – North Policy: *THO-North Employee Screening & Immunisation (January 2015)*

Tasmanian Health Organisation – North West Policy: *Occupational Assessment, Screening and Immunisation Protocol (November 2013)*

Victoria

Victorian Tuberculosis Program
Peter Doherty Institute for Infection and Immunity
792 Elizabeth Street, Melbourne, Victoria
General Enquiries: 03 9342 9478
Public Health Nurse Manager: 03 9342 9475
Email: vtpadmin@mh.org.au
Policy: Victorian TB Guidelines ("Management, control and prevention of tuberculosis" www.thermh.org.au/health-professionals/clinical-services/victorian-tuberculosis-program)

Western Australia

Anita Clayton Centre
1/311 Wellington Street, Perth, Western Australia
T: 08 9222 8500
F: 08 9222 8501
Email: ACCadmin@health.wa.gov.au
Policy: *Policy 6.3 TB and Health Care Workers*

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Other

National position statement for the management of latent tuberculosis infection

David Stock and the National Tuberculosis Advisory Committee (NTAC)

Background

The primary role of any tuberculosis (TB) control program is to ensure the prompt identification and effective treatment of active disease. The host immune system often succeeds in containing the initial (or primary) infection with *Mycobacterium tuberculosis* (Mtb), but may fail to eliminate the pathogen. The persistence of viable organisms explains the potential for the development of active disease years or even decades after infection. This is known as latent tuberculosis infection (LTBI) although, rather than a distinct entity, this probably represents part of a dynamic spectrum.[1] Individuals with LTBI are asymptomatic and it is therefore clinically undetectable.

The World Health Organization (WHO) estimates that one-third of the global population has been infected with Mtb[2], with highest prevalence of LTBI in countries/regions with the highest prevalence of active disease.[3] In 2013, 88% of 1322 notifications in Australia were in the overseas-born population (incidence 19.5 per 100,000 v. 1.0 per 100,000), with this proportion rising over the course of the last decade.[4] Combined with epidemiological evidence of low local transmission, this strongly implies that the vast majority resulted from reactivation of latent infection acquired prior to immigration.[5, 6] Contrasting trends in TB incidence in other developed countries probably reflect differences in policy regarding LTBI.[7]

Conclusion: The diagnosis and treatment of LTBI represents an important opportunity for intervention by jurisdictional TB control programs.

Targeted testing

The development of initiatives with the ultimate goal of eliminating TB on a global scale could lead one to conclude that highly inclusive, if not universal, testing should be undertaken in order to optimise capture of LTBI. However, such an undertaking would be prohibitively expensive, impractical and inevitably compromise the positive predictive value of the chosen test(s). We must therefore focus our resources on at-risk groups who would benefit from treatment.

Given the very low rates of transmission within Australia, it is clear that progressing toward TB elimination is largely contingent on the implementation of strategies to detect and treat LTBI in migrants from high incidence countries.

The 2 key factors to take into account when identifying an individual or population at risk are the pre-test probability (PTP) of LTBI and the risk of progression to active disease.

High PTP:

- Close (household) contacts of pulmonary TB
- Migrants# from countries with a high incidence of TB*
- Healthcare workers from settings with high TB incidence[8]

Migrants comprises those who have moved to Australia with the intent of staying long-term and those whose residence is time-limited, e.g. overseas students
*A cohort study from the United Kingdom showed that programmatic testing of migrants from countries with a range of TB incidence thresholds from 40 to 250 per 100,000 would be cost-effective and identify the majority of individuals with LTBI.[9] Lowering the threshold to 40 in 100,000, as recommended by the National Institute of Clinical Excellence (NICE)[10], while also cost-effective, substantially increases the cohort size, consequently increasing the workload for local TB services[11]. A recent publication supports the implementation of a similar, targeted strategy across Australia[12], although there is, as yet, no local cost-effectiveness data.

Increased risk of progression to active disease:

- Evidence of recent infection
- Fibrotic change consistent with TB on chest radiograph without history of previous treatment
- Human immunodeficiency virus (HIV) infection

- Other co-morbidities, including silicosis, renal failure (chronic kidney disease stage V), poorly controlled diabetes mellitus, certain malignancies (haematological, head & neck, lung), previous gastrectomy or jejuno-ileal bypass surgery, malnutrition and alcohol abuse
- Treatment with anti-tumour necrosis factor (anti-TNFα) inhibitors
- Solid organ transplant recipients
- Other immunosuppressive therapy, including long-term oral corticosteroids (prednisolone ≥15mg/day or equivalent)
- Young children, especially those aged <5 years

NTAC recommends that the following groups are tested for LTBI:

- Those identified by contact tracing within Australia
- Migrants (from any country) with a history of TB contact within the last 2 years
- Migrants from countries with a high incidence of TB*
  - Aged 35 or under
  - Aged over 35 with one or more risk factors for reactivation

  Prioritisation of recent migrants and those staying permanently is advisable.

  NTAC acknowledges that implementing this recommendation may require an increase in resources and the relative importance of competing demands would need to be carefully considered at a jurisdictional level.
- People living with HIV infection
- Patients commencing anti-TNFα therapy
- Patients being assessed for solid organ transplantation
- Australian residents returning from a prolonged period working in a healthcare setting in a high incidence country, and migrants from high incidence settings intending to work in Australian healthcare settings

Testing should generally be performed on an intention-to-treat basis, i.e. on the understanding that a diagnosis of LTBI will result in an offer of treatment. An individual risk-benefit assessment should be undertaken to inform this decision.

Testing

Two types of tests are currently in use for the diagnosis of LTBI in Australia, the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). Both TST and IGRA are indirect tests, demonstrating immune sensitisation to Mtb. They cannot, therefore, distinguish between elimination and persistence of Mtb following primary infection. There is also the potential for test failure in the setting of impaired host immunity. Furthermore, neither test can distinguish between recent and distant infection, nor reliably predict progression to active disease.

The principal advantage of IGRA over TST is in terms of specificity. Unlike TST, the test outcome is unaffected by previous testing, Bacille Calmette-Guerin (BCG) vaccination (typically high coverage in at risk populations) or exposure to non-tuberculous mycobacteria (NTM), with the exception of *M. marinum, M. szulgai and M. kansasii*. The major drawbacks have been the relative unfamiliarity and higher cost of the test. There is also a possibility that an indeterminate result may be returned due to failure of the positive or negative control.

Both TST and IGRA are acceptable for the diagnosis of LTBI. This is consistent with recently published WHO guidelines[13] on testing in high income, low prevalence countries. For further information please refer to the following NTAC document: *Position Statement on Interferon-γ Release Immunoassays in the Detection of Latent Tuberculosis Infection*[**].

The following represents a reasonable approach to the interpretation of TST results:

Regard as TST-positive if

a. ≥15mm

* ≥ 100 per 100,000 based on WHO estimates (http://who.int/tb/country/data/profiles/en/). This threshold has been chosen by consensus, considering both epidemiological risk of LTBI and cohort size. Targeted testing for migrants from countries of incidence 40 – 99 per 100,000 should be considered where resourcing is favourable or where underlying medical conditions suggest a significant risk of disease progression or severe manifestations of disease not otherwise specified in the above recommendations.

** http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3601i.htm Please note this position statement is currently under review and an updated version will be published shortly.

b. ≥ 10mm but < 15mm with a history of close contact or an abnormal chest radiograph (calcified nodules, upper lobe fibrosis). Consider performing IGRA as a supplementary test

c. ≥ 5 but < 10mm in those age < 5 years with high PTP AND increased risk of progression to active disease. If age ≥ 2 years consider performing IGRA as a supplementary test, noting that indeterminant IGRA results may be more likely in very young children[14]

d. ≥ 5mm and immunosuppressed (IGRA can be performed concurrently – treat if either is positive)

Treatment can be offered to HIV-infected and preschool age contacts of an infectious case without prior testing in recognition of their susceptibility to meningitis and disseminated infection[15]

Preventive treatment

A diagnosis of LTBI requires ensuring that active disease is excluded. Prior to initiation of LTBI treatment, patients should have a chest x-ray performed, sputum (induced if necessary) cultured for TB where feasible, and be reviewed by a clinician with experience in the diagnosis and management of TB.

Isoniazid

This is the most widely used and evidence-based regimen, although there is debate as to the most appropriate duration of treatment. A risk reduction in excess of 90% can be achieved after 12 months of daily self-administration but, as one would expect, field effectiveness is compromised by declining adherence.[16] Extrapolation from trial data had suggested that treatment for 9 months is optimal[17], but subsequent meta-analyses concluded that there is no demonstrable benefit in continuing beyond 6 months.[18, 19] There are no head-to-head studies of 6 versus 9 months isoniazid (INH).

There is evidence of an extremely durable treatment response in a low-prevalence setting.[20] The principal safety concern has been the hepatotoxic potential of this drug[21], although more recent data has shown very low rates of significant hepatitis, perhaps as a result of better patient selection and treatment monitoring[22].

Dose: 10mg/kg daily, up to a maximum of 300mg***.

The challenges faced by both physicians and patients in trying to maintain treatment adherence over many months led to a search for equally effective but shorter regimens.

Rifampicin (RIF)

Evidence in the literature is limited to a single trial in silicosis patients[23] and some observational data[24, 25]. The Centers for Disease Control and Prevention (CDC) in the United States recommend treatment for 4 months as an alternative to INH.[26] Acceptable safety and completion rates have been established for this regimen[27] and a trial is currently recruiting in an attempt to address the lack of efficacy data[28]. RIF is a cytochrome P450 inducer and the potential for drug interactions may need to be carefully considered.

Dose: 10mg/kg daily, up to 600mg.

Rifampicin-isoniazid (RIF-INH)

This combination has been shown to have an equivalent efficacy and safety profile to INH.[29] Evidence supporting its use in the treatment of LTBI comes predominantly from studies conducted in children.[30, 31, 32] Daily treatment for 3 months is recommended as an alternative to INH monotherapy by NICE[10] but is not in widespread use in Australia.

Isoniazid-rifapentine (INH-RPT)

Rifapentine is a potent, long-acting rifamycin. An open-label study of weekly, directly observed therapy (DOT) with this combination for 12 weeks showed non-inferiority to 9 months of daily, self-administered INH.[33] It also appears to be efficacious and well-tolerated in HIV-infected adults.[34] Durability of response and performance in certain settings (e.g. no DOT, age < 2yrs) are yet to be established. This regimen is now recommended by the CDC.[35] It is not currently registered for use in Australia but is the subject of considerable interest.

Important - Rifampicin-pyrazinamide (RIF-PZA) is not generally recommended due to an unacceptable risk of significant hepatotoxicity in non-HIV infected individuals[26].

NTAC recommends that:

- INH for 6-9 months is the standard of care

*** Pyridoxine (Vitamin B6) 25mg daily may be co-prescribed in adults for all regimens containing isoniazid to minimise the risk of peripheral neuropathy.

for the treatment of LTBI in adults

- RIF-INH for 3 months is an acceptable alternative, especially when treating LTBI in children
- Rifampicin for 4 months can be used in the event of intolerance of INH or infection by a suspected/known INH-resistant organism

Infection with a multi-drug resistant (MDR) organism

Isoniazid and rifamycins are unlikely to be effective in the setting of MDR-TB infection. As is the case for fully-drug susceptible organisms, the great majority will not progress to active disease. The potential consequences of MDR-TB transmission are, however, substantial and contacts should therefore be managed by an experienced TB physician. Fluoroquinolone-based preventative therapy has been used in Australia and internationally, with accumulating evidence relating to the magnitude of protection provided[36, 37]. Regardless of preventative therapy administered, contacts should be closely monitored for signs of active disease for at least 2 years.[38]

Monitoring

Routine monitoring of liver function is not necessary in the under 35's without risk factors (regular alcohol consumption, pre-existing liver disease). Otherwise these should be checked monthly for a minimum of 3 months. Transaminases over 5 times the upper limit of normal (ULN) according to your local laboratory reference range should prompt cessation of treatment, with a lower cut-off of 3 times the ULN if symptoms are present.

All patients should be educated about symptoms of hepatitis and advised to stop treatment pending assessment by a doctor if they are concerned.

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Original Article

Tuberculosis screening in an aged care residential facility in a low-incidence setting

Nompilo Moyo, James Trauer, Peter Trevan, Ann-Marie Baker, Joseph Musemburi, Kerry McGrath, Aine Nolan, Eamon McIntyre, Jane Hulls, Justin T. Denholm

Abstract

This is a retrospective cohort study of tuberculosis contact tracing and screening in an elderly residential facility in Victoria. In the absence of specific guidelines regarding an optimal test for this population, 18 residents were tested with both tuberculin skin test (TST) and interferon-gamma release assay (IGRA), and all underwent symptom assessment and chest x-ray (CXR).

Keywords: latent tuberculous infection; contact tracing; interferon-gamma release assays; tuberculin skin test

Introduction

Residents in long-term aged care residential facilities (ACRF) have previously been recognised as having higher incidence of tuberculosis (TB) than the general community.[1, 2, 3] This increased incidence is reflective of both extended lifetime potential for latent TB infection (LTBI) acquisition and increasing risk of TB reactivation caused by comorbidities and immune senescence.[4]

In other congregate settings, such as schools or childcare centres, notification of cases of tuberculosis prompts an assessment of transmission risk by jurisdictional authorities, including testing those at risk for TB disease and LTBI ("contact tracing"). Contact tracing serves two primary purposes; first to diagnose further patients with TB disease ("active case finding"), and secondly to identify individuals at risk of future progression to active TB by use of tests for LTBI, in order to provide treatment to prevent disease occurring.

Optimal approaches to contact tracing in elderly aged care facilities are not clear. While the elderly are at somewhat higher risk of LTBI reactivation, they are also at substantially higher risk of toxicity from preventive therapies, and risk/benefit considerations mean that preventive therapy may not be indicated. In addition, the performance of LTBI diagnostic tests, including tuberculin skin test (TST) and interferon-gamma release assays (IGRA) are less well described in the very elderly. We therefore describe an opportunistic contact tracing exercise in an ACRF in an Australian context, to assist in refining practical approaches to contact tracing in such environments.

Methods

In September 2015, a health care worker at an ACRF in Victoria, Australia was diagnosed with cavitatory, smear-positive, drug-sensitive pulmonary TB. Following assessment of potential infectivity, staff and residents were identified as being at risk of exposure, and eligible for contact tracing.

Both TST and IGRA are used for post-exposure contact testing in Victoria.[5] In the absence of specific guidelines regarding an optimal test for this population, residents were tested with both TST and IGRA (Quantiferon Gold In-Tube assay, Qiagen), and all underwent symptom assessment and chest x-ray (CXR). TST were defined as positive if induration of ≥10 mm was present at 48–72 hours, while IGRA were reported as per manufacturer's guidelines. Residents found to be positive by either test or with abnormalities on CXR, were referred to appropriate clinical services for assessment. TB testing and CXR were provided free of charge by the Victorian Tuberculosis Program.

In accordance with normal public health responses, demographic and clinical data were collected and recorded in an existing database (Public Health Events Surveillance System). Descriptive statistics were performed on de-identified data for this report, with analysis conducted in Stata version 14.0. TB Program clinical nurse consultants were also asked to provide qualitative feedback on testing and follow up, with thematic analysis of responses reported.

The data in this report were collected and used under the legislative authority of the Public Health and Wellbeing Act 2008 and therefore approval from a Human Research Ethics Committee was not required under the rules of our institutions.

Results

A total of 19 residents with epidemiological contact were identified for contact tracing, with 18 consenting to evaluation. Demographic details of residents are provided in Table 1.

In addition, 41 staff were identified for screening. Staff members were screened with TST and, IGRA was only used for staff who failed to attend the screening. 39 members of staff consented for screening, with four testing positive for TB test: two were Australian born with no known risk factors and the remaining two were born in high TB incidence countries. No TB disease was found among staff, who were referred for consideration of preventive therapy.

Table 1. Positivity on either TST or IGRA by participant characteristics

Variable	Number of residents	TST or IGRA positive	Percentage positive
Under 70	1	1	100%
70-79	5	1	20%
80-89	6	0	0%
≥ 90	6	3	50%
Male	6	2	33%
Female	12	3	25%
Australian born	11	3	27%
England born	7	2	29%
Independent for ADLs	6	2	33%
Dependent for ADLs	12	3	25%
All	**18**	**5**	**28%**

ADLs, activities of daily living. As per information provided by resident facility.

Results from LTBI testing are shown in Table 2. Of the 5 residents with a positive IGRA, 2 were TST positive. No resident with a negative IGRA was found to have a positive TST. CXR identified abnormalities in 4/18 (22%), with all of these individuals also having positive IGRAs (p=0.002). Both TST positives had abnormal CXRs and all but one positive IGRA had abnormal CXRs. Following specialist evaluation and additional diagnostic testing, none was considered reflective of active TB.

Table 2. IGRA versus TST results

	Positive TST	Negative TST
Positive IGRA	2	3
Negative IGRA	0	13

p=0.065, Fisher exact

Table 3. IGRA versus CXR results

	Positive CXR	Negative CXR
Positive IGRA	4	1
Negative IGRA	0	13

p=0.002, Fisher exact

All residents with positive TST or IGRA were referred for consideration of further management, including preventive therapy. Following specialist evaluation, all were considered to be poor candidates for LTBI therapy based on risk/benefit assessment, and none was treated. Residents were followed for 12 months post-exposure, with no additional cases of active TB identified within this cohort. Following this time, resident's general practitioners were provided with education on TB and recommendations for further investigations if symptomatic.

Qualitative feedback from clinical nurse consultants was collected and reviewed. Consistent themes were that TST administration was difficult due to fragile skin and loss of skin elasticity. It was noted that some residents were not able to cooperate with the procedure, most frequently due to behavioural issues secondary to dementia. Similarly, IGRA collection was also considered problematic due to requirement for phlebotomy. Nursing staff reported a range of additional issues, including challenges with identifying appropriate persons responsible for healthcare decision-making for those residents not able to independently provide consent to testing. We also note that CXR testing required transport of patients to an external radiology facility, which was problematic for some residents and families.

Discussion

This mixed-methods report provides insight into TB contact tracing in an Australian ACRF. While the size of this study is insufficient to draw robust conclusions regarding test performance characteristics in the elderly, our experience is illustrative of the challenges inherent in this setting and has led to changes in local policy and practice. Future contact tracing assessment in similar settings will focus on clinical and radiological assessment for active case finding, with recognition of the limited additional benefit of testing for LTBI in this cohort.

The association between IGRA and TST and the association of positive results with abnormal chest x-ray findings on simple univariate analysis suggest that the positive results may reflect true M. tuberculosis infection. However, this infection may well have been remotely acquired, which would also be consistent with the absence of reac-

tivation after twelve months of follow up. In our cohort, IGRA testing yielded more positive results compared to TST. This is opposite to what was found in a systematic review in which the proportion of positive results was significantly lower for the IGRA than the TST.[6] This may reflect immune senescence, although studies of anergy testing have suggested previously that most elderly people retain an adequate immune response.[7] We suggest that low skin tone may have contributed to the apparent poor performance of TST in this very elderly cohort.

While the investigation described arose following a case of TB occurring in a health care worker, transmission following TB disease in residents may also occur. In some jurisdictions, testing for LTBI/TB is required or recommended at the time of facility entry to minimise risk of exposures. For example in Ontario, Canada, legislation requires all long term care and retirement homes to screen residents for TB with chest x-ray within the 90 days prior to admission. In addition, TST is recommended for all residents aged under 65 years, although TST is not recommended for older residents.[8]Likewise, the US Centers for Disease Control and Prevention (CDC) also recommends that all residents in long-term residential care be screened for TB with TST upon entry to the facility.[9] However, in Victoria there is no recommendation that aged care residents should be screened for TB before admission.[5]

Appropriate policies and practices for preventing TB transmission in ACRF will continue to be explored.

The challenges illustrated in this report should also encourage alternative approaches to reducing the incidence and impact of TB in ACRF. Such strategies include optimising management of comorbidities which increase the risk of TB disease, including diabetes and cigarette smoking. ACRF should also consider strategies to limit the potential for TB exposure, which may include baseline LTBI/TB testing for staff or new residents.

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Original Article

Sexually Transmitted Infections in Melbourne, Australia from 1918 to 2016: nearly a century of data

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Abstract

Introduction

Our aim was to describe trends in the number of bacterial sexually transmitted infections (STIs) diagnosed at Melbourne's sexual health clinic over a century.

Methods

A retrospective analysis of STI diagnoses (gonorrhoea, infectious syphilis and chancroid) among individuals attending Melbourne's sexual health service over 99 years between 1918 and 2016.

Results

Substantial increases in STI rates coincided with World War II, the 'Sexual Revolution of the 1960s and 1970s', and the last 10 years. Substantial declines coincided with the advent of antibiotics and the HIV/AIDS pandemic. There were also key differences between STIs. Chancroid virtually disappeared after 1950. Syphilis fell to very low levels in women after about 1950 and has only rebounded in men. The declines in gonorrhoea were less marked. A substantial peak in gonorrhoea occurred in women in the early 1970s and rates are currently rising in women, albeit much less than in men.

Conclusions

Both antibiotics and changing sexual behaviour have had a powerful effect on STI rates. These data suggest gonorrhoea is more difficult to control than syphilis or chancroid. Indeed, the past rates suggest substantial endemic gonorrhoea transmission in heterosexuals occurred in the third quarter of last century before the appearance of the HIV pandemic. Worryingly, there is a suggestion that endemic heterosexual gonorrhoea may be returning. The data also suggest that future control of gonorrhoea and syphilis in men who have sex with men is going to be challenging.

Keywords: sexually transmitted infections, gonorrhoea, syphilis, chancroid, epidemiology, history, sexual health clinic, Australia

INTRODUCTION

A number of countries, such as the United Kingdom have data on sexually transmitted infections (STIs) over the last 100 years [1]. However in Australia there is only one paper, by Hall, published nearly 25 years ago that describes notifications of STIs over more than a few decades[2]. Furthermore, in that paper there is a gap of 40-years in notifications between 1929 and 1969, a time period that includes significant societal changes including a world war, the advent of antibiotics, and the introduction of the oral contraceptive pill[2]. Considerable efforts have been made by Hall at the time and by the authors of this paper to locate these notifications without success. In the absence of records of these notifications other records may exist to fill this gap in notifications.

A number of publicly-funded sexual health clinics in Australia have been in operation over the last century but only one clinic (Melbourne Sexual Health Centre (MSHC)) has almost continuous recorded data going back to 1918 when it first opened. MSHC has been the only publicly-funded clinic operating in Melbourne over this time for the sole purpose of providing STI care. The clinic is therefore ideally placed to provide historical data over this period and could potentially provide insights into the future [3]. Our aim was to describe the number of cases of bacterial STIs at this clinic over the last 99 years. Furthermore, in the discussion of this paper we describe major events or societal changes that occurred around the time of significant changes in the diagnoses of STIs. For each of these we discuss how these events may have influenced the reproductive rate, and therefore the incidence, of STIs, such as for example the discovery of antibiotics for their treatment.

METHODS

This was a retrospective analysis of STIs diagnosed at the STI clinic in Melbourne (now MSHC) over a 99-year period, from 28 June 1918 to 31 December 2016. The STI clinic in Melbourne has had six previous names (Table 1). The clinic has operated continuously in the metropolitan area of Melbourne, Australia over the study period. Over the entire time, the clinic has provided free clinical consultations for the management and treatment of STIs.

The primary analysis involved the number of diagnoses of gonorrhoea, infectious syphilis, and chancroid, by sex. Several data sources were used to provide data for the 99-year period (Table 2). We include these three STIs because they are mostly symptomatic and therefore diagnosed cases will reflect the cases presenting to the clinic. Chlamydia was not included in this analysis because it was only relatively recently discovered (1970s) and is largely asymptomatic so the diagnoses strongly reflect testing practices, and not necessarily changes in the incidence of infection[4]. We have provided the raw number of chlamydia diagnoses in Supplementary Table S1 for reference. Data on trichomoniasis has been previously published[5].

Syphilis cases were recorded over the entire period by stage; we included infectious syphilis (primary, secondary and early latent (<2 years)) and cases without stage specified, and excluded congenital, tertiary and late latent (>2 years) cases. Definitions of these stages over time were not available. There was no standardised definition for the diagnosis of gonorrhoea or chancroid over the entire 99 year study period. There were a number of years with incomplete or missing data, described in Table 3. For these years, to provide full year data we have taken the average of the periods preceding or following these periods and assumed there were no substantial changes from year to year.

We calculated sex-stratified annual rates for gonorrhoea and syphilis separately. Data for women were available from 1918 and for men only from 1926 as data from earlier years are missing. We calculated sex-stratified annual rates for these two diagnoses made at the centre using the annual population of the greater metropolitan area of Melbourne as the denominator[6,7]. In the last 10 years, MSHC diagnosed about 40% of infectious syphilis notifications and 30% of gonorrhoea notifications in Victoria. We assumed the male-to-female ratio was 1:1 in Melbourne and did not change substantially over the study period. We presented a 3-years centred moving average

Table 1. Names and locations of public sexual health clinics in Melbourne, Australia, from 1918 to 2016.

Clinic Name	Clients	Location	Period
Government Clinic for Males	Males only	440 Lonsdale Street, Melbourne	1918 – 1929
Government Clinic for Females	Females only	372-378 Little Lonsdale Street, Melbourne	1918 – 1929
Unknown	Males and females	372-378 Little Lonsdale Street, Melbourne	1929 – 1948
Unknown	Males and females	201 Little Lonsdale Street, Melbourne	1948 – 1961
Government Clinic	Males and females	136 Gertrude Street, Fitzroy	1961 – 1979
Melbourne Communicable Diseases Centre	Males and females	364-370 Little Lonsdale Street, Melbourne	1979 – 1992
Melbourne Sexual Health Centre (MSHC)	Males and females	580 Swanston Street, Carlton	1992 – present

Table 2. Description of data sources.

Year	Description of data sources
1918-1982	Admittance registers (Photo 1) housed in the MSHC archive included line-by-line consultation data. An admittance register is a list of individuals and their specific diagnoses.
1926-1964	Clinic ledgers included aggregate consultation data. A clinic ledger is a list of monthly total of the number of clients with specific diagnoses. These have been used when data from admittance registers is unavailable.
1982-2001	Laboratory book data records all clients who had at least one laboratory investigation for a STI and their specific diagnoses.
2002-2016	Individual consultation data were available from the current clinic practice management system database, which is a custom built medical software package used to record all consultations. This is the only dataset with sexual practice information, where men who have sex with men or women can be differentiated. For the purpose of analysis men who had sex with other men in the previous 12 months were defined as MSM and all other men as heterosexual males.

Photo 1. Admittance registers housed in the MSHC archive included line-by-line consultation data for the period 1918-1982.

Table 3. Formulas of adjusted data.

Year	Available data		Adjusted number used in analysis
	Males	Females	
1918	No data	6 months	(1918 number) ×2
1926	6 months	12 months*	(1926 number) ×2
1964	1 month	12 months*	Average of (1961-1963 number)
1965 and 1966	No data	12 months*	Average of (1961-1963 number)
1967 and 1968	No data	12 months*	Average of (1969-1971 number)
1969	7 months	12 months*	(1969 number) ×12/7
1982	12 months*	6 months	(1982 number) ×2
2002	6 months	6 months	(2002 number) ×2

* Data not adjusted.

for the rates of diagnoses for each STI over the study period. These have been calculated for every year by taking the average of the year itself, the previous year and the subsequent year. Chancroid diagnoses were presented as the raw number of diagnoses due to low numbers of diagnoses.

Analyses were conducted using SPSS version 23 (SPSS Inc., Chicago IL). Ethical approval for this was obtained from the Alfred Hospital Ethics Committee (approval number 473/15).

RESULTS

Over the 99-year period, there were 77,290 gonorrhoea, 9,381 syphilis, and 1,048 chancroid diagnoses among individuals attending the clinic.

Gonorrhoea

Figure 1 shows the rate of gonorrhoea by sex per 100,000. For men, the rates fell to a low in 1953, then rose until about 1980, fell dramatically until about 2000, from which time they steadily rose

again. In women, there were two peaks (in 1930 and in 1972), after which rates declined to very low levels but began rising again in the early 2000s.

Syphilis

Figure 2 shows the rate of syphilis by sex per 100,000. Rates in men fell rapidly from a peak in 1928 to almost zero by about 1990. During this decline two substantial peaks occurred in 1942 and 1949. Rates in men began to rise again from early 2000s to the levels not seen since the 1940s. In women, rates fell from 1918 to an initial nadir in 1924, and then rose to peak in 1929. They then fell fairly rapidly to very low levels from the 1950s.

Chancroid

Figure 3 shows the number of chancroid diagnosis by sex for males from 1926 and for women from 1918. In men, two peaks occurred in 1927 and then again in 1950 with virtually no cases between these peaks or after 1952. In women only a few sporadic cases were seen in the years before the mid-1940s.

DISCUSSION

This is the first paper describing the temporal trends of three key STIs over a period of nearly 100 years in any part of Australia and importantly fills the 40-year gap between 1929 and 1969. This his-

Figure 1. Centred 3-year moving average of the annual adjusted rate of gonorrhoea diagnoses by sex in sexual health clinics in Melbourne, 1918-2016. *Raw number of gonorrhoea diagnoses in each year by sex and male sexual practice is presented in Supplementary Table S1.*

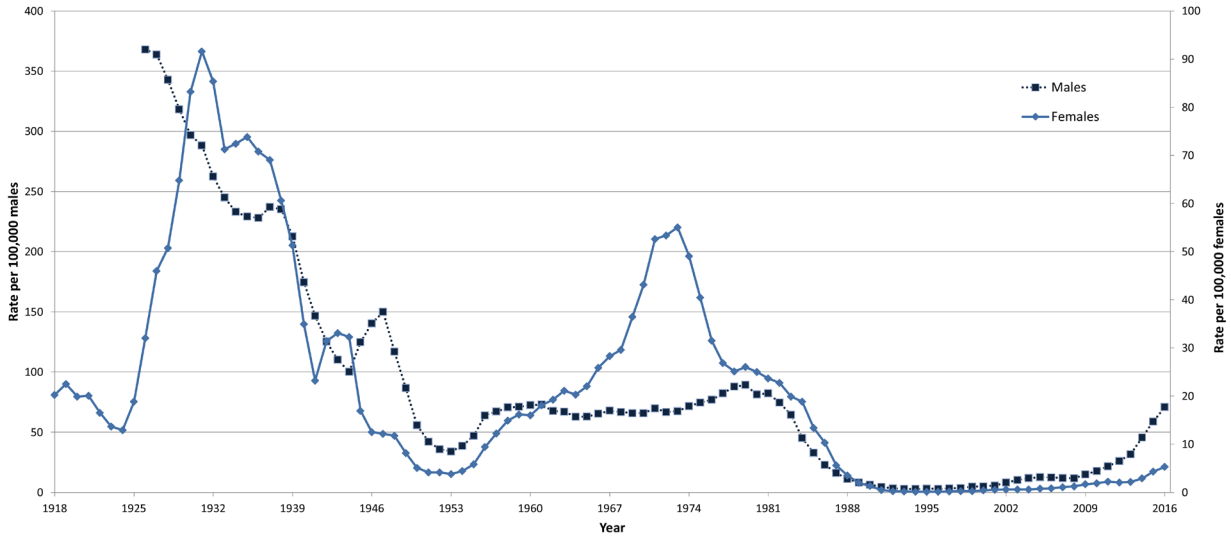


Figure 2. Centred 3-year moving average of the annual adjusted rate of infectious syphilis diagnoses by sex in sexual health clinics in Melbourne, 1918-2016. *Raw number of infectious syphilis diagnoses in each year by sex and male sexual practice is presented in Supplementary Table S1.*

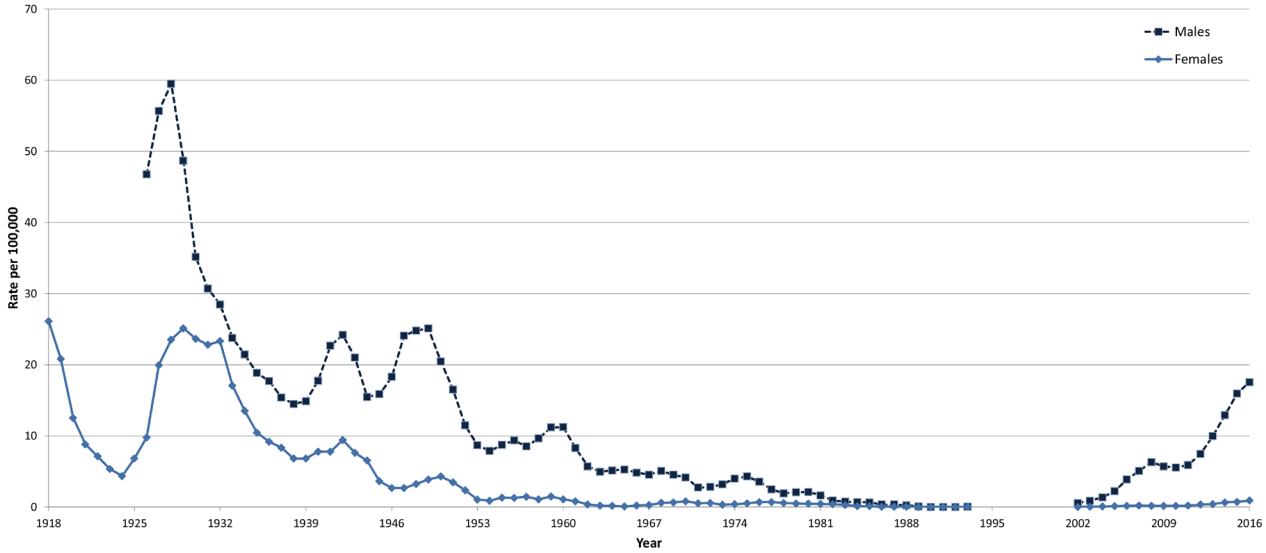
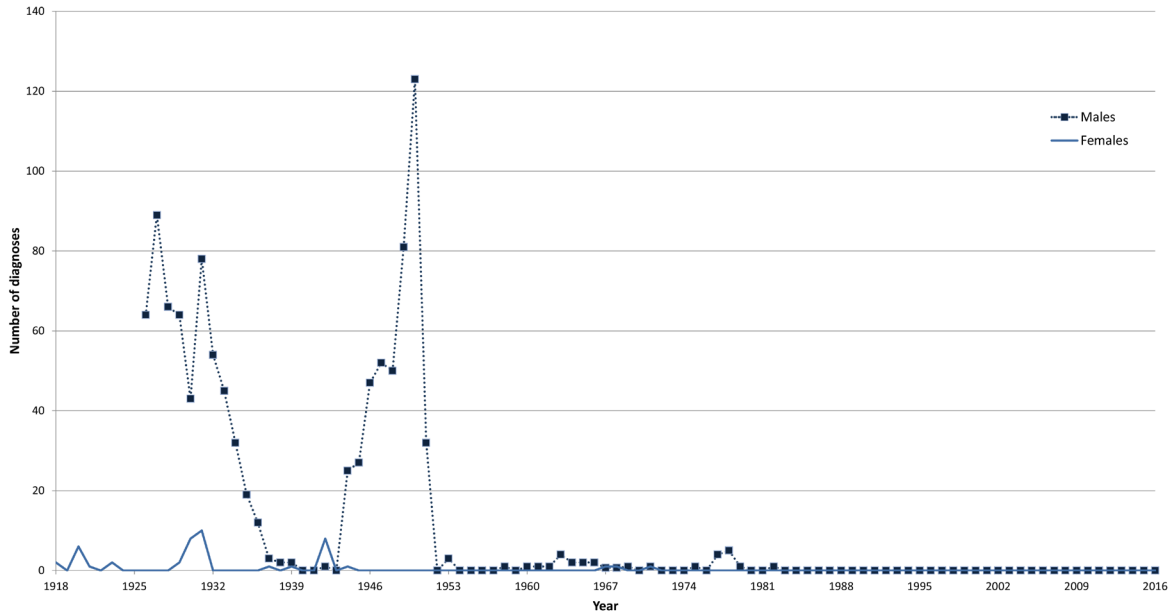


Figure 3. Number of chancroid diagnoses by sex in sexual health clinics in Melbourne, 1918-2016.



toric data may be Australia's only complete record for this period [2]. In our data the rises and falls of STIs occurred at similar times to key historical events that may have influenced changes in the rates of different STIs. While some of the changes were specific to Australia, most trends broadly mirror those seen in the UK and elsewhere[8,9]. These historical trends may offer guidance for the future public health interventions for Australia, as we enter an era when most STI rates are again rising rapidly.

There are a number of factors that need to be considered when interpreting our data. Firstly, we did not have a denominator for most of the time periods. This is why we displayed the data as a rate for the Melbourne population. This method too is a weakness because it's likely that the proportion of cases diagnosed in Melbourne who attended the clinic varied over time and also clearly this significantly underestimates the rate, MSHC currently diagnoses about 30-40% of the notifications of both syphilis and gonorrhoea in Victoria. Additionally, it is likely the age distribution of the population of Melbourne would have changed over the 99-year period. However, this data was not publicly available over this period and we were not able to adjust for this as a potential confounder in our analysis. Nevertheless, our data are the only continuous data in Australia and the general trends observed are very large in magnitude and fit with overseas data. While there were seven different iterations of the same clinic over 99 years, all clinics existed continuously and for the same public health purpose. Secondly, we also acknowledge strongly that no causality can be implied, although some associations are likely given their plausible nature such as the large declines in rate of syphilis and gonorrhoea diagnoses with the beginning of the mass production of penicillin in the late 1940s[10]. We have taken the liberty of suggesting possible reasons for these changes, acknowledging these suggestions are hypotheses, for which it is unlikely firm evidence for or against them will ever be forth coming. Finally, the data was taken from four distinct sources for the length of the study. The way these sources were recorded was different, and it is likely that both changes in the way data was recorded and improvements in testing methodologies with increasing sensitivity over time have occurred and influenced the rate of STIs diagnosed. However, the magnitude of the changes is large and not likely to be influenced greatly by these changes. Acknowledging these biases we point out that these data do provide the first continuous record of STIs in Australia's second largest city.

The most striking feature in all of the three STIs is the dramatic decline with the introduction of antibiotics in the late 1940s [10,11]. Indeed for gonorrhoea and syphilis rates in men and women have never exceeded the levels seen before the pre-antibiotic era. While not well documented, trends in the number of sexual partners and age of first intercourse in Australia suggest that this pre-antibiotic era was associated with substantially lower rates of sexual partner change, implying that if the current rate of partner change were replicated in the pre-antibiotic era, STI rates would have been much higher [12,13]. This same dramatic decline with antibiotics also occurred in the UK, Sweden and elsewhere which highlights the fundamental importance of access to health care for the effective control of curable STIs[1,14-16]. Extending the logic that access to health care for the treatment

of STIs reduces their rate, there is the impression that the introduction of the universal healthcare scheme, Medicare, in about 1975 could have lowered gonorrhoea rates for women through greater access to health care. No reduction in men is seen, but rates of STIs were rising rapidly in men most likely because of the large rises in men who have sex with men (MSM) which may have overwhelmed any changes in heterosexual men[17]. In addition, this change however may simply be an artefact of Medicare which could have artificially lowered rates at the sexual health clinic because women could now seek health care through their general practitioners[18]. The importance of accessible health care for the effective control of STIs is highlighted in remote Indigenous communities where high STI rates are in part due to reduced access to health care in these communities[19].

A second feature of the patterns seen in all three STIs is the rise around the time of world wars[20]. Rates temporarily rose at around the time men returned to Australia from the World War II which is consistent with social disruption and the greater rate of partner change in young servicemen in foreign cities[20]. The rise seems short lived although around this time antibiotics were also becoming more available so it is possible that these two factors were both contributing[10,11]. Again these trends are also evident in the UK and Swedish data[1,14].

The third feature that is evident in the trends of gonorrhoea is the influence of changes in sexual risk that occurred over time [12,15,21,22]. For example the oral contraceptive pill was introduced on prescription in Australia in 1961 around the time that sexual risk (e.g. increasing partner number and condomless sex) rose in Australia and elsewhere[12]. The more pronounced rise in gonorrhoea in men compared to women around this time also coincided with the repealing of laws prohibiting same-sex sexual activity between men and the gay and lesbian political movements[23]. Finally, the precipitous fall in gonorrhoea in men with the appearance of HIV and dramatic reduction in sexual risk among MSM is evident not only in our data but was virtually universal around the world [1,14,15,24]. Falls were also seen in women as condom use rose in heterosexuals, but it should be noted that around this time Victoria also regulated sex work which also saw dramatic falls in STIs in sex workers [25-27]. More recently the rapid rise in gonorrhoea and syphilis in MSM is a common feature around the world and coincided with successful HIV treatment [22,24,28].

These data also highlight some important differences between gonorrhoea and syphilis, particularly in heterosexuals, which in our data is largely reflected by rates in women. The graphs show that when sexual risk rose after the 1950s, rates of gonorrhoea rose in women but syphilis did not [13]. This indicates that for heterosexuals syphilis is an easier infection to control at a population level, although widespread antenatal screening for syphilis was also introduced about this time [13]. This suggestion that gonorrhoea is harder to control in heterosexuals is also evident in the last few years of data analysed here, as rates of gonorrhoea but not syphilis were rising in women albeit not to levels seen in the 1970s[29]. The concept that syphilis is easier to control than gonorrhoea is also supported in the US[30] and among Indigenous Australians living in remote settings[31] where endemic gonorrhoea is common but syphilis tends to be associated with intermittent epidemics [19].

The national Australian notification data also show rising rates of gonorrhoea in women as do some international data[3,29]. This trend may be in part explained by the recent introduction of more widespread and sensitive testing for gonorrhoea that has detected infections that may have been previously missed[29]. However the concern is that the recent rises in rates among heterosexuals may be real and indicate population rates are rising again. A key public health issue then is how far will it rise? The significance of this finding is that it may herald the start of endemic heterosexual gonorrhoea once again in Australia for the first time in 30 years and the emerging trend requires careful observation.

Finally, the pattern of chancroid suggests it is a particularly easy infection to control at a population level. Not only did it virtually disappear after the early 1950's, but many of the male cases diagnosed between 1942 and 1952 in Australia were likely to have been acquired overseas, on the basis that 29% were seamen (data not shown). In contrast, while occasional cases occurred in women these infections appeared to be treated without substantial ongoing heterosexual spread on the basis that cases in women were very sporadic. It seems unlikely that these were infections in predominantly MSM because this infection has not been associated with MSM in the past and the very high ratios of men to women occurred only in the latter half of last century with the legalisation of same sex sexual practices[23].

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Christopher K. Fairley conceived the idea of this study. Emile Jasek, Christopher K. Fairley and Eric P.F. Chow designed the study. Tiffany Phillips was involved in data entry and management. Emile Jasek undertook the analysis and interpretation, and prepared the first draft of the manuscript. Eric P.F. Chow and Christopher K. Fairley assisted with data analysis and data interpretation. Meredith Temple-Smith and David Lee were consulted for the historical data during the writing of the manuscript. All authors contributed in data interpretation and revising the manuscript critically for important intellectual content.

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Table S1. Number of gonorrhoea, infectious syphilis, chancroid and chlamydia diagnoses by sex and male sexual practice, sexual health clinics, Melbourne, 1918-2016.

Year	Gonorrhoea diagnoses				Infectious syphilis diagnoses				Chancroid diagnoses				Chlamydia diagnoses			
	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males
1918	96				130				1							
1919	53				62				0							
1920	103				39				6							
1921	74				43				1							
1922	61				23				0							
1923	71				22				2							
1924	44				24				0							
1925	57				12				0							
1926	162	1,698			59	146			0	32						
1927	240	1,829			69	304			0	89						
1928	269	1,761			164	364			0	66						
1929	244	1,490			117	213			2	64						
1930	458	1,515			95	151			8	43						
1931	545	1,451			143	164			10	78						
1932	366	1,344			103	144			0	54						
1933	363	1,123			102	117			0	45						
1934	336	1,194			50	94			0	32						
1935	389	1,185			51	111			0	19						
1936	392	1,085			57	80			0	12						
1937	297	1,208			32	79			1	3						
1938	373	1,355			39	78			0	2						
1939	272	1,095			35	68			1	2						
1940	163	911			34	90			0	0						
1941	128	820			58	132			0	0						
1942	95	715			38	159			8	1						
1943	316	601			65	122			0	0						
1944	164	593			29	83			1	25						
1945	83	562			20	66			0	27						
1946	52	1,057			15	132			0	47						
1947	91	912			13	132			0	52						
1948	81	770			21	178			0	50						
1949	48	503			27	155			0	81						
1950	26	375			26	146			0	123						
1951	25	205			31	97			0	32						
1952	32	259			12	85			0	0						
1953	28	268			5	51			0	3						
1954	20	192			5	48			0	0						
1955	53	412			10	79			0	0						
1956	67	521			17	81			0	0						
1957	112	634			4	68			0	0						
1958	130	535			15	65			0	1						

Year	Gonorrhoea diagnoses				Infectious syphilis diagnoses				Chancroid diagnoses				Chlamydia diagnoses			
	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males
1959	145	661			9	119			0	0						
1960	157	705			16	116			0	1						
1961	144	656			5	76			0	1						
1962	230	769			2	47			0	1						
1963	214	634			4	50			0	4						
1964	214				0				0							
1965	220				1				0							
1966	289				2				0							
1967	361				4				1							
1968	319				4				1							
1969	356	696			13	81			0	1						
1970	638	845			6	30			0	0						
1971	618	916			11	42			1	1						
1972	773	930			4	34			0	0						
1973	730	803			8	36			0	0						
1974	715	991			1	59			0	0						
1975	553	1,127			7	68			0	1						
1976	395	954			14	50			0	0						
1977	358	1,109			7	30			0	4						
1978	368	1,379			8	24			0	5						
1979	330	1,201			9	27			0	1						
1980	402	1,190			4	37			0	0						
1981	333	1,068			7	26			0	0			103	2		
1982	280	1,277			8	7			0	1			300	4		
1983	373	884			2	7			0	0			408	2		
1984	216	651			3	19			0	0			432	6		
1985	243	453			1	4			0	0			362	23		
1986	137	354			1	6			0	0			261	2		
1987	82	218			1	6			0	0			154	2		
1988	36	159			1	4			0	0			125	0		
1989	44	136			0	1			0	0			104	11		
1990	12	93			0	0			0	0			90	78		
1991	7	71			0	0			0	0			21	43		
1992	5	52			1	1			0	0			0	0		
1993	1	41			0	0			0	0			0	0		
1994	4	48							0	0						
1995	1	46							0	0						
1996	2	64							0	0						
1997	5	34							0	0				81		
1998	3	70							0	0			81	117		
1999	5	79							0	0			95	137		
2000	5	93							0	0			71	162		
2001	11	88							0	0			91	224		
2002	14	122	94	28	0	10	4	6	0	0	0	0	186	352	148	204

Year	Gonorrhoea diagnoses				Infectious syphilis diagnoses				Chancroid diagnoses				Chlamydia diagnoses			
	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males	Female	Males	Men who have sex with men	Heterosexual males
2003	7	224	191	33	1	10	8	2	0	0	0	0	218	401	130	271
2004	12	209	189	20	2	28	24	4	0	0	0	0	213	425	152	273
2005	15	214	170	44	1	37	36	1	0	0	0	0	257	456	178	278
2006	15	283	252	31	4	60	54	6	0	0	0	0	307	522	236	286
2007	19	203	175	28	5	123	108	15	0	0	0	0	287	498	218	280
2008	28	200	173	27	3	111	104	7	0	0	0	0	327	617	278	339
2009	26	292	239	53	3	139	128	11	0	0	0	0	377	764	412	352
2010	48	418	380	38	4	94	80	14	0	0	0	0	404	911	504	407
2011	43	382	330	52	3	109	92	17	0	0	0	0	352	724	405	319
2012	46	545	487	58	5	162	151	11	0	0	0	0	414	946	511	435
2013	40	704	622	82	14	192	178	14	0	0	0	0	530	1,250	706	544
2014	51	743	679	64	7	273	256	17	0	0	0	0	600	1,360	730	630
2015	96	1,489	1,404	85	21	366	329	37	0	0	0	0	640	1,671	1,048	623
2016	137	1,629	1,525	104	19	406	366	40	0	0	0	0	754	2,079	1,454	625

Original Article

The effects of culture independent diagnostic testing on the diagnosis and reporting of enteric bacterial pathogens in Queensland, 2010 to 2014

Fiona J May, Russell J Stafford, Heidi Carroll, Jennifer MB Robson, Renu Vohra, Graeme R Nimmo, John Bates, Martyn D Kirk, Emily J Fearnley and Benjamin G Polkinghorne

Abstract

Changes in diagnostic laboratory testing procedures can impact on the number of cases notified and the public health surveillance of enteric pathogens. Culture independent diagnostic testing using a multiplex polymerase chain reaction (PCR) test was introduced for the rapid detection of bacterial enteric pathogens in pathology laboratories in Queensland, Australia, from late 2013 onwards. We conducted a retrospective descriptive study using laboratory data to assess the impact of the introduction of PCR testing on four common enteric pathogens, *Salmonella*, *Campylobacter*, *Shigella* and *Yersinia*, in Queensland between 2010 and 2014.

The number of stool specimens tested and the proportion positive for each of the four pathogens increased in 2014 after the introduction of culture independent diagnostic testing. Among the specimens tested by both PCR and culture, 12% of *Salmonella* positive stools, 36% of *Campylobacter* positive stools, 74% of *Shigella* / enteroinvasive *Escherichia coli* positive stools and 65% of *Yersinia* positive stools were PCR positive only. Including those where culture was not performed, 19% of *Salmonella* positive stools, 44% of *Campylobacter* positive stools, 83% of *Shigella* positive stools and 79% of *Yersinia* positive stools had no cultured isolate available for further characterisation. The detection and tracking of foodborne and non-foodborne gastrointestinal outbreaks will become more difficult as culture independent diagnostic testing becomes more widespread. Until new techniques for characterisation of pathogens directly from clinical specimens have been developed, we recommend laboratories continue to culture specimens concurrently or reflexively with culture independent diagnostic tests.

Introduction

For bacterial enterocolitis, identification of the causative agent is important to inform clinical management and prevent ongoing transmission. Most cases only require supportive treatment.[1] For public health surveillance to examine trends in disease, detect outbreaks and monitor antimicrobial resistance, additional information about the pathogen strain or serotype is required. Traditional laboratory methods of culture followed by characterisation of isolates provide essential information for these purposes.

Culture independent diagnostic testing (CIDT) includes any laboratory test that does not require the agent to be cultured prior to identification. CIDT currently used by pathology laboratories worldwide include tests that amplify and/or detect nucleic acid (most commonly polymerase chain reaction [PCR]) and tests that detect antigens, such as enzyme immunoassays.[2-4] These tests are often fast, easy to perform, sensitive and reliable. However, they are generally unable to identify serotypes or genotypes that are used to link cases in an outbreak, or provide antimicrobial susceptibility for treatment. CIDT may also detect non-viable organisms or residual DNA and are unable to distinguish between symptomatic cases and asymptomatic carriage.[5-7] Improved diagnostic sensitivity may provide a more accurate estimate of burden of disease. In addition, the ability of multiplex PCR to detect polymicrobial infections provides new insight into diseases and pathogen interactions.[3,4] The change in methodology makes interpreting disease trends over time difficult.[3]

Clinical diagnostic pathology in Queensland (Qld), Australia, is predominantly provided by two private laboratories and one public laboratory, covering approximately 95% of the pathology market in Qld. Both private laboratories introduced a Roche PCR (https://lifescience.roche.com/en_au/brands/lightmix.html) for enteric bacterial pathogens in late 2013 and the public laboratory introduced a non-commercial in-house PCR for enteric pathogens in late 2015. These laboratories continue to culture enteric pathogens,

either concurrently with the PCR, or reflexively for PCR positive stools only. Culture alone was performed if requested.

Salmonella (non-typhoidal), *Campylobacter, Shigella* and *Yersinia* together contribute approximately 99% of the potentially foodborne bacterial infections notified to Qld Health every year.[8] We assessed the impact of changed testing procedures on these four pathogens in Qld between 2010 and 2014.

Methods

Data collection

The three participating laboratories provided data on all *Salmonella*, *Campylobacter*, *Shigella* and *Yersinia* test results for stool samples from people with Qld residential postcodes performed between 2010 and 2014, inclusive. Each laboratory provided the date the sample was received by the laboratory, the organism(s) identified by culture where applicable, and the results of PCR testing where applicable. The public laboratory, despite catering to a different population to the private laboratories, was used as a culture-only comparison group for observing the change in stool submission rates and pathogen incidence.

Data analysis

Samples positive for *Salmonella* Typhi or *Salmonella* Paratyphi were excluded as the public health response for these two serotypes is different from the public health response for other *Salmonella* serotypes.

The number of stool tests positive and the percent of tests positive (percent positivity) were calculated for each pathogen by month of sample receipt. The denominator data used to calculate the percent positivity was the total number of stool specimens tested for bacterial enteric pathogens at each laboratory during each month, whether they were positive or negative for any pathogen.

Percent positivity before the introduction of PCR (data from 2010 to 2012 [pre-PCR]) and after the introduction of PCR (data from 2014 [post-PCR]) were compared for all laboratories. Data from 2013 was not included in the comparison as the private laboratories introduced PCR in different months during 2013. An alternative pre-PCR period of July 2012 to June 2013 was used for *Campylobacter* to compensate for the decline in incidence in early 2012. Significance ($P \leq 0.05$) was assessed using the two sample test of proportions.

Percent positive agreement (PPA) between culture and PCR was calculated for each pathogen as a measure of agreement between these two tests. This measure is the percentage of the total number of stools where both tests were positive divided by the total number of tests positive by at least one test, where both tests were performed and is used to measure agreement when a gold standard test is unavailable for calculating sensitivity and specificity.[9] This method disregards samples that were negative by both methods in order to reduce the impact of large numbers of negative specimens. Specimens where one of the test methods was not performed were also disregarded.

All data were cleaned and analysed using StataSE 13 (Stata Corp, College Station, TX, USA) and Microsoft Excel.

Ethics approval

Human research ethics approval for the study was obtained through both the Australian National University Research Ethics Committee (reference number 2015/429) and the Royal Brisbane and Women's Hospital Human Research Ethics Committee (reference number HREC/15/QRBW/404).

Results

A total of 740,327 stools were tested for gastrointestinal pathogens at the three laboratories during the study period. The number of stool specimens submitted for testing at the three participating laboratories increased considerably following the introduction of PCR in late 2013 (Figure 1). The stool submission rate post-PCR was 3,920 per 100,000 population compared to a mean annual rate of 3,038 per 100,000 for the period pre-PCR. For the private pathology laboratories combined, the mean number of stools tested per month increased significantly by 45% ($P < 0.001$) post-PCR compared to pre-PCR. The public pathology laboratory reported a significant 9% increase ($P < 0.001$) during the same period without the introduction of PCR testing.

The number of stools that tested positive for *Salmonella* was significantly higher post-PCR when compared to the number positive during the pre-PCR period (Figure 2). Similarly, the proportion of positive stools each month increased post-PCR compared to the pre-PCR period. The proportion of stools positive for *Salmonella* at the private laboratories combined increased from 2.0% to 2.6% ($P = 0.006$) (Table 1). Public laboratory data showed a small, but non-significant increase in stools positive for *Salmonella* (2.9% to 3.5%).

Figure 1. Total number of stools tested by each laboratory, and the rate of stools tested per 100,000 population, by month and year, Qld, 2010 to 2014. The private laboratories introduced PCR in late 2013.

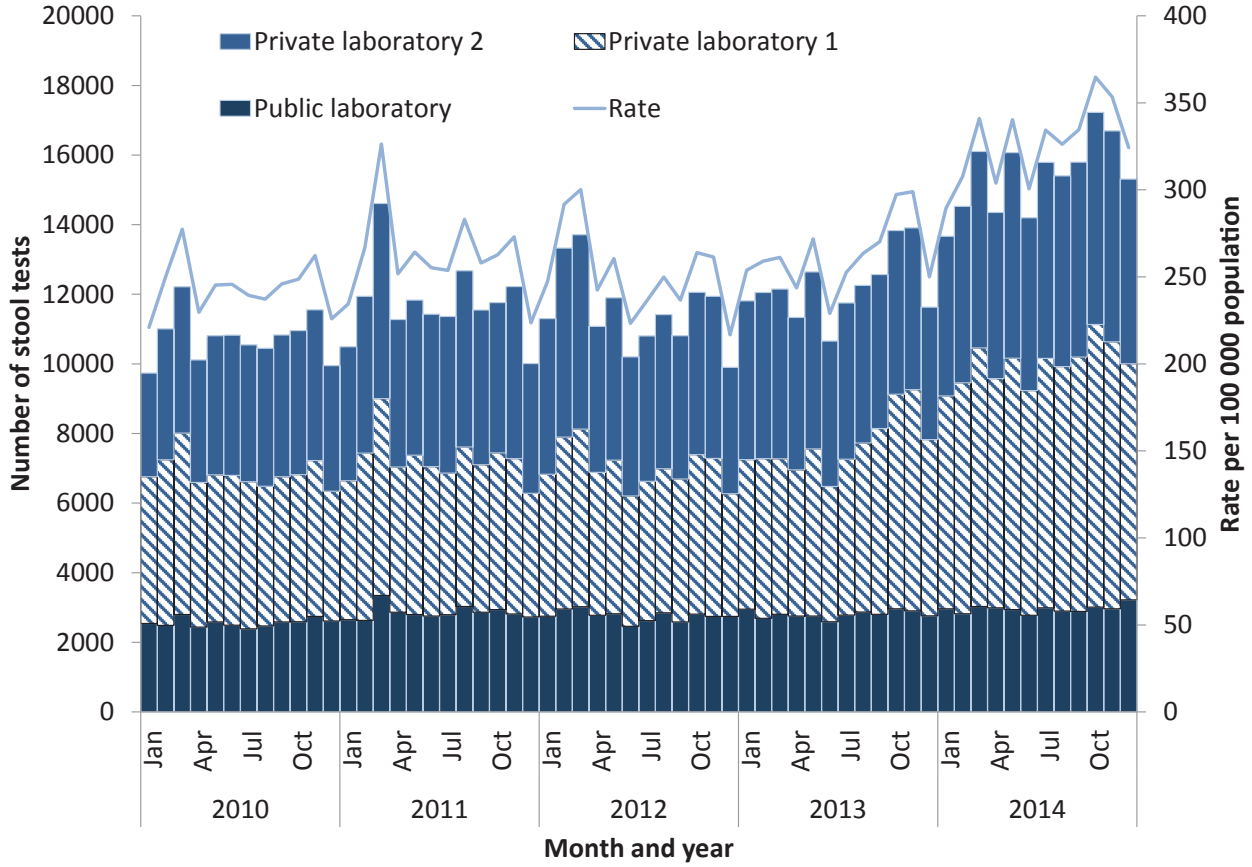


Figure 2. Number of stools positive for *Salmonella* by culture and/or PCR at the Qld private laboratories, and the proportion (%) of positive stool specimens by month and year, 2010 to 2014. The private laboratories introduced PCR in late 2013.

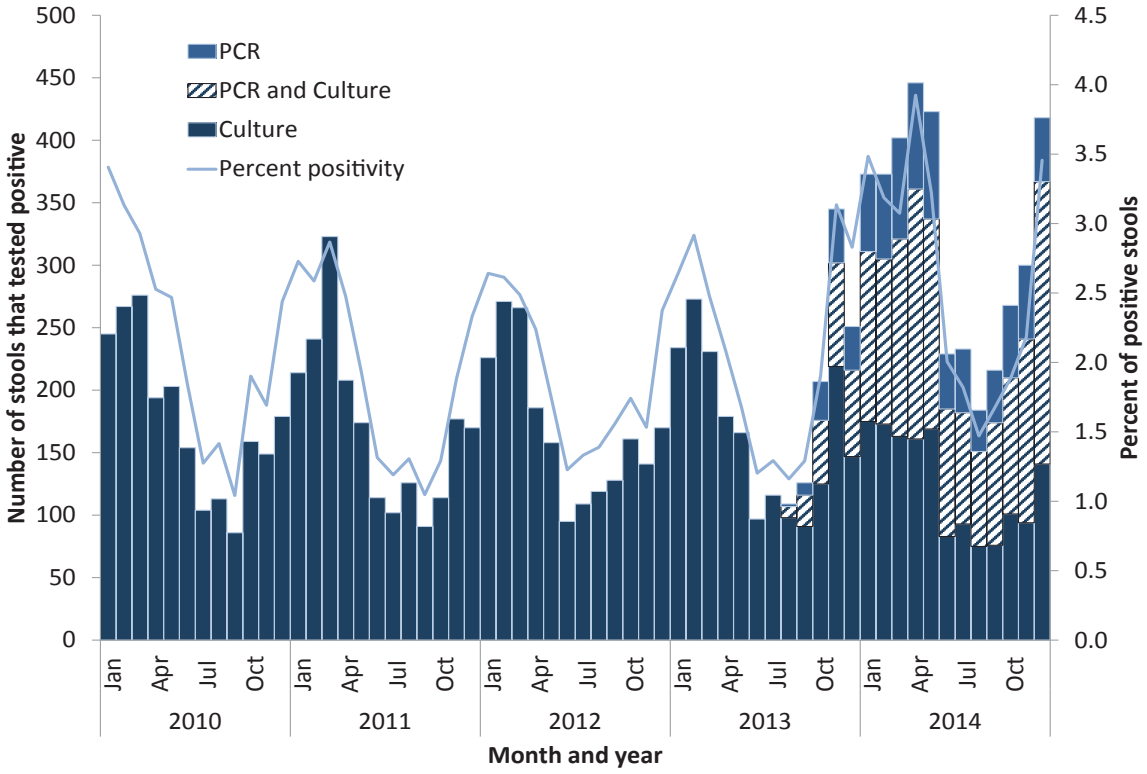
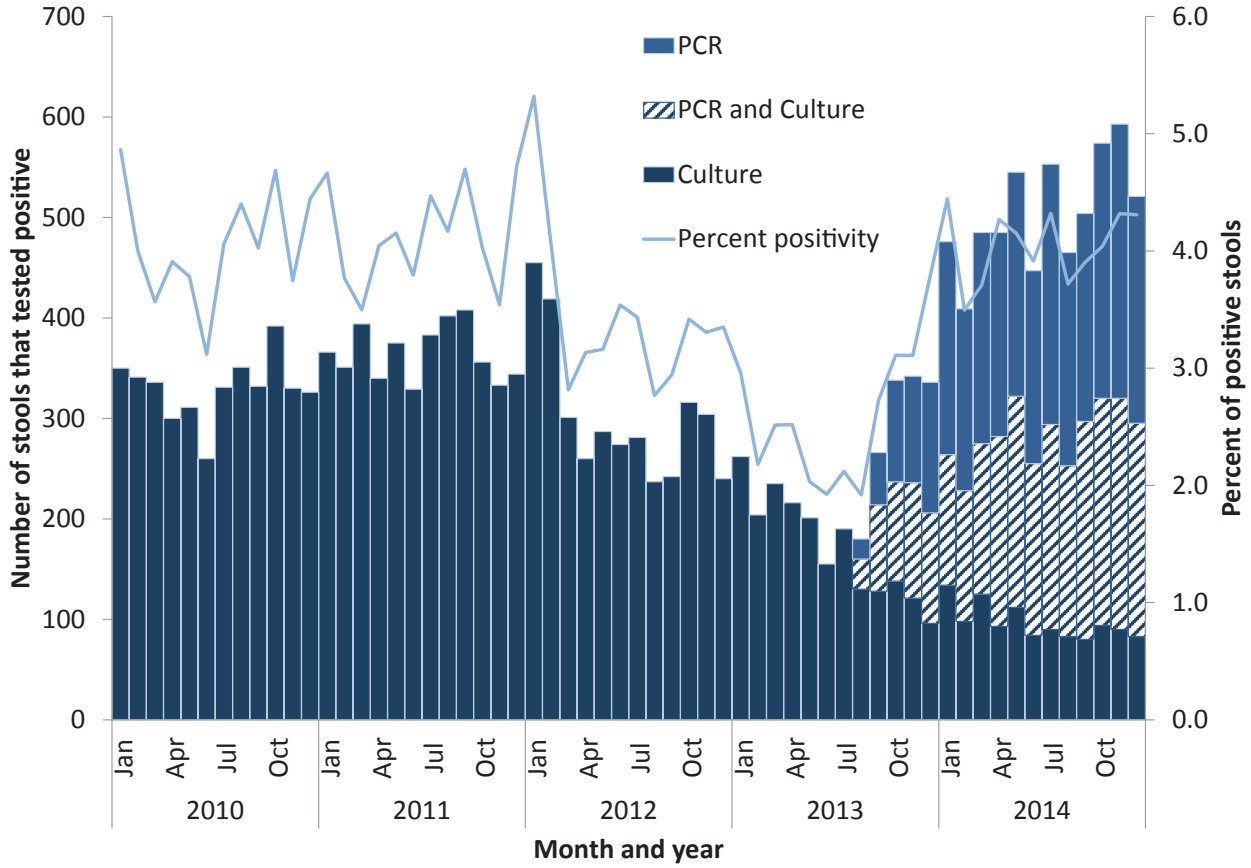


Table 1. Proportion of stools positive and monthly mean for each pathogen before and after introduction of PCR, by whether the laboratory had introduced PCR.

Pathogen	Type of laboratory	Pre-PCR		Post-PCR		
		%	Monthly mean	%	Monthly mean	P value†
Salmonella	Private (PCR)	2.0	173	2.6	322	0.006
	Public (no PCR)	2.9	78	3.5	103	0.22
Campylobacter	Private (PCR)	2.8	241	4.0	505	<0.001
	Public (no PCR)	3.2	89	3.1	91	0.72
Shigella	Private (PCR)	0.03	3	0.32	40	<0.001
	Public (no PCR)	0.14	4	0.16	5	0.97
Yersinia	Private (PCR)	0.06	5	0.39	49	<0.001
	Public (no PCR)	0.07	2	0.12	4	0.63

† Two sample test of proportions

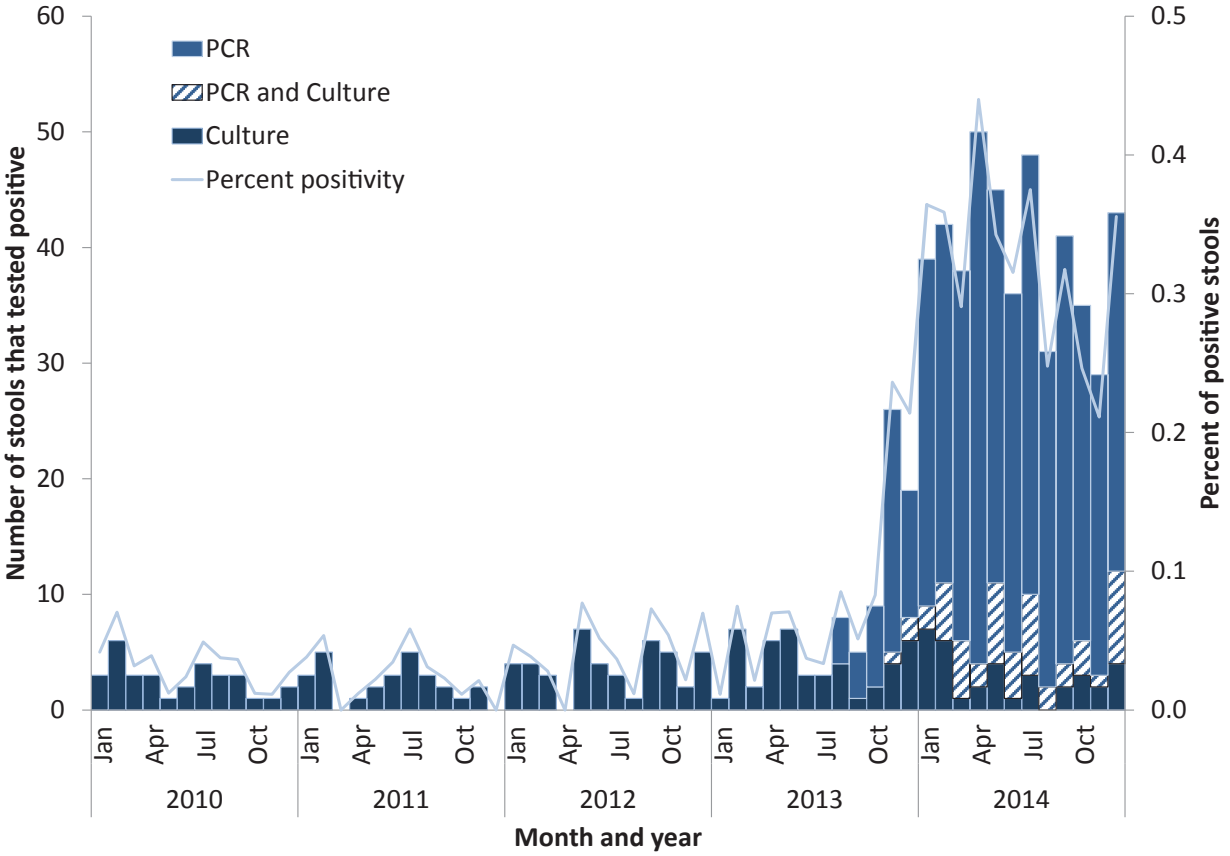
Figure 3. Number of stools positive for *Campylobacter* by culture and/or PCR at the Qld private laboratories, and the proportion (%) of positive stool specimens, by month and year, 2010 to 2014. The private laboratories introduced PCR in late 2013.



The number of stools positive for *Campylobacter* was higher post-PCR when compared to the monthly number positive pre-PCR (Figure 3) and the proportion of stools that tested positive increased significantly from 2.8% to 4.0% (P <0.001) when comparing 2012/13 pre-PCR period with the post-PCR period (Table 1). The public laboratory showed a non-significant decrease in the proportion of *Campylobacter* positive stools per month when the 2012/13 pre-PCR period was compared with post-PCR (Table 1).

The proportion of stools positive for *Shigella* at the private laboratories combined increased significantly from 0.03% pre-PCR to 0.32% post-PCR (P <0.001) (Figure 4, Table 1). The public laboratory showed only a slight increase in the proportion of stools positive per month post-PCR compared with pre-PCR (Table 1). The increase was not significant.

Figure 4. Number of stools positive for *Shigella* by culture and/or PCR (*Shigella*/EIEC) at the Qld private laboratories, and the proportion (%) of positive stool specimens, by month and year, 2010 to 2014. The private laboratories introduced PCR in late 2013.



The proportion of stools positive for *Yersinia* at the private laboratories combined increased from 0.06% pre-PCR to 0.39% post-PCR (P <0.001) (Figure 5, Table 1). The public laboratory showed no significant difference in the proportion of stools positive per month post-PCR compared with pre-PCR (Table 1).

Table 2 shows the number and proportion of positive test results that were concordant (both tests gave the same result) or discordant (one positive result and one negative result) for PCR and culture at the private laboratories combined in 2014. Of those stools that tested positive for *Salmonella,* 17% had discordant results. More so, 36% of stools positive for *Campylobacter*, 74% of stools positive for *Shigella* and 65% of stools positive for *Yersinia* had discordant results.

The PPA for samples positive by culture and PCR (at the private laboratories combined) in 2014 was 71% (1,641/2,316) for *Salmonella*, 51% for *Campylobacter* (2239/4427) and 12% (48/400) for *Shigella*. PPA was not calculated for *Yersinia* as culture for this pathogen was not routinely performed prior to the introduction of PCR.

Discussion

Introduction of PCR diagnostic testing of stools by the two Qld private pathology laboratories significantly impacted public health surveillance of *Salmonella, Campylobacter, Shigella* and *Yersinia* by markedly increasing the number and proportion of stools testing positive for these four pathogens. The changing baseline will have a major impact on interpretation of surveillance data and the reduction in the number of isolates available for characterisation will reduce the ability to detect clusters of related cases.

Much of the increase in the proportion of stools testing positive for *Salmonella* in 2014 can be attributed to the introduction of PCR and increase in testing in the private laboratories. At least 12% of *Salmonella* positive stools identified at the private laboratories in 2014 would not have been identified if PCR had not been in use (PCR positive, culture negative). Further characterisation of *Salmonella* strains by typing was unable to be performed for almost one fifth of stools as they were PCR positive only (culture negative or no culture performed) for *Salmonella* in 2014. Although maintaining concurrent or reflexive culture for PCR positive stools will not

Figure 5. Number of stools positive for *Yersinia* by culture and/or PCR at the Qld private laboratories, by month and year and the proportion (%) of positive stool specimens, 2010 to 2014. The private laboratories introduced PCR in late 2013.

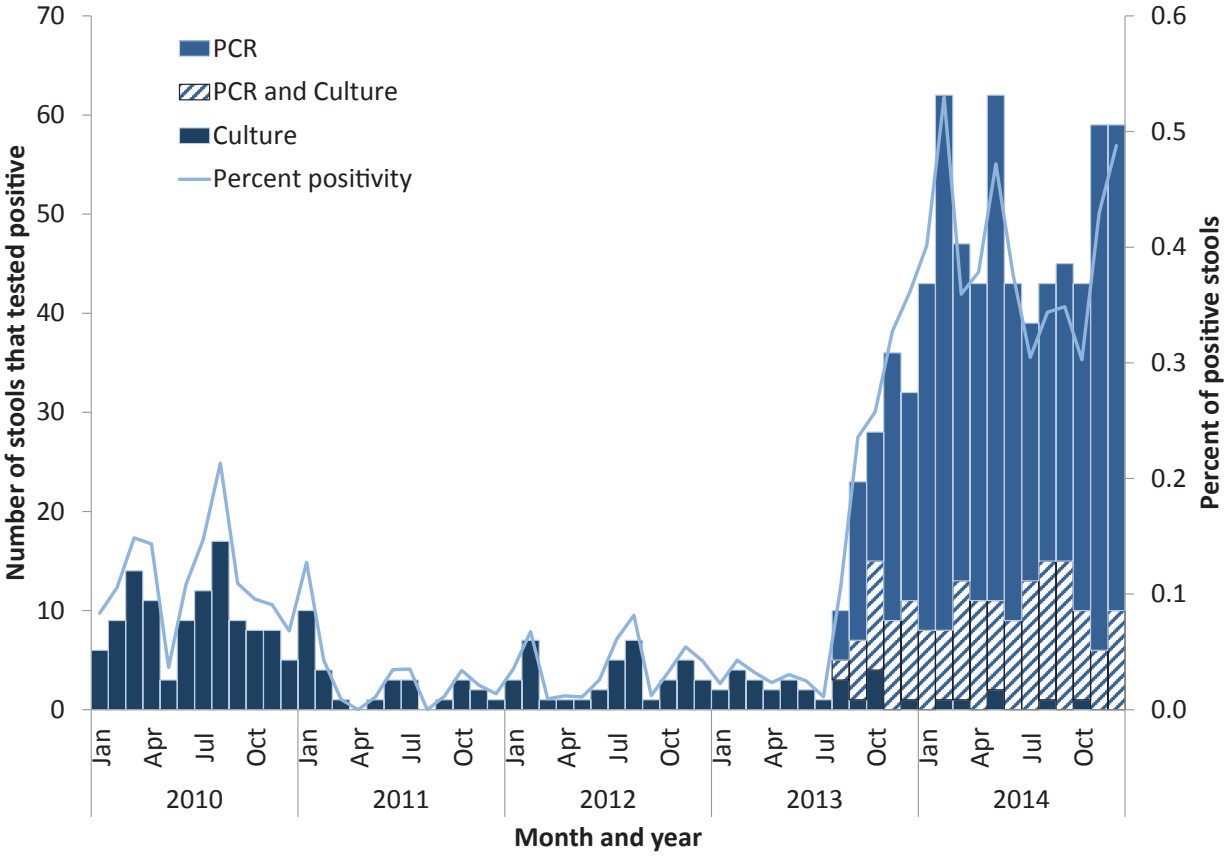


Table 2. Number and proportion of positive stools by test type (private laboratories only), 2014. Shading shows discordant results.

PCR	Culture	*Salmonella*		*Campylobacter*		*Shigella*		*Yersinia*	
		n	%	n	%	n	%	n	%
+	+	1,641	42	2,239	37	48	10	123	21
+	-	482	12	2,176	36	352	74	379	65
-	+	193	5	12	0	0	0	1	0
+	ND*	238	6	476	8	42	9	80	14
ND*	+	1,311	34	1,154	19	35	7	5	1
Total		3,865	100	6,057	100	477	100	588	100

* ND – not done

always result in an isolate,[3] it remains of public health importance to attempt to acquire an isolate for as many cases of salmonellosis as possible.

The sharp decline in the number of *Campylobacter* positive stool specimens during 2012 and 2013 may reflect a real drop in the incidence of campylobacteriosis following commencement of the national Primary Production and Processing Standard for Poultry in 2012 after a two year implementation period.[10] The decrease was observed in notification data in other jurisdictions.[11] There was a significant increase in the proportion of positive stools in 2014 at the private laboratories that was not evident at the public laboratory. This suggests any increase in the total number of stools positive for *Campylobacter* in 2014 was primarily a result of the introduction of PCR at the private laboratories. The PPA for *Campylobacter* was 51%; almost all of the positive stools with discordant results had a negative culture. *Campylobacter* is difficult to culture as it requires specific environmental conditions (microaerophilic) and fresh stool samples in order to recover viable bacteria for culture,[12] and culture based methods are less sensitive for detecting *Campylobacter* than PCR.[13,14]

Current PCR methods for identifying *Shigella* are unable to distinguish between *Shigella* species and enteroinvasive *Escherichia coli* (EIEC) as both are closely genetically related.[15,16] However, EIEC typically causes milder symptoms than *Shigella*[17] and is not notifiable in Australia. As 74% of stools positive for *Shigella* by PCR did not yield a culture, the large increase in the number of stools positive for *Shigella* may in part be due to cases of EIEC being detected by the *Shigella* PCR. However, since *Shigella* can be difficult to culture,[18] the possibility that a proportion of the PCR positive samples were true cases of *Shigella* cannot be discounted. The case definition for *Shigella* in Qld requires isolation of the pathogen, so only those samples with an associated isolate are notified to the Qld Notifiable Conditions System and the National Notifiable Diseases Surveillance System.[19] Thus, in 2014, over 80% of stools positive for *Shigella* by PCR were not notified or were rejected from the notification system. Nevertheless, although these possibly false positive samples were rejected when an isolate was unable to be obtained, they had already resulted in an increase in workload at both primary and reference laboratories where isolate characterisation is performed.

Not all pathology laboratories routinely use culture methods to select for *Yersinia* unless specifically requested by the clinician. However, as *Yersinia enterocolitica* is included in the multiplex PCR test, it was detected even when it was not specifically requested. This may explain some of the increase in the number of tests positive for *Yersinia* after introduction of PCR, and is a reflection of the true incidence of *Yersinia* in Qld. However, 65% of all stools positive for *Yersinia* were positive by PCR and negative by culture, suggesting a much higher sensitivity of PCR than culture for *Yersinia*.

An additional explanation for the increase in stools with a positive culture in Qld during the study period may be associated with the nature of reflexive testing with laboratory technicians searching more intensely for pathogens when they are aware of PCR positive samples.[20]

The proportion of tests positive by PCR only in Qld is higher than that seen in a United States (US) study, where 5% of *Salmonella* infections, 24% of *Campylobacter* infections, 14% of *Shigella* infections and 9% of *Yersinia* infections were positive by CIDT methods only (including PCR and other methods) in 2015.[4] However, the US study only included tests done in a subset of the population, and adoption of PCR (compared with other CIDT) has been slow in some areas.[4] Indeed, the proportion of salmonellosis cases in the US diagnosed by CIDT alone increased substantially in 2015 compared with 2012-2013.[2]

All three laboratories in the current study reported an increase in the total number of stool specimens tested for enteric pathogens, although the percent increase at the public laboratory, where PCR wasn't introduced, was considerably lower than that reported by the private laboratories. It is likely that the increase is predominantly due to the availability of the more rapid PCR test leading to more requests for stool testing by general practitioners.

A limitation of this study is that only one year of data was available after the introduction of PCR at the private laboratories. Comparison of multiple years of data would ensure that the increased incidence of the pathogens in 2014 was not an anomaly. Publicly available notification data suggests that notifications of these four pathogens in Qld has stabilised at a higher rate than the pre-PCR period (data available from http://www9.health.gov.au/cda/source/cda-index.cfm). In addition, only Qld data was analysed, and only for four enteric pathogens. This study should be extended in the future to other jurisdictions across Australia, and for other pathogens. However, the results of this study can be used by laboratories and public health units to inform the way forward for diagnosis, referral and subtyping of enteric pathogens.

We have shown that the introduction of PCR has led to an increase in the detection of these four pathogens in stools, leading to an increase in incidence. Furthermore, PCR introduction has been associated with an increase in the number of stool specimens being submitted for testing though a significant proportion of positive stools are not yielding an isolate to enable strain characterisation for public health surveillance. Should pathology laboratories reduce or terminate concurrent and reflex culture, the number of specimens without an isolate for further characterisation will continue to increase. Until new techniques such as amplicon or whole genome metagenomics (direct sequencing of clinical specimens without need for isolates) are introduced, culture (reflex or concurrent) of enteric pathogens should remain a priority to enable appropriate public health surveillance for detection of outbreaks and monitoring of trends.

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Original Article

The epidemiology of tuberculosis in the Australia Capital Territory, 2006-2015

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Abstract

Aim

To review the epidemiology of tuberculosis (TB) in the Australian Capital Territory (ACT) over a 10 year period.

Methods: A retrospective analysis of the ACT TB notification data from 1 January 2006 to 31 December 2015 was conducted.

Results

Over the 10 year study period there were 171 TB notifications in the ACT, with an increasing trend in the number of notifications over time. The median age of cases was 36 years (range 14 to 91 years) and 53.8% of cases were male. Most TB cases (84.2%) were born overseas. Among Australian-born cases the most common risk factor for acquiring TB was close/household contact with a known case of TB (30.8%). The most common risk factor in the overseas-born population was past travel or residence in a high-risk country (86.9%). Of all the TB cases notified, 82.4% successfully completed treatment.

Conclusion

There was an increasing trend in the number of TB notifications in the ACT over the study period. The highest rate of TB notifications remained in the overseas-born population; with other studies suggesting this is commonly due to reactivation of latent tuberculosis infection (LTBI). As Australia starts working towards TB elimination, options for the screening and management of LTBI, especially in high risk populations, need to be explored.

Introduction

Despite a significant decline in the incidence of tuberculosis (TB) over the past few decades, it remains a significant cause of morbidity and mortality worldwide.[1] The World Health Organization (WHO) estimated that globally there were 10.4 million cases of TB in 2015.[1] Between 2006 and 2015, the rate of TB notifications in Australia has remained fairly stable; in 2015 this was 5.3 per 100,000 population per year;[2] corresponding to 1,244 individual notifications.[3] While Australia experiences low rates of TB, importation of cases associated with migration and overseas visitors remains an important source of new cases, highlighting the necessity for ongoing screening and control measures. Of further concern is the rise in the number of cases of multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) in some of Australia's close neighbours, such as Papua New Guinea, Vietnam and the Philippines, and the potential public health implications associated with this.[4, 5]

The Australian Capital Territory (ACT) is a relatively small jurisdiction with an estimated population of just over 390, 000 in 2015.[6] Data from the 2011 census reported only 1.5% of the ACT population were Aboriginal or Torres Strait Islander, and 36% of the ACT population were born overseas.[6] In the ACT, TB is a notifiable condition under the *Public Health Act 1997,* with notifications made to the ACT Health Protection Service. Information on risk factors, treatment and treatment outcomes is collected and sent to the Commonwealth National Notifiable Disease Surveillance System (NNDSS). Clinical management of pulmonary TB is provided by the Department of Respiratory and Sleep Medicine at the Canberra Hospital, whilst extrapulmonary TB is managed by the Infectious Diseases Department. The Department of Respiratory and Sleep Medicine is also responsible for TB screening for health care workers, provision of LTBI treatment and contact tracing.

The aim of this study was to review the epidemiology of TB cases notified in the ACT over the 10 year period between 2006 and 2015.

Materials and method

Data for all TB cases notified to the ACT Health Protection Service between 1 January 2006 and 31 December 2015 were reviewed. Case inclusion was based on notification receipt date. The Communicable Disease Network of Australia case definition was used to classify cases of TB, which requires either laboratory confirmation through

isolation of *Mycobacterium tuberculosis* or detection through nucleic acid, or a clinically consistent picture as assessed by a clinician experienced in the diagnosis of TB.[7]

Data were obtained from the ACT Notifiable Disease Management System database and associated enhanced data spreadsheets. This included: demographics, year of arrival to Australia (if applicable), notification date, diagnostic testing results, site(s) of infection, risk factors for TB, HIV status, resistance profile, case classification and outcome.

Annual rates of TB were calculated using the mid-year ACT population estimate for each year, taken from the Australian Bureau of Statistics Estimated Resident Population, States and Territories.[8] Age group rates were calculated using 2010 mid-year estimated ACT resident population data.[9]

When reviewing the country of birth or travel history of cases, high-incidence countries were those with an annual incidence of more than 40 TB cases per 100,000 population as estimated in the World Health Organization Tuberculosis Report 2016.[1]

Negative binomial regression analysis was used to determine the trends in the number and rate of TB notifications over the 10-year study period. The data were analysed using Microsoft Excel® (2007) and SPSS® (Grad Pack v23.0 for Mac). STATA 14® was used for the trend analysis.

Results

Rates of TB

The ACT received 171 notifications of TB between 1 January 2006 and 31 December 2015, with a range of 10 to 30 notifications per year (Figure 1). Over the 10-year review period there was a single cluster of TB involving 10 cases with the same whole genome sequence, 8 of whom had an epidemiological link.

Between 2006 and 2015 the rate of TB notifications in the ACT ranged from 2.8 per 100,000 ACT population per year to 7.8 per 100,000 ACT population per year. In 2009 and 2014, the ACT notification rate was higher (6.5 and 7.8 per 100,000 ACT population per year, respectively) than the national average (6.0 and 5.7 per 100,000 national population per year, respectively).

Analysis of the trend in TB notifications over the 10 year period showed a significant increase in the number of cases ($p = 0.05$). An upward trend in notification rate was also seen, although this was not statistically significant ($p= 0.15$).

Socio-demographic characteristics of TB notifications

Of the TB notifications, 53.8% (n=92) were male. The median age of cases was 36 years (range 14 to 91 years) (Figure 2). The majority of cases (84.2%) were overseas-born (Figure 3). Of these, 127 (87.6%) cases were born in a high-incidence country. The most common countries of birth were India, Vietnam and China. The majority of the overseas-born population (68.1%) were Australian residents (citizens or permanent visa holders), and the remainder were overseas students (15.3%), visitors (12.5%), 5 cases (3.9%) were classified as 'other', and one case (0.8%) was a refugee (Figure 4). Only a small number of overseas-born cases (7.6%, n =11) were diagnosed through a TB health undertaking. One case occurred in a person of unknown country of birth. Of these cases, 15.2% (n=26) were in Australian-born individuals, none of whom identified as being of Aboriginal or Torres Strait Islander origin.

Of the TB cases in people born in a high-incidence country, the median time between arrival in Australia and diagnosis of TB was 4 years (range of <1 year to 66 years) (Figure 5). A high proportion of the notifications occured within the first 3 years of arrival in Australia (47.2%).

Clinical characteristics

Site of infection

Nearly half of the TB notifications (49.7%) between 2006 and 2015 were for pulmonary-only disease (Table 1), 40.4% were extrapulmonary, and 9.9% were both pulmonary and extrapulmonary disease. Sites of extrapulmonary infection included lymph node (44.2%), pleura (14%), bone (8.1%), peritoneal (8.1%), genitourinary (7.0%), and meningeal (2.3%). Disseminated TB disease occurred in 4.7% of cases.

Case classification

The majority of TB notifications (91.2%, n=156) were classified as new cases (Table 1). Eleven cases (6.4%) were classified as relapse (relapse of previously treated disease or a new episode of TB caused by re-infection) following treatment in Australia or overseas. The relapse rate was 0.8 per 100,000 population per year in 2012 and 0.5 per 100,000 population per year in 2013.

Laboratory confirmation

Approximately one third (35.3%) of pulmonary or pulmonary plus extrapulmonary cases were sputum smear positive on microscopy. The majority of

Figure 1: Number of TB notifications in the ACT and rates of TB notifications per 100,000 population per year in the ACT and Australia, by year, 1 January 2006 to 31 December 2015.

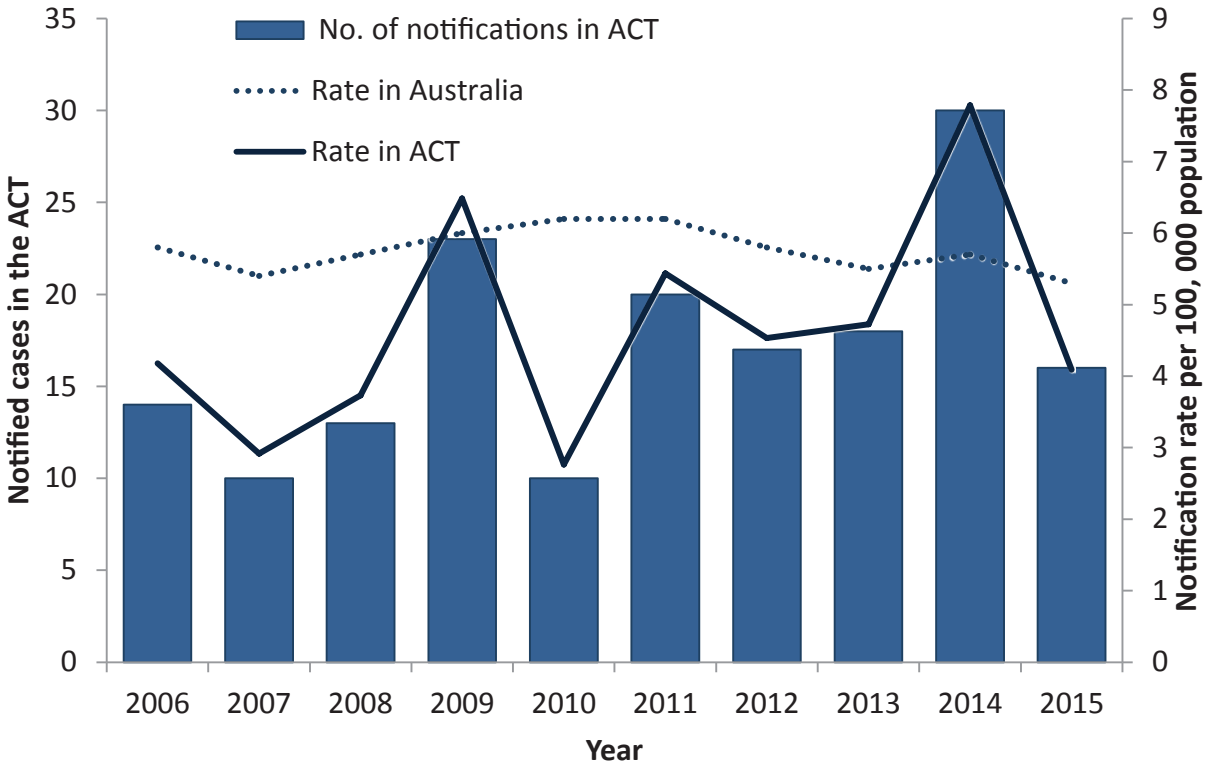


Figure 2: Age specific rate of TB notifications, ACT, 1 January 2006 to 31 December 2015.

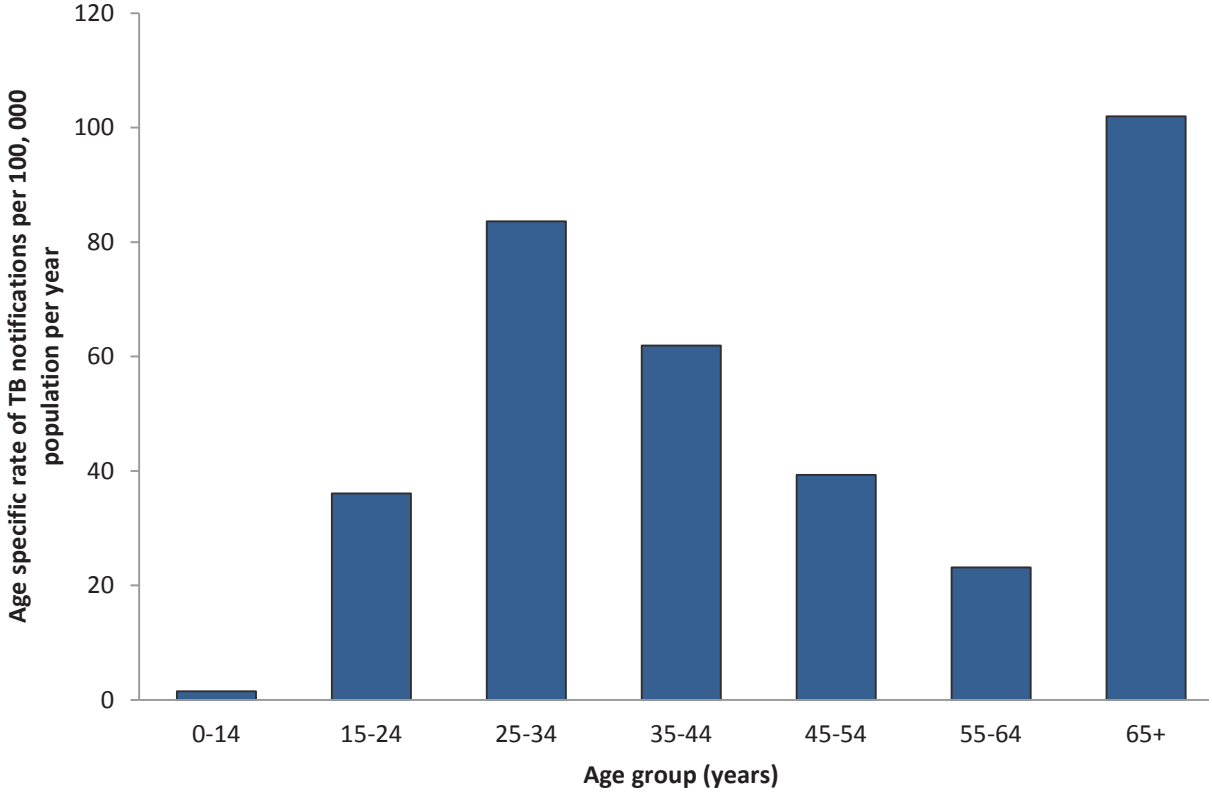


Figure 3: Number and rates per 100,000 ACT population per year of TB notifications in Australian-born versus overseas-born cases, by year, ACT, 1 January 2006 to 31 December 2015.

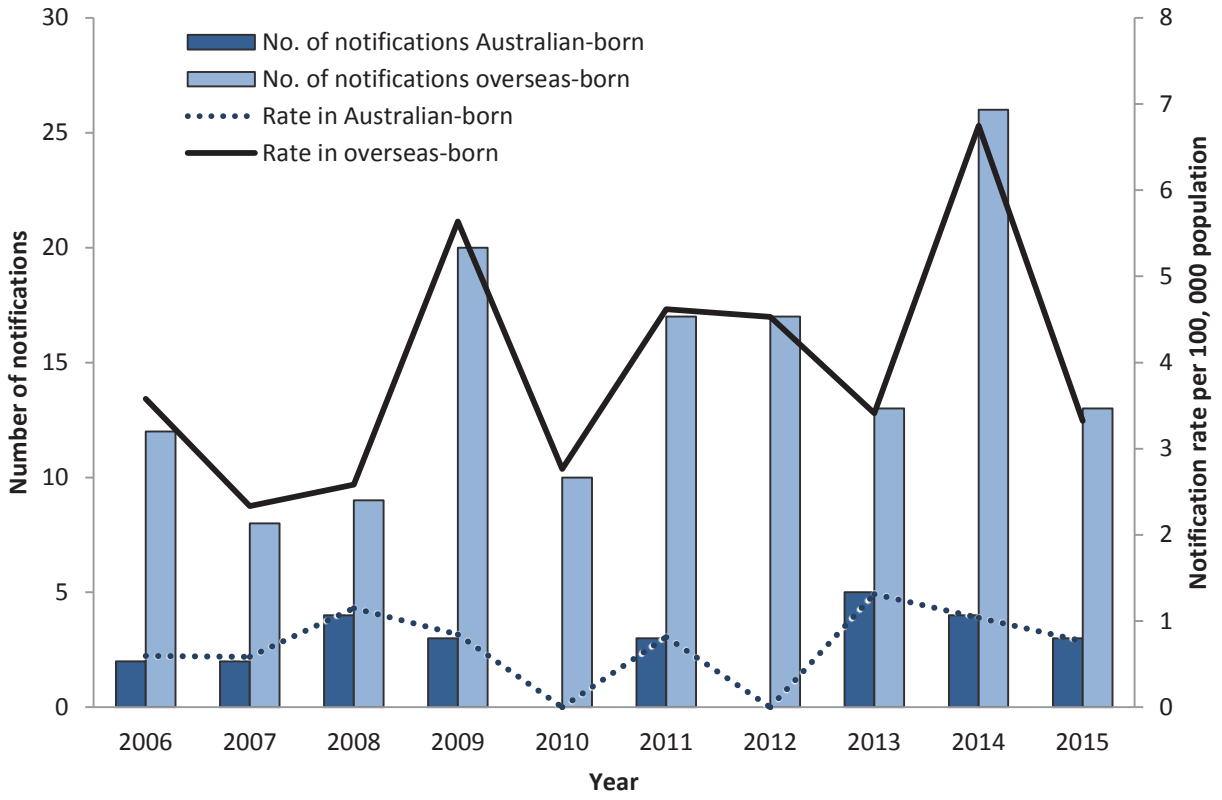


Figure 4: Number of TB notifications by residency status, ACT, 1 January 2006 to 31 December 2015

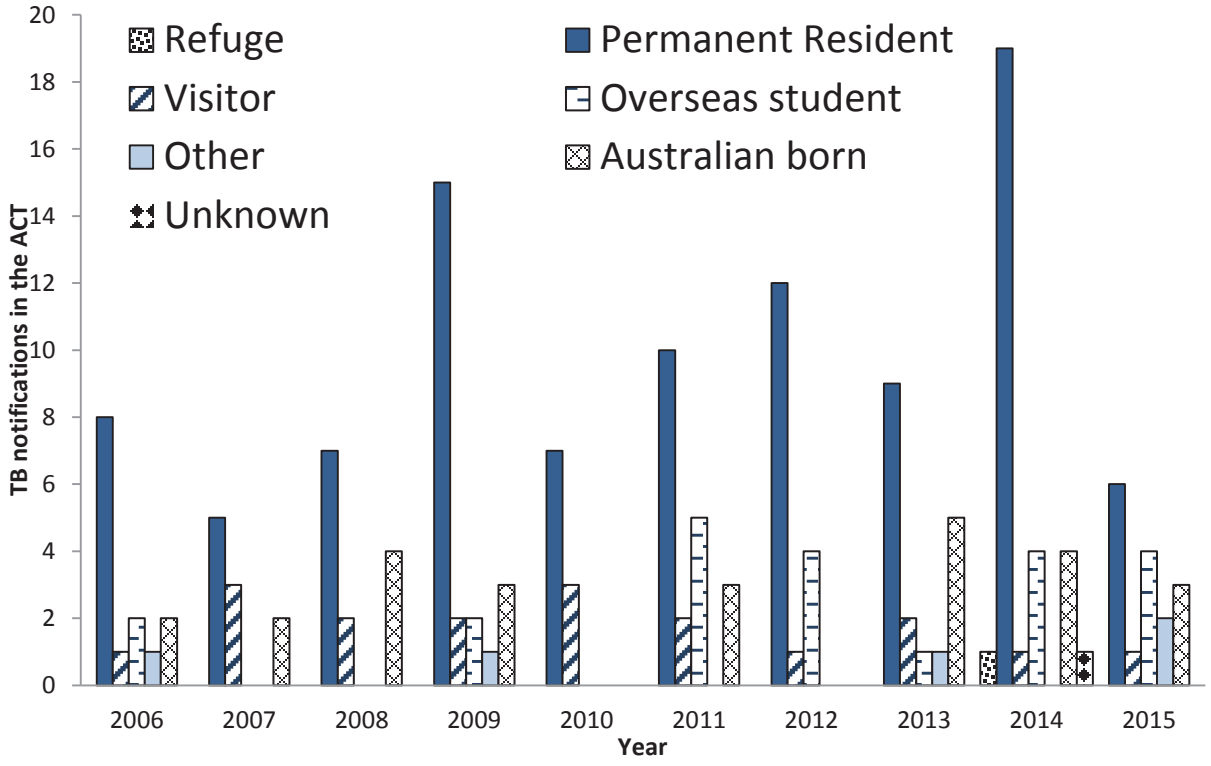
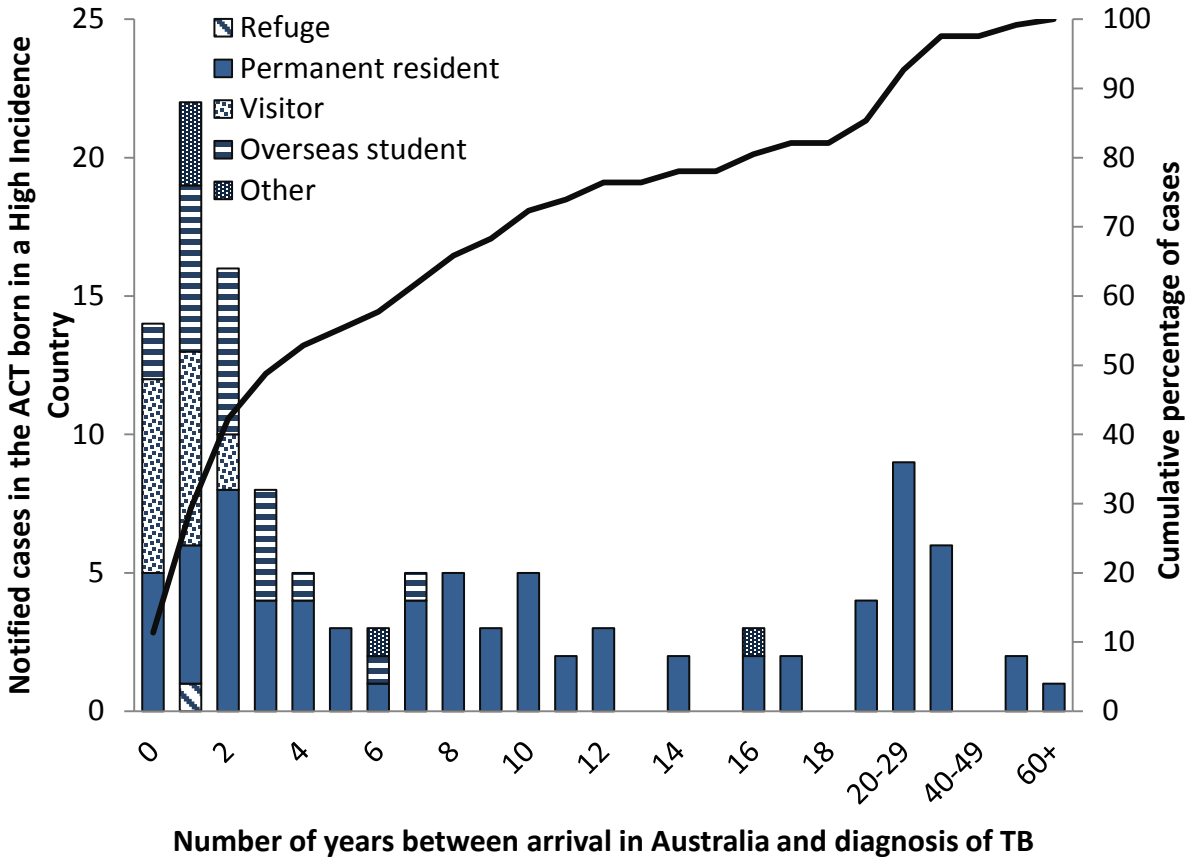


Figure 5: Number of years between arrival in Australia and diagnosis of TB for cases born in a high incidence country*, by number of cases and residency status, and cumulative percentage, ACT 1 January 2006 to 31 December 2015



*High-incidence countries were those with an annual incidence of more than 40 TB cases per 100,000 population as estimated in the World Health Organization Tuberculosis Report 2016.[1]

TB cases (78.3%) were either pulmonary sputum culture or other-specimen culture positive. Only 3 cases were diagnosed by PCR only and 12 cases were confirmed by histology only. Twenty-two cases were diagnosed on clinical grounds only (i.e. negative for TB on culture, microscopy, nucleic acid testing and/or histology); of these, 13 cases were diagnosed with pulmonary TB.

HIV co-infection

Over the 10 year period, the majority of cases (74.3%, n=127) tested as HIV negative and only 5 cases (2.9%) were identified as having HIV co-infection (Table 1). Four of the 5 TB-HIV co-infected cases were born overseas, and four cases were male. Twenty-three percent of TB notifications (n=39) were not tested or had unknown HIV testing history.

Resistance

There were 23 cases of TB with resistance to one or more anti-tuberculous drugs. Of these, the majority (n=16, 69.6%) had resistance to one drug, most commonly isoniazid. Three cases fit the classification of MDR-TB, defined as resistance to at least isoniazid and rifampicin.[10] There were no cases of XDR-TB.

Risk factors

The most common TB risk factor in the Australian-born population was having a household or close contact with TB (30.8%, n= 8) followed by past travel and/or residence in a high-risk country (19.2%, n= 5) (Table 2).In the overseas-born population the most common risk factor was past travel or residence in a high-risk country (86.9%). Prior to 2013, data collected regarding past travel or residence in a high-risk country may have included the country of birth, however following agreement from the National TB Advisory Committee, future recording of this data field was to only include travel and residence in high risk country excluding country of birth.[11]

Treatment and outcomes

Most TB cases notified between 2006 and 2015 completed treatment (82.5%), with a small proportion (2.9%) still undergoing treatment at the

Table 1: Clinical characteristics of TB cases, ACT, 1 January 2006 to 31 December 2015.

		Number (n)	Percentage (%)
Site of infection	Pulmonary only	85	49.7
	Pulmonary plus other sites	17	9.9
	Extra pulmonary only	69	40.4
Extra pulmonary site *	Pleural	12	14.0
	Lymph node	38	44.2
	Genitourinary	6	7.0
	Meningeal	2	2.3
	Bone/joint	6	7.0
	Disseminated TB	4	4.7
	Peritoneal including other GI sites	7	8.1
	Other	12	14.0
Case classification	New case	156	91.2
	Relapse following treatment overseas	7	4.1
	Relapse following treatment in Australia	4	2.3
	Unknown	4	2.3
Laboratory confirmation †	Sputum culture positive	74	43.2
	Other culture positive	83	48.5
	PCR	93	54.4
	Histology	64	37.4
	Nil	22	12.9
HIV	Negative	127	74.3
	Positive	5	2.9
	Not tested/unknown testing history	39	22.8
Resistance	Fully Sensitive	112	65.5
	Resistance ≥1 drug (not meeting criteria for multi-drug resistant TB)	13	7.6
	Multi-drug resistant TB	3	1.8
	Unable to test sensitivity (culture negative)	43	25.1

* Categories are not mutually exclusive, one case had more than one extrapulmonary site.
† Categories are not mutually exclusive, some cases had more than one method of laboratory confirmation

time of the review. Of those who completed treatment, only one case had interrupted treatment. Among sputum smear and culture positive cases (n=34), 11 (32.3%) met the criteria of being cured (defined as a smear positive, culture positive case who completes treatment and is documented to be culture negative on two separate occasions, one of which is in their last month of treatment). A small proportion of cases (14.6%, n=21) fell under another treatment outcome category: one case died as a result of TB, 11 died from other causes, and 9 had their care transferred to another health facility. Only two cases had an unknown treatment outcome.

Discussion

Between 2006 and 2015 the ACT experienced low annual TB notifications, ranging from 10 to 30 notifications per year. Over this period, the rate of TB has generally remained lower than national rates, with the exception of in 2009 and 2014 where the notification rates were higher. The reason behind the high notification rates in these two years is unclear as these cases were not linked to clusters or outbreaks, and screening practices have remained largely unchanged. Of note, in 2009 and 2014 there were a higher number of TB cases in overseas-born permanent residents (figure 4).

Analysis of the trend in the number of TB notifications in the ACT over the 10 year period revealed a statistically significant increase, although the observed upward trend in the notification rate was not statistically significant. This reflects that while the number of TB cases notified has generally increased over the past 10 years, increasing population growth has kept the rate fairly stable. This is consistent with national increases in the number of notifications seen over the same time period.[2]

Table 2: Risk factors for TB cases, ACT, 1 January 2006 to 31 December 2015. ‡

	Australian-born		Overseas-born		Total	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Household or close contact	8	30.8	15	10.3	23	13.5
Ever resided in a correctional facility	0	0	2	1.4	2	1.2
Ever resided in an aged care facility	1	3.8	0	0	1	0.6
Ever employed in an institution	1	3.8	4	2.8	5	2.9
Previous employment in health industry						
Australia	3	11.5	8	5.5	11	6.4
Overseas	0	0	8	5.5	8	4.7
Current employment in health industry (past 12 months)						
Australia	1	3.8	8	5.5	9	5.3
Overseas	1	3.8	3	2.1	4	2.3
Ever homeless	0	0	4	2.8	4	2.3
Past travel to or residence in a high-risk country (> 3 months)	5	19.2	126	86.9	131	76.6
Chest X-ray suggestive of old untreated TB	1	3.8	26	17.9	27	15.8
Currently on immunosuppressive treatment	2	7.7	4	2.8	6	3.5
None of the above risk factors	7	26.9	1	0.7	8	4.7
Not assessed	1	3.8	2	1.4	3	1.8

‡ Risk factor categories are not mutually exclusive, some cases had more than one risk factor

While the overall number of TB notifications in the ACT remains small, there are significant resource implications even with small increases in cases. Appropriate ongoing resourcing of TB services is particularly important as the proportion of the ACT population born overseas is projected to increase in the future.[12, 13]

Most of the notifications over the study period occurred in the overseas-born population, consistent with observations from other jurisdictions in Australia, where the proportion of overseas-born TB cases ranged from 55 to 100% of notifications in 2013.[11] In the ACT, overseas-born cases were primarily from high-incidence countries, with a median interval between arrival in Australia and TB diagnosis of 4 years. The majority (67.6%), of overseas-born cases were permanent residents with the second most common group being overseas students (15.2%).

These findings are consistent with national data from 2012 and 2013 which also found the highest proportion of cases amongst these two groups.[11]

Findings from other epidemiological studies in low-incidence countries suggest most cases of TB are due to reactivation of LTBI, rather than people arriving with active disease or as a result of local transmission.[14-17]

An increased rate of reactivation in migrants from high-incidence countries may be due to a number of factors making this population more susceptible such as acquiring LTBI just prior to migrating, stress, low socioeconomic status, underlying medical conditions or household crowding.[14, 17] Re-exposure to TB when travelling back to their country of birth may also be another important consideration.[14]

The most common risk factors for TB in the overseas-born population were travel or residence in a high-incidence country (86.9%) and previous chest x-ray findings suggestive of old untreated TB (17.9%). What this points to is the need for sustained efforts to target screening for TB infection among new migrant arrivals. Migrants, refugees and long-term visitors to Australia undergo pre-

migration screening for active disease, with any cases identified required to undergo treatment prior to entering Australia, thereby minimising the risk of spreading TB within Australia.[18] Expanding efforts to systematic screening and treatment of LTBI among overseas-born populations, particularly new permanent residents, in Australia is a potentially cost-effective method to further reduce the rates of TB.[14, 19, 20]

Currently, LTBI cases are not reported at a national level, and while screening for LTBI is recommended in some high risk groups such as refugees,[18,21]there are no national guidelines for LTBI screening. The National TB Advisory Council is currently developing a National Position Statement for the management of LTBI, which would facilitate a coordinated national approach.[22] Identification of higher risk populations such as new permanent residents from high-incidence countries could allow for more tailored screening approaches, although care would need to be taken to prevent stigmatising groups who are already potentially marginalised.[23]

The most common risk factor for TB amongst Australia-born cases was having a household or close contact with TB (30.8%), highlighting the importance of contact tracing and screening efforts. This is slightly higher than the 2012 and 2013 national data, which reported 26% and 22% of Australian-born cases as having household or close contact with TB as a risk factor, respectively. [11]

The low rates of other high risk groups for LTBI reactivation, such as people living with human immunodeficiency virus (HIV) or those with immunosuppression, observed over the study period suggest that these are not drivers for the persistence of TB in the ACT. However, 23% of TB notifications were not tested for HIV or had unknown testing history. Ideally, all patients with TB should be tested for co-infection with HIV. This is because TB is more common in patients with HIV and the treatment of tuberculosis can be more complex (e.g. the potential for undesirable drug interactions).[24] Indigenous Australians are another high risk group for TB;[11, 25] however none of the cases of TB notified in the ACT were reported as being Aboriginal or Torres Strait Islander Peoples. This may reflect the relatively small Indigenous population living in the ACT compared with other states, or inaccurate identification and/or recording of Aboriginal or Torres Strait status.[26]

Treatment failure and disease relapse are of particular concern, as they can lead to the development of drug-resistant TB and can counter efforts to reduce TB rates.[27] Global data estimates that 3.3% of new TB diagnoses are multi-drug-resistant.(1) In this study, the number of cases with MDR-TB was low (1.8%). Of note, all cases of MDR-TB were people born in high-incidence countries, and all were new cases that had not previously been treated for TB. Over 90% of cases in the ACT were newly diagnosed, however there were a small number of cases of relapse after treatment in either Australia (n=4) or overseas (n=7). Compared to the national relapse rate of 0.2 per 100,000 population per year in 2012 and 2013, the ACT had higher rates of 0.8 and 0.5 per 100,000 population per year, respectively.[11]

Without the use of molecular techniques, it was not possible to determine whether relapse was due to treatment failure or re-infection. Previous studies suggest that recurrent tuberculosis in high-income countries with low rates of tuberculosis is most commonly due to relapse of infection with the same strain.[28] Although the overall number of relapse cases is small, over a third of cases were in individuals treated in Australia, which is of concern as relapse in this context is one indicator of TB control. This highlights an area of potential future focus for the ACT and every effort should be made to reduce the relapse rate by identifying high-risk groups for consideration of a longer treatment course (e.g. patients with extensive cavitations on chest X-ray) and to differentiate true relapse from re-infection where possible, using molecular techniques.[28]

A significant number of TB cases were negative on all diagnostic testing, (12.9%, n = 22), with a diagnosis made on clinical grounds only. Lack of diagnostic confirmation has implications for resistance testing and treatment. Over half (59%, n =13) of these cases were pulmonary only, suggesting that improved methods of induced sputum collection may help improve diagnostic testing results in these cases.

The use of TB notification data, which is compiled from mandatory reporting of all TB diagnoses in the ACT under the *Public Health Act 1997,* reduces the likelihood that any TB cases will be missed during our study period. Although notifications cannot capture TB cases that remain undiagnosed, this is presumed to be low in Australia due to the availability of free TB services to anyone in the country.[29, 30] This study was conducted using existing notification data without a review of medical charts. Although the data quality and completion of some fields was inconsistent over the study period, this is unlikely to have made an impact on the overall findings. The relatively small number of TB notifications in the ACT reflects the size of this jurisdiction. While this limits the statistical

power for analysing trends, it was still possible to compare ACT rates with national TB notification rates.

Conclusion

The number of TB notifications in the ACT has remained relatively low over the past 10 years although it appears to be increasing. The majority of TB notifications are in the overseas-born population. This highlights a potential group that can be identified for more targeted screening and intervention programs to work towards eliminating TB in Australia. Managing an increasing number of TB cases in the ACT, as well as screening for and treating LTBI in high-risk groups, has significant resource implications. Future national and jurisdictional plans to address the goal of TB elimination will need to take this into account.

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Quarterly report

Meningococcal Surveillance Australia

Reporting period 1 April to 30 June 2017

Monica M Lahra and Rodney Enriquez

The reference laboratories of the National Neisseria Network, Australia report laboratory data on invasive meningococcal disease (IMD) cases confirmed by laboratory testing using culture and non-culture based techniques for the Australian Meningococcal Surveillance Programme (AMSP).

Culture positive cases, where Neisseria meningitidis is grown from a normally sterile site or skin lesions, and non-culture based diagnoses, derived from results of nucleic acid amplification testing (NAAT) and serological techniques, are defined as IMD according to Public Health Laboratory Network definitions.

Data contained in quarterly reports are restricted to a description of the numbers of cases by jurisdiction and serogroup, where known. Some minor corrections to data in the Table may be made in subsequent reports if additional data are received.

A full analysis of laboratory confirmed cases of IMD in each calendar year is contained in the AMSP annual report published in CDI.

Table: Number of laboratory confirmed cases of invasive meningococcal disease by jurisdiction and serogroup, Australia, second quarter 2017.

Jurisdiction	Year	Serogroup													
		A		B		C		Y		W		ND/other		All	
		Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd
Australian Capital Territory	**2017**	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**
	2016	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**
New South Wales	**2017**	0	**0**	7	**16**	1	**3**	1	**3**	3	**5**	2	**2**	14	**29**
	2016	0	**0**	5	**10**	0	**1**	4	**4**	5	**9**	0	**3**	14	**27**
Northern Territory	**2017**	0	**0**	0	**0**	0	**0**	0	**1**	0	**1**	0	**0**	0	**2**
	2016	0	**0**	1	**1**	0	**0**	0	**0**	0	**0**	0	**0**	1	**1**
Queensland	**2017**	0	**0**	4	**14**	0	**0**	2	**11**	4	**6**	0	**1**	10	**32**
	2016	0	**0**	2	**6**	0	**0**	2	**6**	3	**4**	0	**0**	7	**16**
South Australia	**2017**	0	**0**	5	**6**	0	**0**	0	**2**	2	**4**	0	**0**	7	**12**
	2016	0	**0**	5	**11**	0	**0**	0	**0**	0	**1**	0	**0**	5	**12**

Jurisdiction	Year	Serogroup													
		A		B		C		Y		W		ND/other		All	
		Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd	Q2	ytd
Tasmania	**17**	0	**0**	2	**2**	0	**0**	0	**0**	1	**5**	0	**0**	3	**7**
	16	0	**0**	0	**0**	0	**0**	0	**0**	0	**2**	0	**0**	0	**2**
Victoria	**17**	0	**0**	3	**8**	2	**2**	3	**7**	9	**17**	0	**0**	17	**34**
	16	0	**0**	4	**7**	0	**1**	2	**2**	9	**14**	0	**0**	15	**24**
Western Australia	**17**	0	**0**	2	**5**	0	**1**	0	**0**	2	**6**	0	**1**	4	**13**
	16	0	**0**	1	**2**	0	**0**	0	**0**	0	**1**	0	**0**	1	**3**
Australia	**17**	0	**0**	23	**51**	3	**6**	6	**24**	21	**44**	2	**4**	55	**129**
	16	0	**0**	18	**37**	0	**2**	8	**12**	17	**31**	0	**3**	43	**85**

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Annual report

Tuberculosis notifications in Australia, 2014

Cindy Toms, Richard Stapledon, Chris Coulter, Paul Douglas and the National Tuberculosis Advisory Committee, for the Communicable Diseases Network Australia, and the Australian Mycobacterium Reference Laboratory Network

Abstract

In 2014, the National Notifiable Diseases Surveillance System received 1,339 tuberculosis (TB) notifications, representing a rate of 5.7 per 100,000 population. Australia has achieved and maintained good tuberculosis (TB) control since the mid-1980s, sustaining a low annual TB incidence rate of approximately 5 to 6 cases per 100,000 population. The number of multi-drug resistant TB (MDR-TB) cases diagnosed in Australia is low by international standards, with approximately 1-2% of notifications per year being classified as MDR-TB. Australia's overseas-born population continued to represent the majority (86%) of TB notifications and Australia's Aboriginal and Torres Strait Islander population continue to record TB rates around 6 times higher than the Australian born non Indigenous population. Whilst Australia has achieved excellent and sustained control of TB in Australia, sustained effort is still required to reduce rates further and contribute to the achievement of the World Health Organization's goal to end the global TB epidemic by 2035.

Keywords: Australia, tuberculosis, *Mycobacterium tuberculosis*, communicable disease surveillance, epidemiology, annual report.

Introduction

Australia has one of the lowest tuberculosis (TB) incidence rates in the world and has maintained excellent TB control for the last three decades.[1] However, Australia's proximity to some of the highest TB incidence countries in the world and its large migrant intake from these regions means that continued vigilance is required to sustain and improve on Australia's already low TB incidence rate.

At the sixty-seventh World Health Assembly (WHA) in May 2014, the Australian Government endorsed the new *Global strategy and targets for tuberculosis prevention, care and control after 2015*, also known as the World Health Organization (WHO) post 2015 global TB Strategy.[2] The post 2015 global TB Strategy's goal is to end the global TB epidemic by 2035 and sets targets to reduce TB incidence by 90% and TB deaths by 95% worldwide by this time.[3]

Australia is well placed to achieve TB elimination with an excellent health care system and robust surveillance and governance frameworks already in place. However, like other low-incidence countries with positive migration policies, reducing domestic incidence rates will continue to challenge TB control programs. It is likely that the greatest reduction in Australia's TB incidence rates will be achieved through the improvement of TB control globally but in particular the Western Pacific and South-East Asian regions.

Surveillance of TB in Australia is overseen by the National Tuberculosis Advisory Committee (NTAC), a subcommittee of the Communicable Diseases Network Australia (CDNA). NTAC has the key role of providing strategic, expert advice to CDNA, and subsequently the Australian Government, on a coordinated national approach to TB control. NTAC also develops and reviews nationally agreed policy and guidelines for the control of TB in Australia.

This report describes the epidemiology of notified cases of TB in Australia in 2014 and includes some discussion on the factors that impact on the control of TB in Australia. Annual reporting of TB notifications in Australia ensures that Australia's TB control progress can be monitored and provides evidence for the development of new TB control strategies.

Methods

TB is a nationally notifiable disease in Australia and is monitored using the National Notifiable Disease Surveillance System (NNDSS). Medical practitioners, public health laboratories and other health professionals are required under state and territory public health legislation to report cases of TB to jurisdictional health authorities. The *National Health Security Act 2007* provides the legislative basis for the national notification of communicable diseases and authorises the exchange of health information between the Australian Government and State and Territory Governments. State and territory health departments transfer these notifications regularly to the

NNDSS. The primary responsibility for public health action resulting from a notification resides with state and territory health departments.

The Tuberculosis Data Quality Working Group (TBDQWG), a working group of NTAC, has representation from states and territories, the Australian Government and the Australian Mycobacterium Reference Laboratory Network (AMRLN). It ensures routine and timely reporting of trends and emerging issues in TB. The TBDQWG is also responsible for maintaining national consistency and currency in data standards and systems for TB surveillance that are relied upon to produce this report.

With the exception of the premigration screening data, the data presented in this report represent a point-in-time analysis of notified cases of TB in Australia. This report presents data extracted from NNDSS during June 2015. Due to the dynamic nature of the NNDSS, data in this report may vary from data reported in other NNDSS reports and reports of TB notifications at the state or territory level. Detailed notes on case definition, data collection, quality control and the categorisation of population subgroups are available in the 2007 annual report.[4]

In accordance with the Torres Strait Treaty, some Torres Strait Islanders and coastal people from PNG are allowed free movement (without passports or visas) within the northern Torres Strait Islands of Australia and PNG. This free movement is to allow for traditional activities to take place and does not include visits for health treatment.[5] However, at times PNG nationals do still present with TB to QLD health care clinics in the Torres Strait. In these instances, the patient's diagnosis of TB is notified in Australia, and identified in the NNDSS as "Residents of the TSPZ accessing TB treatment in Queensland", but the patient is transferred back to PNG for treatment providing they are well enough to travel.

This report presents data analysed by date of diagnosis, a derived field within the NNDSS. The methodology for date of diagnosis for TB changed in January 2014 and was applied to notifications retrospectively. The diagnosis date for TB is now equivalent to the 'notification received date'[1] , whereas previously the diagnosis date represented either the onset date or where the date of onset was not known, the earliest of the specimen collection date, the notification date, or the notification receive date.

Reported rates were calculated using population data published by the Australian Bureau of Statistics (ABS). Overall population rates were calculated using mid year estimated resident population (ERP) data described by the 3101.0 - Australian Demographic Statistics, Dec 2014 dataset.[6] Rates by country of birth were calculated using 2014 ERP data described by the 3412.0 - Migration, Australia, 2013-14 dataset.[7] Rates for population subgroups (i.e. overseas born, Australian born Indigenous and Australian born non Indigenous) by age and by state and territory were calculated using 2011 ERP data described by the 3412.0 - Migration, Australia, 2013-14 dataset.[8] Note that ERP data by country of birth by state and territory are based on the 2011 Census as data is only available for Census years and ERP data for the Indigenous population is also based on the 2011 Census data.[9, 10]

I. The date the notification of the disease was received by the Communicable Disease Section of the Health Authority (i.e. the date the notification was received by the state or territory health department).

Table 1: Notifications of tuberculosis, Australia, 2009 to 2014, by state and territory and year

State / Territory	2009	2010	2011	2012	2013	2014	5 year mean*	Range*	
								Lower	Upper
ACT	23	10	20	17	18	30	18	10	23
NSW	520	511	540	470	443	472	497	443	540
NT	21	37	35	28	43	28	33	21	43
Qld	159	177	221	171	153	165	176	153	221
SA	58	74	73	83	69	48	71	58	83
Tas	9	10	17	6	8	9	10	6	17
Vic	410	436	360	369	380	448	391	360	436
WA	107	109	123	172	149	139	132	107	172
Australia	**1,307**	**1,364**	**1,389**	**1,316**	**1,263**	**1,339**	**1,328**	**1,263**	**1,389**

** Covers the period 2009 to 2013.*

The premigration screening data represents a calendar year analysis of TB cases detected through the offshore premigration screening process. Cases of TB identified through this process are not included in the NNDSS as they are identified prior to entry to Australia. Premigration screening data are provided by the Australian Government Department of Immigration and Border Protection (DIBP).

Results

Epidemiological situation in 2014

In 2014, 1,339 cases of TB were reported to the NNDSS, representing a rate of 5.7 cases per 100,000 and a 4% increase on the number of cases reported in 2013 (n=1,263) (Table 1). A case classification (whether new or relapse) was reported for 99% of cases in 2014 (n=1,331) and of those, 95% were classified as new (n=1,263) (Table 2). A case is classified as new when a patient has never been treated for TB or when a patient has been treated previously for less than one month. Relapse was reported in 68 cases in 2014 with the majority of those cases (65%, 44/68) having a treatment history of full or partial treatment overseas (Table 3).

In the last decade, the rate of TB in Australia has ranged from 5.0 per 100,000 in 2003 to 6.2 per 100,000 in 2010 and 2011. A small but steady rise was observed from 2003 to 2011, followed by a small decline is recent years (Figure 1). A comparison of the 5-year mean rates for the last 20 years shows only a small mean rate rise (range: 5.3 per 100,000 to 5.9 per 100,000) and comparisons between the 5-year means were found not to be statistically significant (Table 4).

Geographic distribution

In 2014, New South Wales and Victoria accounted for just over two thirds of the cases notified in Australia (NSW: n=472; Vic: n=448), while Tasmania reported the least number of cases (n=9) (Table 1). Similar to previous years, the high-

Table 2: Notified cases and rates of tuberculosis, Australia, 2014, by case classification and state or territory

State / Territory	New cases		Relapse cases		Total cases*	
	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000
ACT	25	6.5	3	0.8	30	7.8
NSW	448	6.0	24	0.3	472	6.3
NT	26	10.6	2	0.8	28	11.4
Qld	156	3.3	7	0.0	165	3.5
SA	46	2.7	2	0.0	48	2.8
Tas	9	1.7	0	0.0	9	1.7
Vic	420	7.2	24	0.4	448	7.7
WA	133	5.2	6	0.2	139	5.4
Australia	**1,263**	**5.4**	**68**	**0.3**	**1,339**	**5.7**

** Total includes 8 cases reported without a case classification (ACT n=2, QLD n= 2, Vic n=4).*

Table 3: Notified cases of tuberculosis classified as a relapse, Australia, 2014, by treatment history

Treatment History	Notifications (n)	Percentage of Relapse cases (%)
Relapse following full treatment only in Australia.	19	28%
TB following partial treatment only in Australia	5	7%
Relapse following full or partial treatment overseas.	44	65%
Total	**68**	**100%**

Table 4: Tuberculosis notifications and rates for 5-year intervals, Australia, 1995 to 2014

5-year interval	5-year mean		IRR (95% CI)*	p-value*
	Notifications (n)	Rate per 100,000		
1995-1999	1,009	5.5	-	-
2000-2004	1,045	5.3	0.98 (0.89 - 1.07)	0.5749
2005-2009	1,193	5.7	1.06 (0.98 - 1.16)	0.1399
2010-2014	1,334	5.9	1.04 (0.96 - 1.12)	0.3724

**Incident rate ratio (IRR), confidence intervals (CI) and p-values have been calculated using the previous 5-year interval as the denominator*

est jurisdiction specific rate was reported in the Northern Territory (11.4 per 100,000) and the lowest was reported in Tasmania (1.7 per 100,000) (Table 2).

The Australian Capital Territory recorded a rate of 7.8 per 100,000 (n=48), a 65% increase on the rate in 2013 (4.7 per 100,000) and the highest rate recorded in the Australian Capital Territory since the collection of NNDSS data commenced in 1992. South Australia recorded a rate of 2.8 per 100,000 (n=30), a 31% decrease on the rate in 2013 (4.1 per 100,000) and the lowest rate recorded in the South Australia since 1996 (2.6 per 100,000) (Table 2).

In 2014, the Australian Capital Territory and Victoria reported a jurisdiction specific rate higher than the five-year mean rates of the two preceding five-year intervals for these two jurisdictions (Figure 2).

Tuberculosis in the Australian-born population

In 2014, the rate of TB in the Australian born population was similar to previous years at 1.1 per 100,000 (n=183). The rate of TB in the Australian born Indigenous population was 5.8 per 100,000 (n=39) and remains approximately six times the rate of TB in the Australian born non Indigenous population (0.9 per 100,000, n=183) (Table 5).

The rate of TB in the Australian born non Indigenous population continues to remain relatively stable and has not exceeded 0.9 per 100,000 in the last decade. While the rate in the Australian born Indigenous population has ranged from 3.1 per 100,000 to 6.3 per 100,000 in the last decade (Figure 3).

Tuberculosis in the overseas-born population

In 2014, all but five cases were reported with country of birth information, with 86% (n=1,151) of those notifications being reported as overseas born (Table 5). The proportion of cases reported as being overseas born ranged from 61% of cases in the Northern Territory (n=17) to 96% of cases in South Australia (n=46). In 2014, the rate of TB in the overseas born population (19.1 per 100,000) was approximately 17 times the rate in the Australian born population and a 4% increase on the rate in 2013. In the last decade, the rate of TB in the overseas born population has ranged from 16.2 per 100,000 to 20.2 per 100,000 (Figure 3).

Country of birth

In 2014, the top five most frequently reported countries of birth for TB cases were India, Viet Nam, the Philippines, China and Myanmar and these five countries contributed to half of all the overseas-born cases (575/1,151) (Table 6). Of the most frequently reported countries of birth listed in Table 6, those born in Myanmar (164 per 100,000), Sudan (113 per 100,000), Papua New Guinea (106 per 100,000) and Nepal (103 per 100,000) recorded the highest estimated rates of TB in 2014.

Note that these estimated rates must be interpreted with caution as temporary residents are included in Australia's TB notifications (the numerator) but may not be included in the ABS' estimated resident population (the denominator).

Residency status

In 2014, residency status was available for 97% (1,116/1,151) of TB cases reported as overseas born. Residency status is self-reported at the time of diagnosis and is not verified against migration records. In 2014, the majority of overseas born cases reported with a residency status were reported as permanent residents (64%, 718/1,116) (Table 7). The second most reported residency status categories were 'overseas students' (11%, 122/1,116) and 'other'[II] (11%, 122/1,116). The proportion of cases reported as 'overseas students' is similar to the proportion reported in 2013 (12%, 130/1,056).

II. Other – A person not defined by any of the other residency status categories. Please note this data item is self-reported.

Figure 1: Notification rates of tuberculosis, Australia, 1960 to 2014

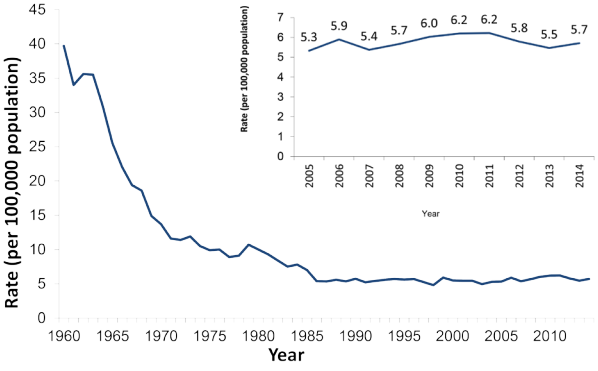


Figure 2: Notification rates of tuberculosis, Australia, 2004-2014, by state or territory

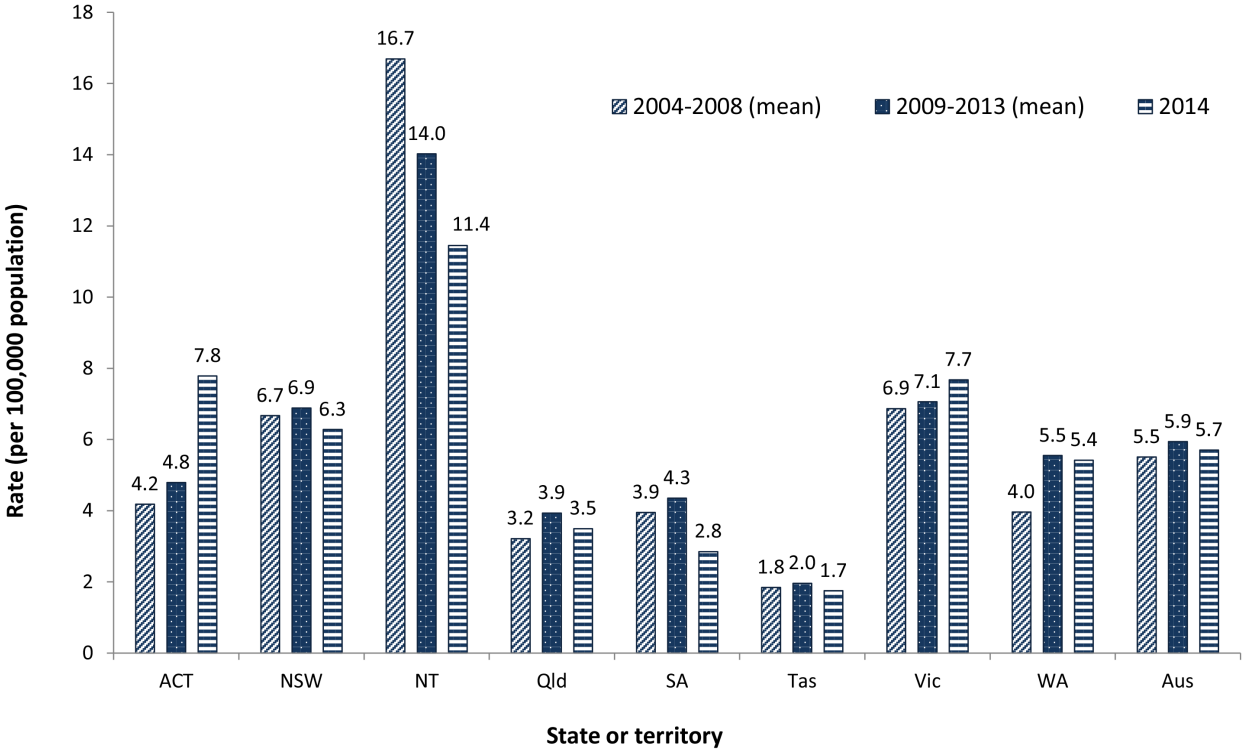


Figure 3: Notified cases and rate of tuberculosis, Australia, 2005 to 2014, by population subgroup

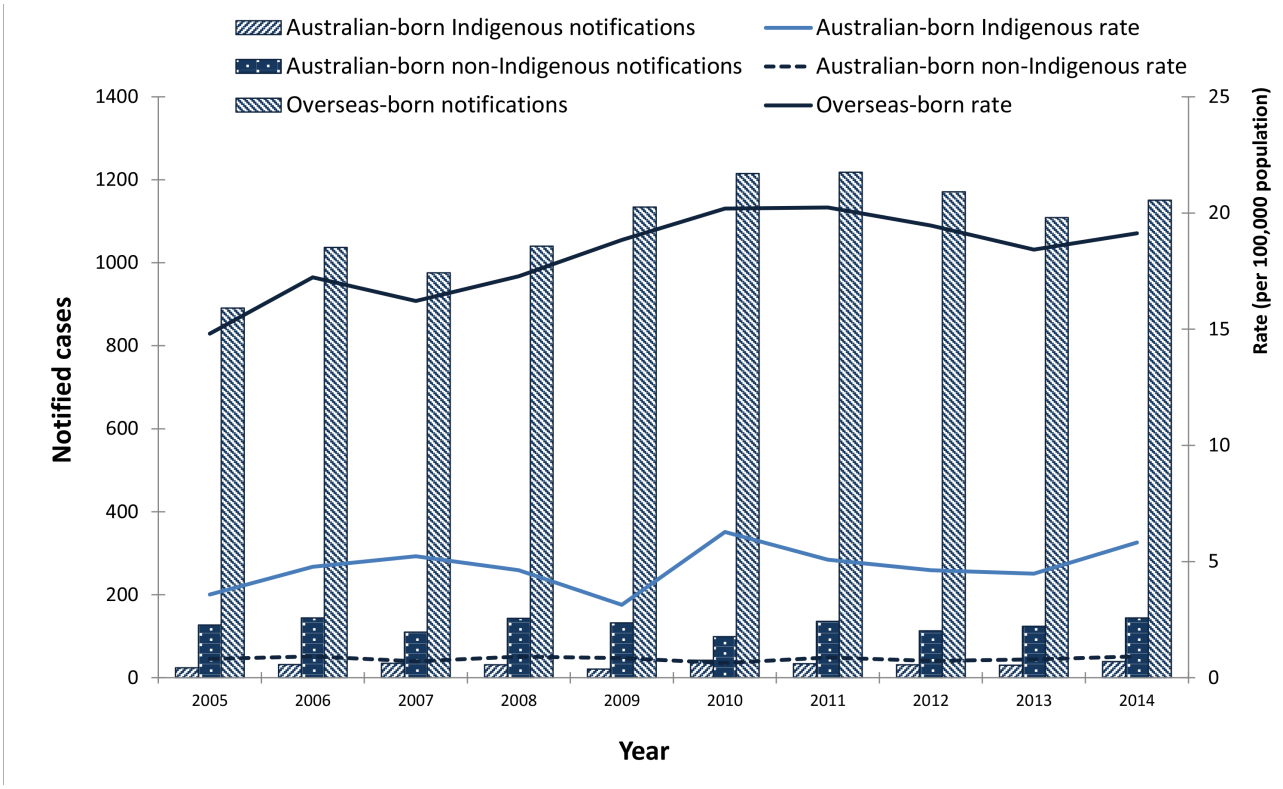


Table 5: Notified cases and rates of tuberculosis, Australia, 2014, by population subgroup and state or territory

State or territory	Australian-Born Indigenous		Australian-born non-Indigenous		Australian-born Total		Overseas born	
	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000
ACT	0	0.0	4	1.5	4	1.5	24	25.0
NSW	8	3.8	53	1.1	61	1.2	411	20.1
NT	11	16.0	0	0.0	11	5.9	17	39.0
Qld	17	9.0	14	0.4	31	0.9	131	13.0
SA	2	5.3	0	0.0	2	0.2	46	11.8
Tas	0	0.0	3	0.7	3	0.7	6	9.3
Vic	0	0.0	58	1.5	58	1.5	390	24.5
WA	1	1.1	12	0.8	13	0.8	126	16.0
Australia	**39**	**5.8**	**144**	**0.9**	**183**	**1.1**	**1151**	**19.1**

* Excludes 5 cases with an unknown country of birth (ACT n=2, QLD n=3)

Table 6: Notified cases and rates of tuberculosis for frequently reported countries of birth, Australia, 2014, by residency status

Country of birth	Residency Status				Estimated resident population 2014†	Estimated rate per 100,000 population	WHO incidence rate per 100,000 population 2014‡
	International Students	Permanent Residents	Other	Total cases*			
India	16	118	78	213	397,180	54	223
Viet Nam	21	81	19	121	223,180	54	140
Philippines	1	77	28	108	225,110	48	322
China (excludes SARs and Taiwan)	14	58	14	86	447,370	19	69
Myanmar, The Republic of the Union of	2	17	29	48	29,300	164	369
Indonesia	11	22	7	40	81,140	49	399
Nepal	14	14	10	38	36,940	103	158
Papua New Guinea	9	9	17	35	33,100	106	432
Afghanistan	0	19	14	33	39,790	83	189
Pakistan	9	14	8	31	49,770	62	270
Sudan	0	22	4	26	23,090	113	94
Cambodia	1	21	2	24	35,000	69	390
Thailand	3	12	9	24	61,910	39	171
Sri Lanka	1	13	8	22	110,520	20	65
New Zealand	0	19	1	20	616,960	3	7.6
Malaysia	6	4	8	18	153,870	12	93
Other overseas-born	14	199	52	265			
Total overseas-born	122	719	308	1,151			
Australian-born	-	-	-	183			
Unknown Country of Birth	-	-	-	5			
Total	**-**	**-**	**-**	**1,339**			

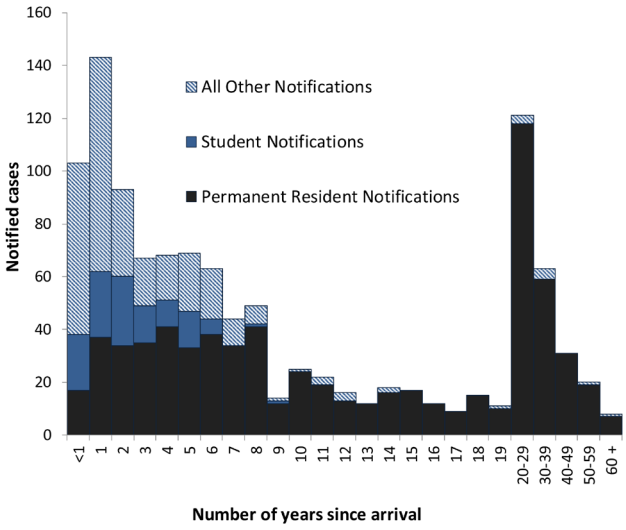
* Total includes cases reported without a residency status.
† 2014 Population data is sourced from the ABS' 3412.0 - Migration, Australia, 2013-14 - Estimated Resident Population by Country of Birth - 1992 to 2014
‡ Rates from the World Health Organization Global Tuberculosis Control Report. [11]

Table 7: Notified cases of tuberculosis in overseas-born people, Australia, 2014 by residency status and state or territory

Residency Status	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	Aust
Refugee/ Humanitarian	2	10	2	6	8	3	22	4	**57**
Permanent Resident	18	281	4	70	8	2	257	78	**718**
Overseas Visitor	0	29	1	12	8	0	20	9	**79**
Overseas Student	4	36	1	20	4	1	44	12	**122**
Unauthorised Person	0	1	4	0	0	0	2	1	**8**
Other[ǂ]	0	44	4	14	1	0	41	18	**122**
Illegal Foreign Fisher	0	0	1	0	0	0	0	0	**1**
Residents of the Torres strait treaty zone accessing TB treatment in Queensland	N/A	N/A	N/A	9	N/A	N/A	N/A	N/A	**9**
Unknown or not reported	0	10	0	0	17	0	4	4	**35**
Total overseas-born cases	24	411	17	131	46	6	390	126	**1,151**

ǂ Other – A person not defined by any of the other residency status categories. Please note this data item is self-reported.

Figure 4: Notified cases of tuberculosis in the overseas-born population, Australia, 2014, by residency status and number of years since arrival in Australia



In 2014, there were 9 cases of TB notified amongst Papua New Guinea (PNG) nationals accessing health care in the Torres Strait Protection Zone (TSPZ), an increase on the 3 cases reported in 2013 (Table 7). In 2014, PNG nationals being diagnosed with TB in the TSPZ accounted for 5% (9/165) of Queensland's TB cases.

Time between arrival in Australia and diagnosis

In 2014, data on year of arrival were available for 97% of overseas born cases (1,113/1,151). Of these cases, 43% (474/1,113) were diagnosed with active TB within four years of arrival in Australia. Of those diagnosed within four years of arrival in Australia, the proportion of these being 'overseas students' (20%, 96/474) is similar to the proportion in 2013 (21%, 103/501) (Figure 4).

Premigration health screening

The Migration Regulations 1994, enabled by the Migration Act 1958, stipulate that visa applicants must meet certain Public Interest Criteria; and these criteria include a stipulation that visa applicants must be "… free from TB" and/or not be a … threat to public health in Australia or a danger to the Australian community".[12] Therefore, permanent resident visa applicants, and some temporary resident visa applicants are required to undergo offshore premigration screening which includes a medical examination and a chest x-ray to screen for active TB. Children aged less than 11 years of age are required to undergo a physical

Table 8: Number of cases and case detection rates of tuberculosis identified through offshore premigration screening process, 2011 to 2014

Year	Number of cases†	Case detection rate (estimated rate per 100,000 medical examinations)
2011	287	80
2012	412	116
2013	467	89
2014	425	80

† The number of cases includes cases newly diagnosed through the premigration screening process and cases that were already on treatment for TB at the time of screening.

examination. Visa applicants who are identified as having active TB during premigration screening are required to undergo treatment for the disease prior to entry to Australia.[13]

In 2014, there was a 9% reduction on the number of TB cases detected through offshore premigration screening when compared to 2013 (Table 8). In 2014, the highest rates of TB detected through offshore premigration screening were in the 40 to 44 year old (166 per 100,000) and 70 to 74 year old (159 per 100,000) age groups and similar to 2013, nearly half of all the TB cases detected were in visa applicants from the Philippines (n=97), Viet Nam (n=54) and China (n=50). Just over two thirds (69%) of the TB cases detected through offshore premigration screening were in temporary visa applicants and of those cases, 43% were detected in students visa applicants.

Some form of drug resistance was observed in 26% of TB cases detected through offshore premigration screening, while multi drug resistant TB (MDR TB) was reported in 8.5% of cases and includes two extensively drug resistant TB (XDR TB) cases. MDR TB was identified in applicants from eight different countries, with the majority of cases being identified in applicants from India (n=8), Viet Nam (n=4) and the Philippines (n=3).

Note that since mid 2013, DIBP has implemented an automated premigration screening data collection process resulting in more accurate data collection than previous years. Therefore, the comparison of premigration screening data to previous years should be interpreted with some caution. Further information on the premigration health screening process and related statistics can be obtained from DIBP's Immigration Health Branch[III].

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Age and sex distribution

Age and sex were reported for all TB cases notified in 2014. Similar to previous years, there were more males than females notified with TB, with a male to female ratio of 1.1:1.

Similar to previous years, TB was predominantly seen in young adults aged 25-34 years (11.7 per 100,000), and again this was driven by the high rates observed in overseas born cases in this age group. In the Australian born Indigenous population, TB was predominantly seen in adults aged 45 years and over (Table 9).

Tuberculosis in children aged under 15 years

One of the most important measures of TB control is the incidence in children aged less than 15 years because these cases represent recent TB infection. In 2014, children aged less than 15 years contributed 4% of all TB cases (54/1,339) (Table 9). In 2014, just over half of the cases in children were reported in the Australian born non Indigenous population (54%, 29/54) and of these, the most frequently reported risk factor was having one or more parent born overseas (n=23) followed by having a 'household member or close contact with TB' (n=14). Note that more than one risk factor may be reported for each notified case of TB. There were 4 cases reported as Australian born Indigenous and all 4 cases reported having a 'household member or close contact with TB'. One of these cases also reported having one or more parent born overseas as an additional risk factor.

The rate of TB in Australian born non Indigenous children has remained relatively stable over the past decade (range: 0.3 per 100,000 to 0.8 per 100,000), whilst the rate in Australian born Indigenous (range: 0.4 per 100,000 to 2.9 per 100,000) has fluctuated over that time. The rate of TB in overseas born children has ranged from 5.7 per 100,000 to 10.1 per 100,000 but overall rates appear to have declined (Figure 5).

Selected risk factors for tuberculosis

In 2014, selected risk factor data were provided for 93% (n=1,249/1,339) of notified cases. Of those cases assessed for risk factors, overall the most frequently reported risk factor was past travel to or residence in a high-risk country (76%, 956/1,249) with the majority of these cases (79%, 753/956) reporting this as the only risk factor (Table 10). When stratified by population subgroup, the most frequently reported risk factor in both overseas-born cases and in Australian born non Indigenous cases was past travel to or residence in a high-risk

Table 9: Notification rates of tuberculosis, Australia, 2014, by population subgroup and age group

Age group	Australian-born Indigenous		Australian-born non-Indigenous		Overseas-born		Total	
	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000	Notifications (n)	Rate per 100,000
0–4	3	3.6	19	1.4	1	1.6	23	1.6
5–14	1	0.6	10	0.4	20	6.6	31	1.1
0–14	4	1.7	29	0.8	21	5.7	54	1.3
15–24	4	3.0	17	0.7	168	27.4	189	6.2
25–34	1	1.1	17	0.8	354	34.0	373	11.7
35–44	3	3.7	18	0.9	197	20.2	218	6.9
45–54	14	22.2	18	0.9	113	11.2	145	4.8
55–64	9	24.5	19	1.2	108	12.2	137	5.3
65+	4	17.6	26	1.3	190	16.8	223	7.2

country (n=904 and n=47 respectively), while in Australian born Indigenous cases having a 'household member or close contact with TB' was more frequently reported (n=23).

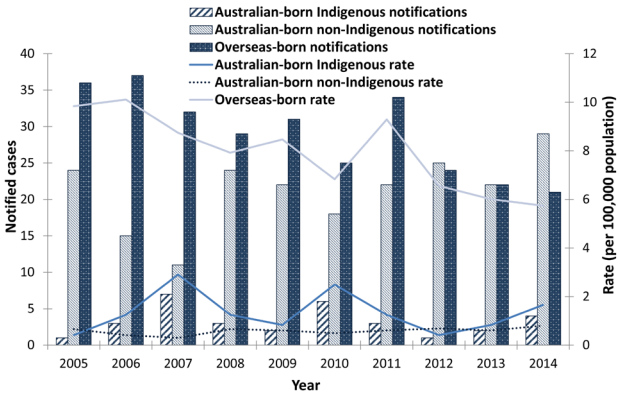
In 2014, a total of 61 cases were reported in people who were currently or had previously worked in a health care setting. Of these, 32 (52%) were reportedly working in a health care setting in Australia at the time of diagnosis or within 12 months of diagnosis and 6 of those reported this as the only risk factor. Of the cases reportedly working in a health care setting in Australia at the time of diagnosis or within 12 months of diagnosis, 50% (16/32) were reported to have extrapulmonary disease only, which is generally not communicable. The remaining 50% (16/32) were reported with pulmonary disease and 3 of those cases were reported as being sputum smear positive.

Tuberculosis and HIV status

According to Australia's 2011 National HIV Testing Policy version 1.3, '…all people with HIV should be tested for tuberculosis, and all people with tuberculosis should be tested for HIV…'[14]. In 2014, the HIV testing history [IV] of notified cases of TB were reported in 97% of cases (n=1,300) and of those cases, 82% (1,069/1,300) were tested for HIV and 55% (716/1,300) were reported with a known HIV status. Of those cases with a known HIV status, 2% (17/716) were reported as HIV positive (Table 11).

In 2014, approximately a quarter of cases with a known HIV testing history were reported as being tested for HIV but the result of that test was unknown (27%, 353/1,300). Nearly all these cases

Figure 5: Notified cases and rate of tuberculosis in children aged 0-14 years, Australia, 2005-2014, by population subgroup



were reported by Victoria (n=335) where policy has prevented the HIV status of an individual being reported with the TB notification to the NNDSS. Victoria has since changed this policy and from 2015 onwards Victoria will report HIV status with TB notifications.

Anatomical site of disease

In 2014, all notified cases had a reported anatomical site of TB disease. Pulmonary disease was reported in 63% of cases (847/1,339) with 86% (725/847) of those cases being reported as having pulmonary disease only. Extrapulmonary disease only was reported in 37% (492/1,339) of cases, with the most frequently reported site of extrapulmonary only site of disease being lymph nodes (n=238). Of the more severe forms of TB, the number of cases of miliary (n=9) and meningeal (n=6) TB were the same as the number of cases reported in 2013 (Table 12).

IV. HIV test history means knowing whether or not the person was tested for HIV, not tested for HIV or refused testing for HIV.

Table 10: Notified cases of tuberculosis, Australia, 2014, by population subgroup and selected risk factors

Risk factor*	Australian-born Indigenous	Australian-born non-Indigenous	Overseas-born	Total
Household or other close contact with TB	23	36	106	165
Ever resided in a correctional facility†	0	4	10	14
Ever resided in an aged care facility†	1	2	4	7
Ever employed in an institution†‡	0	0	13	13
Currently or previously† employed in health industry in Australia or overseas	0	4	57	61
Ever homeless	2	3	16	21
Past travel to or residence in a high-risk country	4	47	904	956
Chest X-ray suggestive of old untreated TB	2	4	57	63
Currently receiving immunosuppressive therapy	1	8	44	53
Australian-born child with one or more parent born in a high-risk country	1	27	0	28
None of the above risk factors	10	35	87	132
Total cases assessed for risk factors	**37**	**138**	**1,073**	**1,249**

* More than one risk factor may be reported for each notified case of TB.
† Within the preceding five years.
‡ Institution is defined as a correctional facility, aged care facility or homeless shelter.

In children aged less than 15 years, pulmonary disease was reported in 63% (34/54) of cases and extrapulmonary disease only was reported in 37% (20/54) of cases. Of the extrapulmonary disease only cases, the most frequently reported extrapulmonary site of disease was lymph nodes (n=8) and there were two cases of miliary TB and two cases of meningeal TB.

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In children aged less than 15 years, pulmonary disease was reported in 63% (34/54) of cases and extrapulmonary disease only was reported in 37% (20/54) of cases. Of the extrapulmonary disease only cases, the most frequently reported extrapulmonary site of disease was lymph nodes (n=8) and there were two cases of miliary TB and two cases of meningeal TB.

Bacteriologically confirmed cases

In 2014, 88% (1,177/1,339) of cases were laboratory confirmed as TB. The remaining 12% of cases were diagnosed using clinical and radiological evidence only.

Of the total number of cases reported with pulmonary disease [V] , 91% (775/847) were bacteriologically and/or histologically confirmed and of those, 87% (676/775) were either sputum culture positive or bronchoscopy washings/aspirate culture positive with half of these cases also being smear positive (50%, 335/676). Smear positive cases of pulmonary TB can be up to ten times more infectious than smear negative cases and are usually the main source of TB transmission in the community.[15, 16]

Of the extrapulmonary only cases, 80% (396/492) were bacteriologically and/or histologically confirmed and of those, 69% (273/396) were 'other culture' [VI] positive. Cases with extrapulmonary disease only are generally not infectious and rarely are a source of transmission.[15]

In 2014, 54% (29/54) of cases in children aged less than 15 years were bacteriologically and/or histologically confirmed as TB. Of these cases, half (17/34) of the cases reported with pulmonary disease and 60% (12/20) of the cases reported with extrapulmonary disease only were bacteriologically and/or histologically confirmed. The WHO

V. Pulmonary cases include both pulmonary only cases and pulmonary cases that also have extrapulmonary sites detected
VI. 'Other culture' includes specimens, other than sputum or bronchoscopy washings/aspirate' in which mycobacteria tuberculosis complex was isolated by culture, at the time of diagnosis.

Table 11: Notified cases of tuberculosis, Australia, 2014, by population subgroup and HIV status

HIV testing history	Australian-born Indigenous	Australian-born non-Indigenous	Overseas-born	Unknown population subgroup	Total
HIV positive	0	1	16	0	17
HIV negative	33	67	599	0	699
HIV tested, result unknown	2	35	314	2	353
Not tested	3	36	185	0	224
Refused testing	1	2	4	0	7
Total - known HIV testing history	39	141	1,118	2	1,300
Total - unknown HIV testing history	0	3	33	3	39
Total	**39**	**144**	**1,151**	**5**	**1,339**

Table 12: Notified cases of tuberculosis, Australia, 2014, by site of disease and case classification

Site	New cases	Relapse cases	Unknown case classification	Total cases
Pulmonary				
Pulmonary only	674	46	5	725
Pulmonary plus other sites	117	4	1	122
Pulmonary - Total	791	50	6	847
Extrapulmonary only†				
Pleural	57	4	0	61
Lymph nodes	230	8	0	238
Bone/joint	33	1	1	35
Genito/urinary	22	0	0	22
Miliary	9	0	0	9
Meningeal	6	0	0	6
Peritoneal	36	1	0	37
Other	67	4	1	72
Unknown extrapulmonary site	29	0	0	29
Extrapulmonary - Total	471	19	2	492
Unknown site of disease - Total	0	0	0	0
Total	**1,262**	**69**	**8**	**1,339**

† More than one extrapulmonary site may be reported for each notified case of TB.

recommends that wherever possible, a diagnosis of TB in a child should be bacteriologically confirmed.[17]

Of the bacteriologically confirmed cases in 2014, 17% (200/1,171) of cases recorded a positive microscopy or culture result on a bronchoscopy obtained washing or aspirate which is a similar proportion to previous years. Of these cases, 12% (23/200) were also reported as being sputum smear positive with one of those cases being identified as MDR TB.

Drug resistant tuberculosis in Australia

In 2014, DST results were available for just over three quarters of the TB cases notified (77%, 1,027/1,339) and of those cases, 12% (125/1,027) had resistance to at least one of the standard first line anti-tuberculosis agents reported. Rifampicin mono-resistance remains low and is reported in less than 1% (0.7%, 7/1,027) of cases with DST results available. Isoniazid mono-resistance is again more common than Rifampicin mono-resistance and was reported in 4.6% (47/1,027) of cases with DST results available. In 2014, there were 17 cases of MDR TB (1.7%, 17/1,027) and one case of XDR TB reported (Table 13).

The majority of Australia's MDR TB and XDR TB cases are reported in the overseas-born population. Of the MDR TB cases, 88% (15/17) were reported in overseas-born persons and of those, three cases were born in Papua New Guinea with two of those cases identified as residents of the TSPZ accessing TB treatment in Queensland. The remaining 12 cases were identified in persons born in Viet Nam (n=4), the Philippines (n=2), China (n=2), Myanmar (n=2), India (n=1) and Nepal (n=1). Of the Australian born MDR TB cases (n=2), both cases were reported as having pulmonary disease with extrapulmonary site involvement but only one case was reported as sputum smear positive at the time of diagnosis. One of the Australian born MDR TB cases was reported as being Indigenous and as having died of the TB infection. Both cases reported having past travel or residence (for a least 3 cumulative months) in a high-risk country or countries, with one case also reporting household or close contact with TB and the other as currently receiving immunosuppressive therapy.

The XDR TB case was reported in a person born in Nepal who was diagnosed with pulmonary disease only but was sputum smear negative at the time of diagnosis. This XDR TB case reported two risk factors – 'past travel to or residence in a high-risk country' and having a 'household member or close contact with TB'.Treatment outcomes of the 2013 tuberculosis patient cohort

The treatment outcomes of an annual patient cohort are reported in the following year's annual report. This allows adequate time for all cases notified in a single year to begin treatment and for the treatment outcomes to be recorded in the NNDSS. Treatment outcomes for the 2013 patient cohort are reported in this annual report. Treatment outcomes for the 2014 patient cohort will be reported in the 2015 annual report.

In 2013, treatment success, which includes those bacteriologically confirmed as cured and those who completed treatment, was reported in 96% (1,084/1,134) of cases with assessable outcomes. Treatment success ranged from 93% (25/27) in Australian-born Indigenous cases to 96% (953/995) in overseas born cases. In 2013, treatment failure was reported in just one case, while 11 (1%, 11/1,134) cases were reported to have died of TB (Table 14).

National performance indicators

In 2014, the performance criterion for annual incidence (less than 1 per 100,000) was met only in the Australian born non-Indigenous cases and incidence rates in Australian born children continue to exceed the performance criteria of less than 0.1 per 100,000. The reporting of HIV testing history continues to improve but still remains just short of the reaching the target of 100%. In 2013, outcome reporting fell just short of the performance criteria with 2% of cases with assessable outcomes reported with an unknown outcome. The performance indicators for treatment success and treatment failure were both achieved in 2013 (Table 15).

Discussion

The 2014 report shows that the incidence of TB in Australia remains at a low level despite increased migration from high TB burden countries. Since 1995, the mean rates for 5 yearly intervals have increased marginally over time from 5.5 to 5.9 per 100,000 population. However, if we consider the mean absolute numbers of cases for the 5 year intervals since 1995, there has been a 32% increase in notifications and this excludes the substantial numbers identified and managed pre-migration (Table 3). This increase represents a significant additional burden to State TB programs and highlights the need to maintain clinical, laboratory and public health expertise, infrastructure and commitment to meet this demand.

The epidemiology of TB in Australia and its steady growth in absolute terms in the past two decades continue to reflect the impact from migration of persons from high burden regions, which is also influenced by national education and employment policies. While there was a 4% increase in overall case numbers from 2013, the significance of this small variation is unclear. In 2014, the overseas

Table 13: Notified cases of tuberculosis with drug susceptibility testing (DST) results available, Australia, 2014, by drug susceptibility profile

Drug Susceptibility Testing (DST) Profile	Notifications (n)	Percentage of notifications (%)
Resistance to at least one first line anti-tuberculosis agents*	125	12%
Mono-resistance to rifampicin†	7	0.7%
Mono-resistance to isoniazid†	47	4.6%
MDR-TB‡	17	1.7%
XDR-TB§	1	0.1%
Total cases with DST results	**1,027**	

*Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin
† Mono-resistance is a case that is resistant to only the specified anti-TB agent and susceptible to all other anti-TB agents
‡Resistance to at least isoniazid and rifampicin but not XDR-TB.
§Resistance to isoniazid and rifampicin, and any of the fluoroquinolones, and to at least one of the three injectable second-line drugs 18.

Table 14: Notified cases of tuberculosis, Australia, 2013, by population subgroup and treatment outcome

Treatment outcome	Australian-born Indigenous cases		Australian-born Non-Indigenous		Overseas-born		Total cases	
	Notifications (n)	Percentage assessable (%)	Notifications (n)	Percentage assessable (%)	Notifications (n)	Percentage assessable (%)	Notifications (n)	Percentage assessable (%)
Assessable outcomes								
Treatment success	25	92.6	106	94.6	953	95.8	1084	95.6
Cured (bacteriologically confirmed)†	0	0.0	6	5.4	46	4.6	52	4.6
Completed treatment	25	92.6	100	89.3	907	91.2	1032	91.0
Interrupted treatment‡	0	0.0	0	0.0	5	0.5	5	0.4
Died of tuberculosis	1	3.7	2	1.8	8	0.8	11	1.0
Defaulted §	0	0.0	0	0.0	13	1.3	13	1.1
Failure ‖	0	0.0	1	0.9	0	0.0	1	0.1
Not followed up, outcome unknown	1	3.7	3	2.7	16	1.6	20	1.8
Total assessable	27	100.0	112	100.0	995	100.0	1134	100.0
Non-assessable outcomes								
Transferred out of Australia	0	0.0	2	1.6	63	5.7	65	5.1
Died of other causes	3	10.0	8	6.5	31	2.8	42	3.3
Still under treatment	0	0.0	2	1.6	20	1.8	22	1.7
Total	**30**	**100.0**	**124**	**100.0**	**1109**	**100.0**	**1263**	**100.0**

† Cured is defined as the bacteriologically confirmed sputum smear and culture positive at the start of treatment and culture negative in the final month of treatment and on at least one previous occasion.
‡ Interrupted treatment is defined as treatment interrupted for two months or more but completed
§ Defaulted is defined as failed to complete treatment.
|| Failure is defined as sputum culture positive at five months or later.

born accounted for 86% of the 1339 cases, with 64% occurring in permanent residents and 11% in overseas students. These latter figures are not significantly different from the previous year.

Premigration Screening

Premigration screening has become an important contributor to TB control in Australia. Although there was a 9% reduction in cases reported pre-migration when compared to 2013, the 425 cases diagnosed and treated would represent an addition of approximately 24% of total TB cases were all to have been diagnosed following travel to Australia. Of these cases 57% were from the Philippines, Vietnam, China and India and 61% were temporary visa applicants. Student and visitor groups predominated, representing more than 50% of applicants, but the highest rate was observed in the refugee/humanitarian group (372 per 100,000) who contributed 11.8% of cases. This data highlights how the make-up of the Australian migration programme influences the trends in the TB epidemiology.

As expected in a screening programme, a high proportion pre-migration were either sputum smear negative/culture positive (48%) or chest x-ray positive/culture negative (28%). Detecting these cases earlier in the disease process benefits the individual by limiting morbidity and the Australian community by preventing future transmission. An important finding from pre-migration screening was the significant level of drug resistance (any resistance 26%, isoniazid 9.4%, MDR-TB 8.5%). Although not necessarily representative of the overall migrating population, this is still a concern and will be an important trend to monitor in terms of the potential implications for TB control in Australia. It also raises a question about the future of isoniazid as the key preventive agent for management of latent TB infection.

Australian born population

The overall rate of TB in the Australian born population remains relatively static at approximately 1 per 100,000 population and has been so since 2005 (figure 3). In Australia's Aboriginal and Torres Strait Islander population, the rate has fluctuated at around 6 times that of the non-indigenous population but the actual numbers and annual rates remain low by international standards. A capacity to respond to each new case with a measure of TB control for the individual, contacts and the community remains a high priority to achieve the incidence level of the non-indigenous Australian born population.

NSW and Victoria continue to experience the highest proportion of TB cases. In 2014 the two states accounted for approximately two thirds of all cases. However compared with the 5 year mean annual rates since 2004, the mean annual rate for NSW has remained relatively steady while in Victoria the mean rate has increased from 6.9 to 7.7 per 100,000. The highest rate recorded was in the Northern Territory and while case num-

Table 15: National tuberculosis performance indicators, performance criteria* and the current status of tuberculosis, Australia, 2013 and 2014

National tuberculosis performance indicator	Performance criteria	2014	2013
Annual incidence of TB (cases per 100,000 population)			
Total	<6.0†	5.7	5.5
Australian-born Indigenous cases	<1.0	5.8	4.5
Australian-born non-Indigenous cases	<1.0	0.9	0.8
Overseas-born cases	*	19.1	18.4
Incidence in children <15 years, by risk group (per 100,000 population)			
Australian-born Indigenous cases	<0.1	1.7	0.8
Australian-born non-Indigenous cases	<0.1	0.8	0.6
Overseas-born cases	*	5.7	6.0
Collection of HIV testing history			
Collection of HIV testing history in all tuberculosis cases	100%	97%	96%
Treatment outcome measures (%)			
Cases evaluated for outcomes	100%	TBA‡	98%
Cases that have treatment completed and are cured (treatment success)	>90%	TBA‡	96%
Cases recorded as treatment failures	<2%	TBA‡	0.1%

* Performance criteria currently under review.
† This performance criterion is based on the key performance indicator published in the DIBP 2014-15 Portfolio Budget Statements under Programme 1.2 Migration and Citizenship Key Performance Indicators, page 31.
‡ TBA is to be assessed: 2014 patient cohort outcomes

bers were low, all cases were in the indigenous Australian and overseas born groups. In contrast South Australia experienced a noticeable fall in case numbers. This was extensively reviewed and concluded to be a natural occurrence unrelated to any significant environmental, policy or procedural changes. As previously reported, the variances across Australia may reflect changing patterns in migrant and temporary resident intakes and placements.

TB notifications in PNG nationals detected in the cross border Torres Strait Protection Zone rose to 9 cases (2 MDR-TB) in 2014 compared to 3 in the previous year. This still remains well below the number reported in 2011 (47) after which bilaterally agreed changes to cross border management of patients were implemented.

The number of re-treatment cases is a measure of TB control program effectiveness. In 2014, 68 (5.1%) notifications were classified as "relapse". However 44 related to previous treatment overseas which does not reflect on the quality of treatment in Australia. The proportion previously treated in Australia was 1.8% (target <2%) but the dataset does not discriminate whether these cases had relapsed following recent or more distant treatment or whether there were contributing factors such as diabetes or HIV co-infection, and additional research into these factors will be of value. Further, the possibility of re-infection either from significant travels to a high burden country or recent transmission in Australia needs to be considered. In low incidence countries the contribution from re-infection to the retreatment group of cases should be low in the absence of recent travel.

TB in children, particularly those less than 5 years, is an important indicator of recent transmission of infection in the community. In the under 15 age group, this proportion has remained steady at 4% of all cases with non-indigenous Australian born contributing 54% (29/54) and overseas born 39% (21/54). In the non-indigenous Australian born group, the key risk factors identified were having at least one parent born overseas (23/29, 80%) and a history of TB contact (14/29, 48%). This latter group of children who were identified as close contacts of an active case were potentially missed opportunities to prevent disease. TB contact investigation is an important public health activity that aims to identify those at risk from recent infection and target with preventive therapy. TB in indigenous Australian born children generally remains low but to maintain this will depend on continued public health capacity to respond in a timely and appropriate manner to any new TB cases.

As routine BCG vaccination is no longer undertaken in Australia, monitoring severe forms of TB in children is important. There were two cases classified as miliary and two as meningeal. These very low numbers based on international recommendations for use of the BCG vaccine in low incidence countries support the present approach.

HIV co-infection

HIV and TB co-infection continues to have minimal impact on TB control in Australia. Of the 55% reported with a known HIV status, only 2% were HIV positive. This rate has not altered significantly over time but routine HIV testing in all new TB cases is still recommended nationally.

Bacteriology /Method of diagnosis/ Bronchoscopy

In 2014, a high proportion (88%) of cases were confirmed based on laboratory evidence. Of the extra-pulmonary cases where a higher proportion of non-bacteriologically confirmed cases is anticipated, the proportion was 80%. An acceptable target is 80% for all cases and these results suggest that over-diagnosis is unlikely to be significant.

In the diagnosis of pulmonary cases, concerns have previously been raised about the use of bronchoscopy, particularly in smear positive patients who represent the most infectious group.[19] Of the 847 pulmonary cases notified, 676 (79.8%) were culture confirmed and of these 335 (50%) were smear positive. Bronchoscopy was the source of a positive culture result in 200 (29.6%) with 12% being smear positive and one case also multidrug-resistant. Despite the recommended infection control precautions (personal protective equipment, negative pressure ventilation and air exchange requirements), these cases can still represent risk to staff and unnecessary morbidity for the patient.[20] The use of "induced sputum" (with appropriate infection control precautions) is strongly encouraged in preference to bronchoscopy in those where obtaining satisfactory spontaneous sputum specimens has not been possible.[21]

Drug Resistance

The rate of isoniazid resistance is low and lower than would be seen in countries of origin for many TB patients diagnosed in Australia. While the absolute number of MDR TB cases is small (n=17) the percentage in new cases (1.7%) is higher than in some of our regional neighbours (New Zealand 0.9%, Hong Kong SAR 0.97%; Malaysia 0.4%) or Canada (1.4%), USA (1.1%) and the UK (1.2%) albeit with overlapping confidence intervals.[11] The most common countries contributing

to Australia's migrant arrivals (India, Viet Nam, China Philippines and Myanmar) all have MDR TB rates in new cases between 2.0 and 5.7%.[11] The number of PNG residents diagnosed with MDR TB in the TSPZ is less in this reporting period than the previous 5 year average.

Treatment Outcomes

Surveillance of TB treatment outcomes is important for monitoring the capacity of jurisdictional programmes to ensure treatment completion and standards of patient management. The high overall treatment success rate (95%) and the low rate of adverse outcomes (deaths 1%, treatment failure 0.1% and loss to follow-up 1.1%) overall have altered little from the previous five years and support the ongoing effectiveness of the State and Territory TB programmes and good standard of management practices.

Concluding comments

If Australia is to achieve the bold target towards TB elimination set by the WHO Global "End TB" Strategy of a 90% reduction in TB incidence by 2035 compared with 2015, then an annual rate of reduction of approximately 18% is required. Based on the present rate (WHO annual estimate for Australia 2000-12 is minus 0.8%) this is a daunting prospect and not achievable using current strategies. Although Australia's rate of TB in Australian born is at pre-elimination levels (<10 per million), its progress towards elimination of TB will be heavily aligned with national policies and global improvements in TB care and prevention. This latter association also highlights the importance of Australia contributing to TB Control efforts beyond its borders particularly with regional partners in the Western Pacific and South East Asian regions.

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Annual report

Surveillance of adverse events following immunisation in Australia annual report, 2015

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Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) for 2015 reported to the Therapeutic Goods Administration and compares them to long-term trends. There were 2,924 AEFI records for vaccines administered in 2015; an annual AEFI reporting rate of 12.3 per 100,000 population. There was a decline of 7% in the overall AEFI reporting rate in 2015 compared with 2014. This decline in reported adverse events in 2015 compared to the previous year was mainly attributable to fewer reports following the HPV vaccine and replacement of monovalent vaccines (Hib, MenCCV and varicella) with combination vaccines such as Hib–MenC, and MMRV. AEFI reporting rates for most individual vaccines were lower in 2015 compared with 2014. The most commonly reported reactions were injection site reaction (26%), pyrexia (17%), rash (16%), vomiting (8%) and headache (7%). The majority of AEFI reports (85%) were described as non-serious events. There were two deaths reported, but no clear causal relationship with vaccination was found.

Introduction

This report summarises national passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) by 28 February 2016. The report focuses on AEFI reported for vaccines administered during 2015 and compares trends in AEFI reporting during 1 January 2000 – 31 December 2015.

An adverse event following immunisation is defined as any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine.[1] The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.[1]

Thus, AEFI may be caused by a vaccine(s) or may be coincidental. Adverse events may also include conditions that occur following the incorrect handling and/or administration of a vaccine(s). The post-marketing surveillance of AEFI is particularly important to detect signals of rare, late onset or unexpected events, which are difficult to detect in pre-registration vaccine trials.

Reports summarising national AEFI surveillance data have been published regularly since 2003. [2-15] Trends in reported adverse events following immunisation are heavily influenced by changes to vaccine funding and availability provided through the National Immunisation Program (NIP). These changes impact on the interpretation of trend data and have been described in detail in reports published since 2003.[2-15] Appendix 1 shows the chronological listing of the changes.

Below is a glossary of the abbreviations on vaccines referred to in this report.

Recent changes that impact on AEFI surveillance data presented in this 2015 report are:

- In March 2015, seasonal influenza vaccine was funded for Aboriginal and Torres Strait Islander children aged 6 months to less than 5 years.
- From March to June 2015, the dTpa vaccine for women during the third trimester of pregnancy was funded by New South Wales, South Australia, Western Australia, the Australian Capital Territory, Victoria and Tasmania. The Northern Territory had funded it since September 2013 and Queensland since July 2014.
- In April 2015, new immunisation requirements for family assistance payments were announced by the federal government (the 'No Jab, No Pay' policy), to come into effect on 1 January 2016. Only parents of children (aged less than 20 years) who are 'fully immunised' or on a recognised catch-up schedule, remain eligible to receive the Child Care Benefit, Child Care Rebate, and/or the Family Tax Benefit Part A end-of-year supplement.

- In March 2015, a booster dose of DTPa was recommended for babies at 18 months of age (commenced under NIP in March 2016).

Refer to Appendix 1

Methods

AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine companies and the public.[16,17] All reports are assessed using internationally consistent criteria[18] and entered into the Australian Adverse Drug Reactions System (ADRS) database. Reports are used in data mining and signal detection activities. Where there is insufficient information in a report to determine causality for a serious adverse event, the TGA will contact the reporter on up to three occasions to elicit further information.

AEFI data

De-identified information on all AEFI reported to the TGA from 1 January 2000 to 31 December 2015 and stored in the ADRS database, were released to the National Centre for Immunisation Research and Surveillance (NCIRS) in March 2016. A description of the surveillance system is available in previous AEFI surveillance reports.[3,6]

Records* contained in the ADRS database were eligible for inclusion in the analysis if a vaccine was recorded as 'suspected'** of involvement in the reported adverse event and either

(a) the vaccination occurred between 1 January 2000 and 31 December 2015, or

(b) for records where the vaccination date was not recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2015.

Study definitions of AEFI outcomes and reactions

AEFI were defined as 'serious' or 'non-serious' based on information in the report sent to the TGA and criteria similar to those used by the World Health Organization[18] and the US Vaccine Adverse Events Reporting System.[19] In this report, an AEFI is defined as 'serious' if it meets one or more of the following criteria: (1) results in death; (2) is life-threatening; (3) requires inpatient hospitalisation or prolongation of existing hospitalisation; (4) results in persistent or significant disability/incapacity; (5) is a congenital anomaly/birth defect or; (6) is a medically important event or reaction.

Typically, each record lists several reaction terms that are symptoms, signs and/or diagnoses that have been coded by TGA staff from the reporter's description into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).[20,21]

In reports published previously, in order to analyse the data, MedDRA® coding terms were grouped to create a set of reaction categories that were broadly analogous to the reactions listed in previous Australian Immunisation Handbooks.[16,17] However, the methodological framework of reporting of adverse events was revised in 2014 and a new format for AEFI analyses using MedDRA

Abbreviations of vaccine types	
BCG	Bacille Calmette-Guérin (i.e. tuberculosis)
dT	diphtheria-tetanus – adolescent and adult formulation
DTPa	diphtheria-tetanus-pertussis (acellular) – paediatric formulation
dTpa	diphtheria-tetanus-pertussis (acellular) – adolescent and adult formulation
DTPa-IPV	combined diphtheria-tetanus-pertussis (acellular) and inactivated poliovirus (quadrivalent)
DTPa-IPV-HepB-Hib	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus, hepatitis B and Haemophilus influenzae type b vaccine (hexavalent)
HepB	hepatitis B
Hib	Haemophilus influenzae type b
Hib-HepB	combined Haemophilus influenzae type b and hepatitis B
Hib-MenC	combined Haemophilus influenzae type b and meningococcal C conjugate vaccine
HPV	human papillomavirus
MenB	meningococcal B vaccine
MenCCV	meningococcal C conjugate vaccine
MMR	measles-mumps-rubella
MMRV	measles-mumps-rubella-varicella
pH1N1	pandemic H1N1 influenza 2009
7vPCV	7-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine

* The term 'AEFI record' is used throughout this report because a single AEFI notification/report to the Office of Product review can generate more than one record in the ADRS database. This may occur if there is a time sequence of separate adverse reactions in a single patient, such as systemic and local reactions.
** Vaccines are classified as 'suspected' if the report contains sufficient information to be valid and the relationship between reported reactions and the vaccine is deemed at least possible.

preferred terms (PTs) was adopted.[22] For this report, MedDRA PTs are used for analysis similar to the previous two published reports.[2,15] Grouping of reactions using PTs is more comparable with data from other countries and internationally accepted.[23-25] In conjunction with the currently used national vaccine-specific reporting form,[26] using PTs allows better reflection of post-marketing surveillance data on vaccines in Australia.

Data analysis

All data analyses were performed using SAS software version 9.4.[27] Average annual population-based reporting rates were calculated for each state and territory and by age group using 2015 population estimates obtained from the Australian Bureau of Statistics.[28] All rates are presented as average annual rates per 100,000 population. Reporting rates per 100,000 administered doses were estimated where information was available on the number of doses administered. This was done for vaccines funded through the NIP for children aged <7 years. The number of administered doses of each of the vaccines given to this age group was obtained from the Australian Immunisation Register (AIR), a national population-based register,[29] a national register that records vaccinations given to people of all ages in Australia.[30] In the future, as reporting in older age groups (>7 years) becomes more complete, denominator data on vaccine doses administered in older age groups will be analysed for the purposes of AEFI reporting.

Notes on interpretation

Caution is required when interpreting this report's data. Due to reporting delays and late onset of some AEFI, the data are considered preliminary, particularly for the fourth quarter of 2015. Data published in previous reports may differ from that presented in this report for the same period, because this report has been updated to include delayed notifications to the TGA that were not included in prior publications. Data can also differ because reports may be updated and recoded when follow-up information is received or when vaccine-specific analyses are conducted.

The information collated in the ADRS database is intended primarily for signal detection and hypothesis generation. While reporting rates can be estimated using appropriate denominators, they cannot be interpreted as incidence rates due to under-reporting and biased reporting of suspected events, and the variable quality and completeness of information provided in individual notifications.[3-14,31]

This report is based on vaccine information and MedDRA preferred terms (similar to previous two published reports)[2,15] collated in the ADRS database and not on comprehensive clinical notes or case reviews. The reported symptoms, signs and diagnoses in each AEFI record in the ADRS database are temporally associated with vaccination but are not necessarily causally associated with a vaccine or vaccines.

Comparison with online Database of Adverse Events Notifications (DAEN)

In August 2012, the TGA made available to the public on its website a searchable database, the Database of Adverse Event Notifications (DAEN), containing reports of all adverse event reports for medicines and vaccines.[32] The data in this report have not been downloaded from DAEN. This report uses data sent to NCIRS by the TGA and includes more detailed information than provided by the DAEN. The numbers published in this report may be different to the numbers in the DAEN database, due to different dates of data extraction and amendment to reports where further information has become available. In addition, this report provides several features that are not available from the DAEN database, including long-term trends and population and dose-based reporting rates, described in the context of changes in vaccine policy and utilisation, and reporting practices.

Results

The ADRS database included a total of 2,924 records where the date of vaccination (or onset of adverse event, if vaccination date was not reported) was between 1 January and 31 December 2015. Of these, 53% were females (n=1,562), 45% (n=1,337) males and 1% (n=25) missing data on gender.2% (n=72) were reported as Aboriginal and Torres Strait Islander Peoples.

In 2015, approximately 81% of AEFI (n=2,368) were reported to the TGA via states and territories, while the rest were reported directly to the TGA by healthcare professionals (13% n=374), members of the public (4% n=105), vaccine companies (2% n=70) and hospitals (2% n=53).

Reporting trends

The overall reporting rate for 2015 was 12.3 per 100,000 population compared with 13.2 per 100,000 in 2014. The highest peak for all years was observed in 2010 (17.4 per 100,000) predominantly due to reports in children following vaccination with the pandemic and 2010 seasonal trivalent influenza vaccines.[12]

The vast majority of reported events in 2015 (from all reporter types) were of a non-serious nature, similar to the previous years (Figure 1).[10,11] Figures 2a, 2b and 2c demonstrate marked variations in reporting levels in association with previous changes to the NIP from 2000 onwards. The decrease in reports in 2015 was predominantly associated with replacement of monovalent vaccines with combination vaccines in children (Figures 2a and 2b) and also a decline in reports of adverse events following immunisation with HPV vaccines in adolescents (Figure 2c).

A seasonal pattern of AEFI reporting was apparent in 2015 as in previous years, with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). This corresponds to the months when influenza vaccine is given and older Australians receive 23vPPV (March to June). However, more AEFI reports following influenza vaccine were received in each of the last five years than years prior to 2009 (pre-pandemic era) (Figure 2c).

Age distribution

The highest population-based AEFI reporting rate per 100, 000 population occurred in infants <1 year of age, the age group that received the largest number of vaccines (Figure 3). Compared with 2014, AEFI reporting rates in children decreased in the 1 to <2 year age group from 117.3 to 108.7. A decline was also observed in the 7 to <20 year age group from 19.7 to 15.1 (Figure 3).

There were no significant differences in reporting rates per 100,000 doses for most individual vaccines in 2015 compared to 2014 (Table 1). For children <7 years of age, rates for varicella, Hib and MenC should be interpreted with caution since these monovalent vaccines were replaced by combination vaccines in July 2013 and hence very few doses were recorded in 2015.

Geographical distribution

Population-based reporting patterns varied among states and territories during 2015 (Table 2). Reporting rates were not significantly different (with overlapping confidence intervals) across jurisdictions in 2015 compared with 2014[2].

Vaccines

There were 2,924 AEFI records received in 2015 (Table 3). The percentage of records where only one vaccine was reported as being the suspected vaccine differed by vaccine administered, typically varying according to whether multiple vaccines were routinely co-administered according to the patient's age. There were slight variations in numbers with outcomes defined as 'serious', which have remained low as in previous years.

The most frequently reported individual vaccine was seasonal influenza vaccine with 599 records (20%) followed by hexavalent DTPa-IPV-HepB-Hib (n=513; 18%), 13vPCV (n=484, 17%), MMR (n=481; 16%), and rotavirus vaccine (n=469; 16%) (Table 3).

Reactions

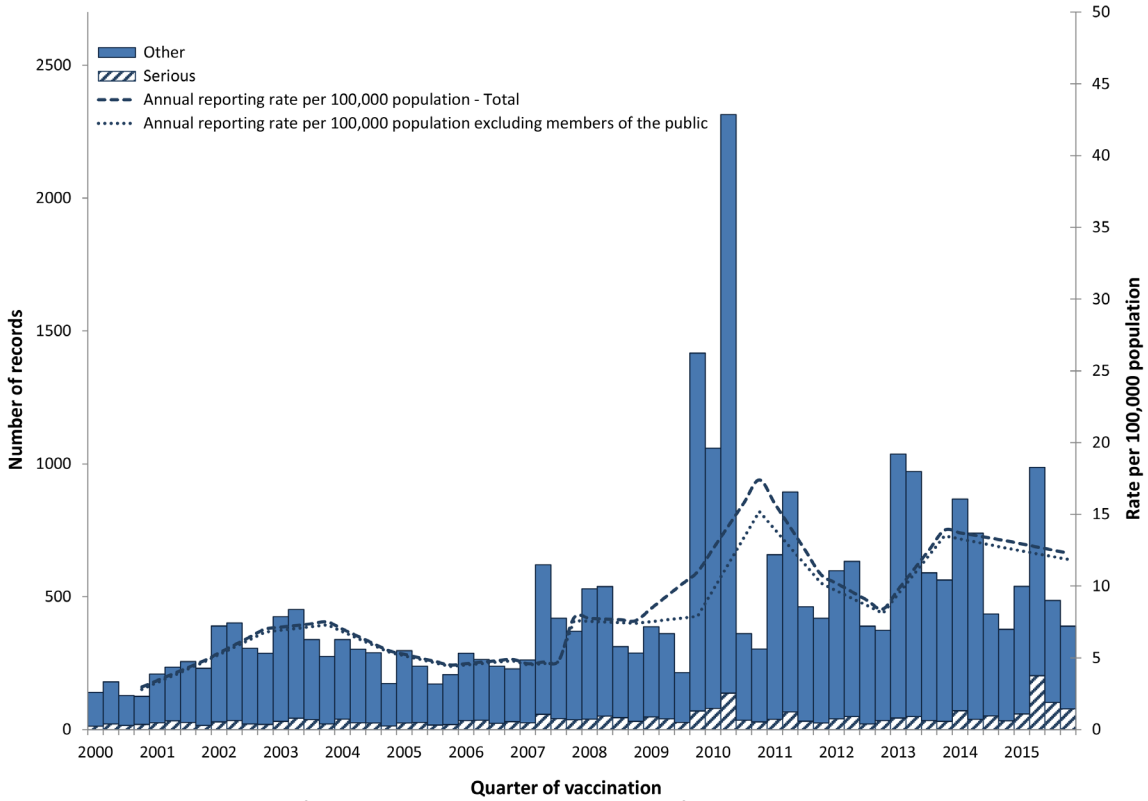
In 2015, out of the 2,924 records, the most frequently reported adverse events were injection site reactions (ISRs) (n=764; 26%), pyrexia (n=497; 17%), rash (n=481; 16%), vomiting (n=225; 8%), headache (n=196; 7%), extensive swelling of vaccinated limb (n=196; 6%) and diarrhoea (n=146; 5%) (Table 4, Figure 4). Among other reactions of interest were: hypotonic-hyporesponsive episode (n=55; 1.9%), convulsions (n=52; 1.8%), intussusception (n=25; 0.9%) and Guillain-Barré Syndrome (n=6; 0.2%) (Table 4). Anaphylaxis (n=22) was reported for less than 1 per cent of AEFI records in 2015.

The number of reports for each reaction has changed over time (Figure 4). The variation in reporting of ISRs is related to changes in the immunisation schedule for vaccines that are known to have higher rates of ISR, including DTPa-containing vaccines, 23vPPV and HPV vaccine.[3-14,33,34] Increases in reports of fever were largely associated with: time periods when new vaccines were added to the NIP in the reporting period, such as 7vPCV and HPV; the extension of seasonal influenza vaccine on the NIP to include persons <65 years at high risk of influenza in 2010; 13vPCV replacing 7vPCV in July 2011; and the extension of HPV to males in 2013.

Severity of outcomes

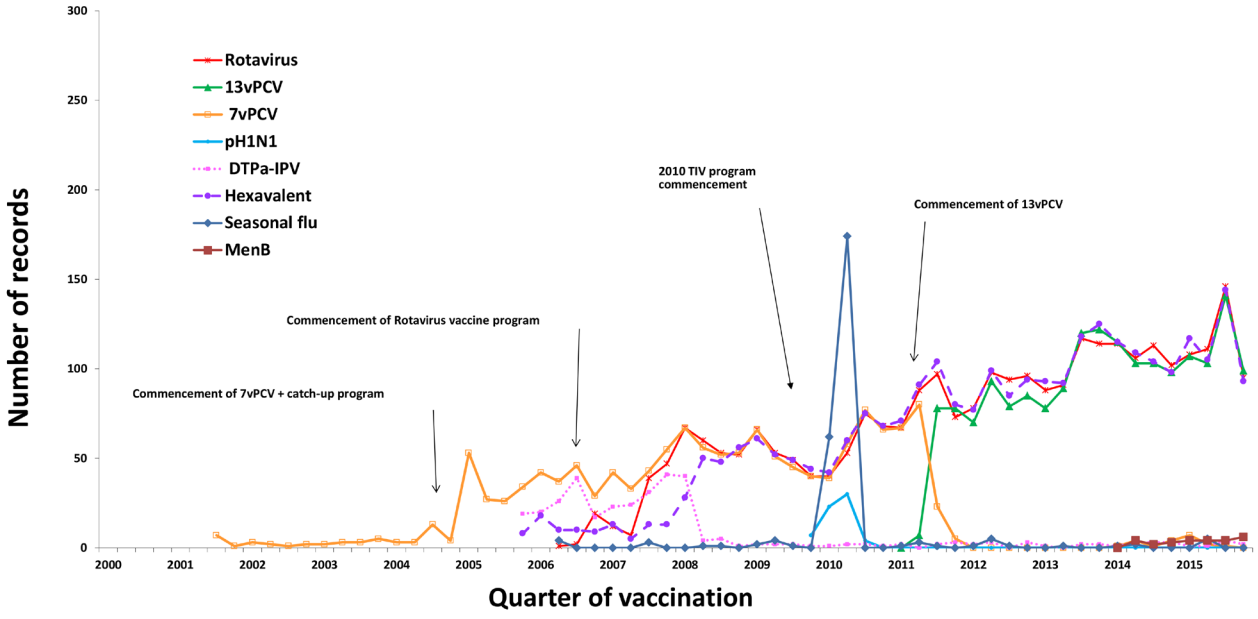
The majority of reported events in 2015 were defined as 'non-serious' (n=2482, 85%). There was a slight increase in percentage of 'serious' events in this reporting period compared to the previous reporting period (Figure 1). This could be due to active surveillance using AusVaxSafety being rolled out more widely throughout Australia, resulting in detection and reporting of events. [35,36]

Figure 1: Adverse events following immunisation, ADRS database, 2000 to 2015, by quarter of vaccination



Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA, was used as a proxy for vaccination date.

Figure 2a: Adverse events following immunisation for children aged <1 year, ADRS database, 2000 to 2015, by quarter of vaccination

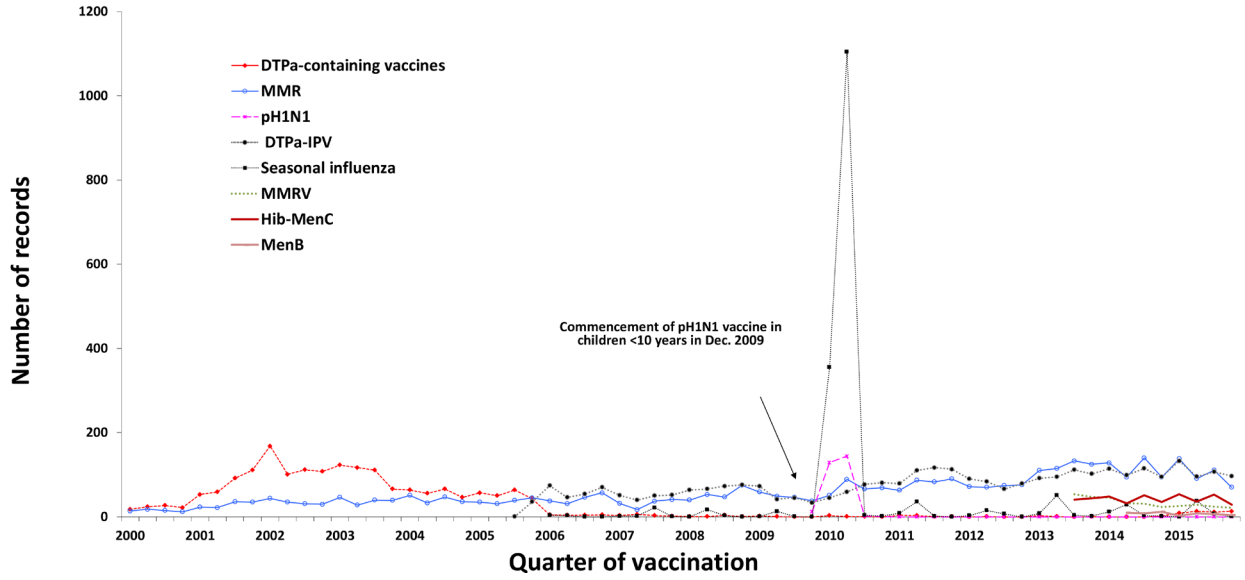


*safety signal for fever and febrile convulsion found to be due to Fluvax 2010 TIV in children.

DTPa-IPV and DTPa-IPV-HepB-Hib (hexavalent) vaccines were introduced into the NIP schedule in November 2005; rotavirus (RotaTeq® and Rotarix®) vaccines on 1 July 2007; pH1N1 influenza vaccine for children 6 months to 10 years in December 2009; seasonal trivalent influenza vaccine in 2010 which was an extension of existing adult and Aboriginal and Torres Strait Islander Peoples programs to at-risk populations; and the 13-valent pneumococcal conjugate vaccine (13vPCV) on 1 July 2011. Also, MenB vaccine is recommended for use in those with increased risk of invasive meningococcal disease and is not currently funded under the NIP.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA, was used as a proxy for vaccination date.

Figure 2b: Adverse events following immunisation for children aged 1 to <7 years in frequently reported vaccines, ADRS database, 2000 to 2015, by quarter of vaccination

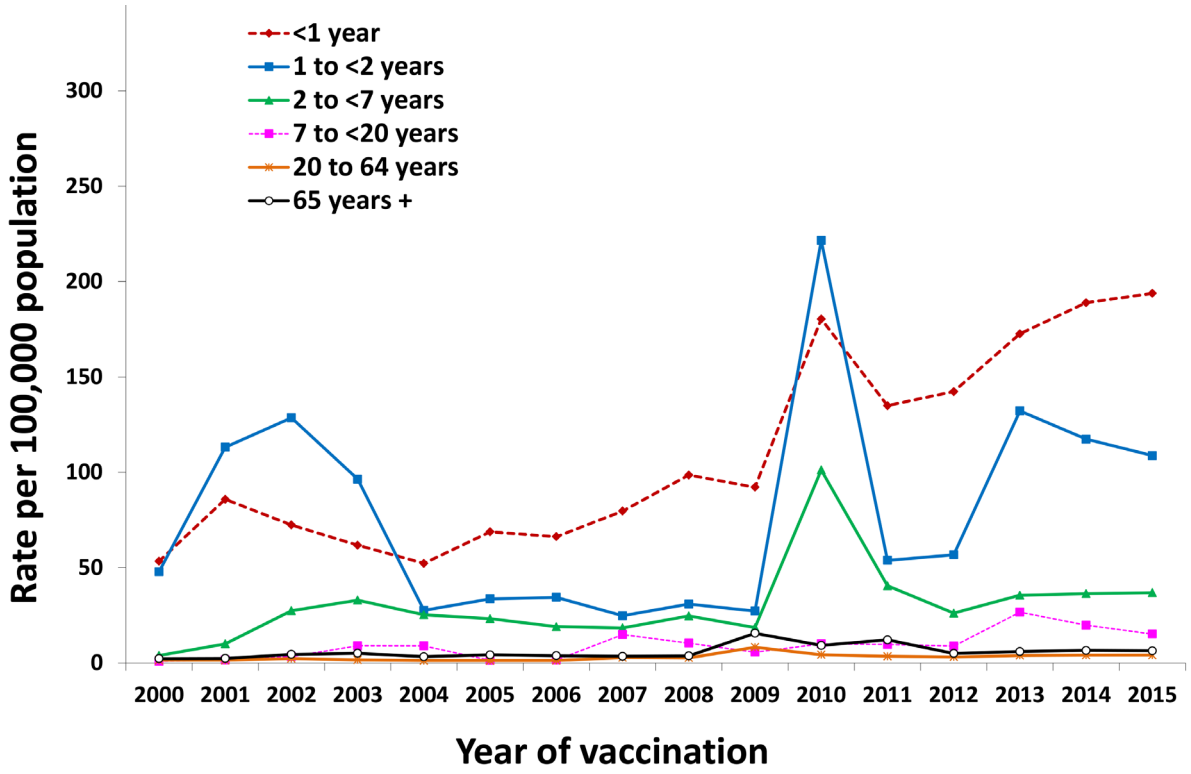


* safety signal for fever and febrile convulsion found to be due to bioCSL Fluvax 2010 TIV in children.

DTPa-IPV was introduced into the NIP schedule in November 2005 replacing DTPa and OPV; seasonal trivalent influenza vaccine in 2010 which was an extension of existing adult and Aboriginal and Torres Strait Islander Peoples programs to at-risk populations; MMRV and Hib–MenC vaccines on July 2013, and HPV program extended to boys in February 2013. Also, MenB vaccine is recommended for use in those with increased risk of invasive meningococcal disease and is not currently funded under the NIP.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA, was used as a proxy for vaccination date.

Figure 3: Reporting rates of adverse events following immunisation per 100,000 population, ADRS database, 2000 to 2015, by age group and year of vaccination



* Associated with administration of bioCSL Fluvax 2010 TIV and associated stimulated reporting.

** The peak in syncope coincided with the enhanced HPV surveillance program in which there was stimulated reporting of syncope for the first 6 months of 2013.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA, was used as a proxy for vaccination date. Also, grouping for reactions are different for this report though these reactions have been mapped back to 2000 as mentioned in the Methods section.

Table 1: Vaccine types listed as 'suspected' in records of adverse events following immunisation by age groups (<7, 7–17, 18–64 and ≥65 years), ADRS database, 2015

Vaccines*	AEFI records† (n)	Vaccine Doses	Reporting rate per 100,000 doses§ (95% CI)	
			2015	2014
<7 years			**Rate (95% Confidence Interval)**	
DTPa-containing vaccines	946	1171740	80.7 (75.7–86.0)	76.5 (71.6–81.6)
Hexavalent (DTPa-IPV-HepB-Hib)	505	862264	58.6 (53.6–63.9)	53.2 (48.5–58.3)
DTPa-IPV	441	309476	142.5 (129.5–156.4)	143.2 (130.3–157.4)
Pneumococcal conjugate -13PCV	479	874250	54.8 (50.0–59.9)	51.1 (46.6–56.0)
Rotavirus vaccine	465	713714	65.2 (59.4–71.4)	61.6 (56.2–67.7)
Measles-mumps-rubella (MMR)	443	575154	77.0 (70.0–84.5)	80.7 (73.8–88.3)
Hib-MenC	199	307737	64.7 (56.0–74.3)	61.0 (52.7–70.6)
Measles-mumps-rubella-varicella (MMRV)	101	303134	33.3 (27.1–40.5)	45.8 (38.8–54.1)
Seasonal influenza	51	79120	64.5 (48.0–84.8)	–
Meningococcal B	40	18995	210.6 (150.4–286.8)	–
Varicella	7	9187	76.2 (30.6–157.0)	94.9 (52.6–171.4)
Meningococcal C conjugate	7	4996	140.1 (56.3–288.7)	124.1 (72.1–213.7)
Haemophilus influenzae type b	5	8051	62.1 (20.2–144.9)	38.6 (16.1–92.8)
Total (<7 years)	**1497**	**4,066,078**	**36.8 (35.0-38.7)**	**37.1 (35.3–39.0)**
7–17 years				
HPV	359	n/a	–	–
dTpa	234	n/a	–	–
Varicella	105	n/a	–	–
Seasonal influenza	48	n/a	–	–
Meningococcal B	9	n/a		
Hepatitis B	7	n/a	–	–
Total (7–17 years)	**553**	**n/a**	**–**	**–**
18–64 years			**–**	
Seasonal influenza	366	n/a	–	–
dTpa	105	n/a	–	–
23vPPV	38	n/a	–	–
Hepatitis B	31	n/a	–	–
MMR	24	n/a	–	–
Q fever	10	n/a	–	–
Meningococcal B	8	n/a		
Total (18–64 years)	**597**	**n/a**	**–**	
≥65 years			**–**	
23vPPV	117	n/a	–	–
Seasonal influenza	111	n/a	–	–
dTpa	5	n/a	–	–
Meningococcal B	3	n/a		
Total (≥65 years)	**226**	**n/a**	**–**	**–**

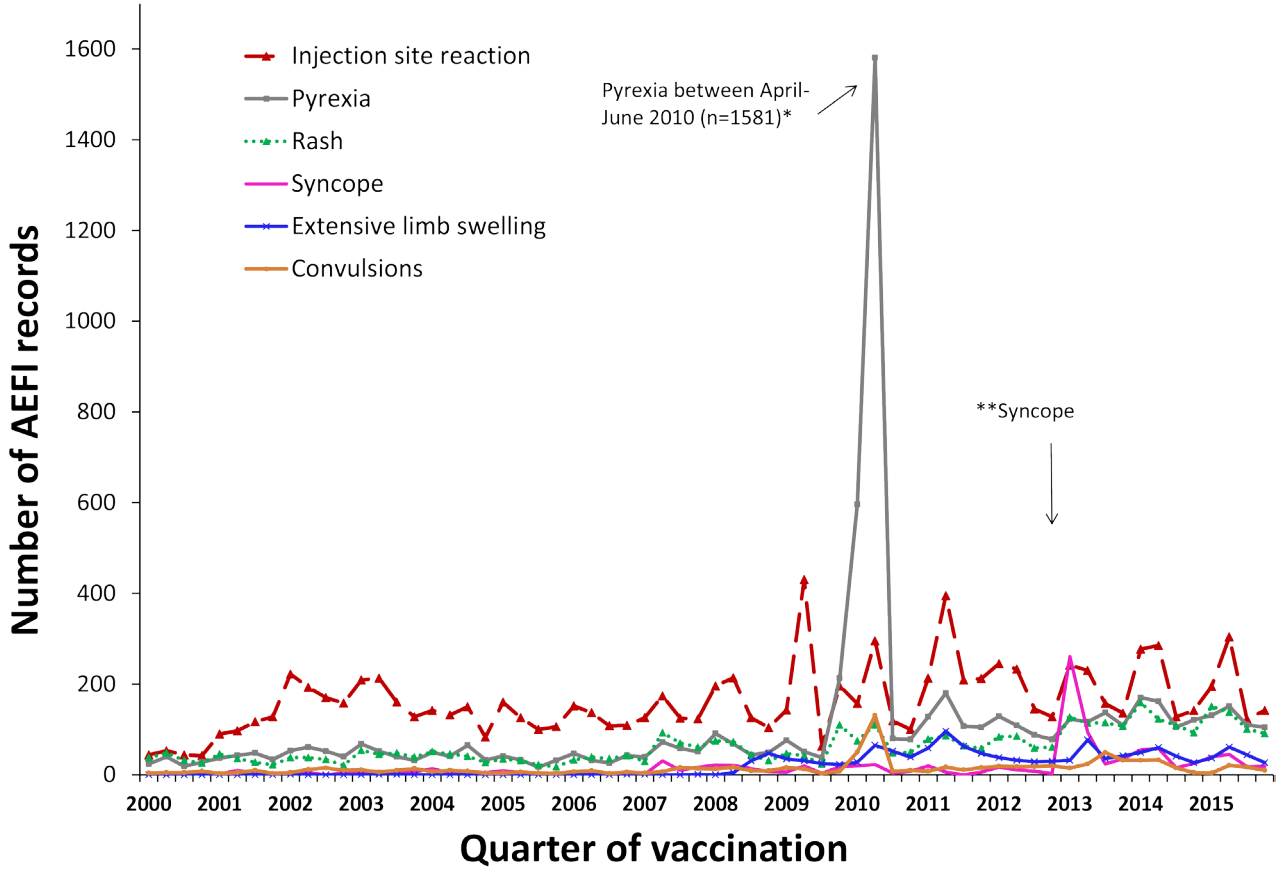
* Records where at least one of the vaccines shown in the table was suspected of involvement in the reported adverse event.
† Number of AEFI records in which the vaccine was coded as 'suspected' of involvement in the reported adverse event and the vaccination was administered between 1 January and 31 December 2015. More than one vaccine may be coded as 'suspected' if several were administered at the same time.
‡ Number of vaccine doses recorded on the AIR/ACIR and administered between 1 January and 31 December 2015.
§ The estimated reporting rate per 100,000 vaccine doses recorded.
n/a Not applicable.

Table 2: Adverse events following immunisation (AEFI) records, ADRS database, January to December 2015, by jurisdiction

State or territory	AEFI records		Annual reporting rate per 100,000 population*			
	N	(%)	'Serious' †	Aged <7 years	Overall Rate	(95% Confidence Interval)
Australian Capital Territory	95	(3.2)	1.8	252.9	24.3	(19.7–29.7)
New South Wales	510	(17.4)	1.1	74.1	6.7	(6.1–7.3)
Northern Territory	54	(1.8)	1.2	205.7	22.1	(16.6–28.8)
Queensland	553	(18.9)	1.3	123.7	11.6	(10.6–12.6)
South Australia	220	(7.5)	1.7	154.8	12.9	(11.3–14.8)
Tasmania	48	(1.6)	0.8	110.5	9.3	(6.8–12.3)
Victoria	1216	(41.6)	3.1	228.7	20.5	(19.3–21.6)
Western Australia	229	(7.8)	2.6	94.8	8.8	(7.7–10.1)
Total	**2924**	**(100.0)**	**1.9**	**133.5**	**12.3**	**(11.8–12.7)**

*Average annual rates per 100,000 population calculated using mid-2015 population estimates (Australian Bureau of Statistics).
†AEFI records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death).

Figure 4: Selected frequently reported adverse events following immunisation, ADRS database, 2000 to 2015, by quarter of vaccination



Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA, was used as a proxy for vaccination date.

Table 3: Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRS database, 2015

Suspected vaccine type	AEFI records		One suspected vaccine only†		'Serious' §		Age group|| <7 years		Age group|| ≥7 years	
	N	(%)	n	(%)¶	n	(%)¶	n	(%)¶	n	(%)¶
Influenza	599	(20.5)	516	(86.1)	112	(18.7)	51	(8.5)	525	(87.6)
DTPa-IPV-HepB-Hib	513	(17.5)	34	(6.6)	143	(27.9)	505	(98.4)	5	(1.0)
13vPCV	484	(16.6)	16	(3.3)	139	(28.7)	479	(99.0)	3	(0.6)
MMR	481	(16.5)	80	(16.6)	64	(13.3)	443	(92.1)	32	(6.7)
Rotavirus	469	(16.0)	43	(9.2)	141	(30.1)	465	(99.1)	0	(0.0)
DTPa-IPV	453	(15.5)	244	(53.9)	37	(8.2)	441	(97.4)	8	(1.8)
HPV	374	(12.8)	147	(39.3)	32	(8.6)	7	(1.9)	364	(97.3)
dTpa	358	(12.2)	161	(45.0)	27	(7.5)	10	(2.8)	344	(96.1)
Hib-MenC	202	(6.9)	13	(6.4)	45	(22.3)	199	(98.5)	2	(1.0)
23vPPV	184	(6.3)	126	(62.7)	14	(7.6)	14	(3.8)	168	(96.2)
Varicella	123	(4.2)	29	(23.6)	8	(6.5)	7	(5.7)	115	(93.5)
MMRV	108	(3.7)	85	(78.7)	26	(24.1)	101	(93.5)	6	(5.6)
Meningococcal B	60	(2.1)	52	(86.7)	9	(15.0)	40	(66.7)	20	(33.3)
Hepatitis B	56	(1.9)	29	(51.8)	5	(8.9)	13	(23.2)	39	(69.6)
Hepatitis A	28	(1.0)	6	(21.4)	2	(7.1)	13	(46.4)	15	(53.6)
BCG	23	(0.8)	18	(78.3)	4	(17.4)	21	(91.3)	1	(4.3)
dT	22	(0.8)	15	(68.2)	1	(4.5)	0	(0.0)	22	(100.0)
Typhoid	18	(0.6)	6	(33.3)	2	(11.1)	5	(27.8)	13	(72.2)
Hepatitis A-Typhoid	13	(0.4)	7	(53.8)	2	(15.4)	0	(0.0)	13	(100.0)
MenCCV	11	(0.4)	3	(27.3)	1	(9.1)	7	(63.6)	4	(36.4)
Q fever	11	(0.4)	10	(90.9)	0	(0.0)	0	(0.0)	11	(100.0)
Zoster	10	(0.3)	10	(100.0)	1	(10.0)	0	(0.0)	8	(80.0)
Rabies	7	(0.2)	4	(57.1)	2	(28.6)	1	(14.3)	6	(85.7)
Hib	7	(0.2)	1	(14.3)	1	(14.3)	5	(71.4)	2	(28.6)
Hepatitis A + B	7	(0.2)	3	(42.9)	0	(0.0)	0	(0.0)	7	(100.0)
Yellow fever	6	(0.2)	3	(50.0)	0	(0.0)	1	(16.7)	5	(83.3)
Japanese encephalitis	3	(0.1)	1	(33.3)	1	(33.3)	2	(66.7)	1	(33.3)
Tetanus	3	(0.1)	3	(100.0)	0	(0.0)	0	(0.0)	3	(100.0)
Cholera	1	(0.0)	1	(100.0)	0	(0.0)	0	(0.0)	1	(100.0)
Total**	**2924**	**(100.0)**	**1678**	**(57.4)**	**442**	**(15.1)**	**1497**	**(51.2)**	**1377**	**(47.1)**

* See appendix for abbreviations of vaccine names.
† AEFI records where only one vaccine was suspected of involvement in a reported adverse event.
‡Causality ratings were assigned to AEFI records using criteria described previously.2,3
§'Serious' is defined in the Methods section.
|| Includes only AEFI records where an age or date of birth has been reported.
¶ Percentages are calculated for the number of AEFI records where the vaccine was suspected of involvement in the AEFI.
** Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and an AEFI record may list more than one vaccine.

Table 4: Selected reported adverse events and reactions of interest* classified by MedDRA Preferred Terms in records of adverse events following immunisation (AEFI), ADRS database, 2015¥

MedDRA Preferred Terms (Adverse events)	AEFI records	Only reaction reported†		'Serious'		Age group‡ <7 years		Age group‡ ≥7 years	
	N	n	(%)||	n	(%)||	n	(%)||	N	(%)||
Injection site reaction**	764	361	(47.3)	41	(5.4)	394	(51.6)	362	(47.4)
Pyrexia	497	34	(6.8)	77	(15.5)	331	(66.6)	158	(31.8)
Rash***	481	189	(39.3)	58	(12.1)	330	(68.6)	144	(29.9)
Vomiting	225	27	(12.0)	37	(16.4)	138	(61.3)	85	(37.8)
Headache	196	6	(3.1)	20	(10.2)	13	(6.6)	180	(91.8)
Extensive limb swelling	169	95	(56.2)	10	(5.9)	103	(60.9)	66	(39.1)
Diarrhoea	146	24	(16.4)	32	(21.9)	113	(77.4)	31	(21.2)
Pain	139	19	(13.7)	12	(8.6)	24	(17.3)	113	(81.3)
Urticaria	138	64	(46.4)	12	(8.7)	87	(63.0)	51	(37.0)
Syncope	122	86	(70.5)	22	(18.0)	24	(19.7)	95	(77.9)
Nausea	116	2	(1.7)	10	(8.6)	8	(6.9)	104	(89.7)
Irritability	104	2	(1.9)	19	(18.3)	103	(99.0)	0	(0.0)
Lethargy	100	0	(0.0)	12	(12.0)	48	(48.0)	49	(49.0)
Dizziness	95	4	(4.2)	9	(9.5)	3	(3.2)	86	(90.5)
Pruritus	80	2	(2.5)	6	(7.5)	20	(25.0)	59	(73.8)
Malaise	77	1	(1.3)	5	(6.5)	8	(10.4)	66	(85.7)
Erythema	76	10	(13.2)	9	(11.8)	40	(52.6)	35	(46.1)
Myalgia	55	6	(10.9)	0	(0.0)	3	(5.5)	50	(90.9)
Hypotonic-hyporesponsive episode	55	42	(76.4)	22	(40.0)	55	(100.0)	0	(0.0)
Abdominal pain	54	3	(5.6)	9	(16.7)	22	(40.7)	31	(57.4)
Paraesthesia	53	3	(5.7)	5	(9.4)	0	(0.0)	51	(96.2)
Convulsions****	52	31	(59.6)	39	(75.0)	51	(98.1)	0	(0.0)
Chills	51	1	(2.0)	9	(17.6)	5	(9.8)	46	(90.2)
Presyncope	44	29	(65.9)	5	(11.4)	8	(18.2)	33	(75.0)
Decreased appetite	39	0	(0.0)	6	(15.4)	26	(66.7)	13	(33.3)
Cough	38	1	(2.6)	5	(13.2)	14	(36.8)	24	(63.2)
Dyspnoea	37	0	(0.0)	9	(24.3)	5	(13.5)	32	(86.5)
Fatigue	36	0	(0.0)	2	(5.6)	2	(5.6)	34	(94.4)
Arthralgia	35	1	(2.9)	0	(0.0)	4	(11.4)	29	(82.9)
Pallor	30	2	(6.7)	6	(20.0)	16	(53.3)	13	(43.3)
Intussception	25	24	(96.0)	15	(60.0)	24	(96.0)	0	(0.0)
Somnolence	23	1	(4.3)	1	(4.3)	13	(56.5)	10	(43.5)
Anaphylactic reaction	22	21	(95.5)	10	(45.5)	3	(13.6)	16	(72.7)
Hyperhidrosis	21	0	(0.0)	3	(14.3)	2	(9.5)	18	(85.7)
Hypoaesthesia	20	2	(10.0)	4	(20.0)	0	(0.0)	20	(100.0)
Haematochezia	18	9	(50.0)	9	(50.0)	18	(100.0)	0	(0.0)
Chest discomfort	18	0	(0.0)	5	(27.8)	0	(0.0)	18	(100.0)
Tachycardia	16	1	(6.3)	5	(31.3)	7	(43.8)	8	(50.0)
Oropharyngeal pain	14	0	(0.0)	3	(21.4)	0	(0.0)	14	(100.0)
Rhinorrhoea	13	1	(7.7)	0	(0.0)	7	(53.8)	5	(38.5)
Tremor	7	1	(14.3)	0	(0.0)	0	(0.0)	7	(100.0)
Guillain-Barre Syndrome	6	6	(100.0)	5	(83.3)	1	(16.7)	5	(83.3)
Lymphadenitis	5	2	(40.0)	0	(0.0)	2	(40.0)	3	(60.0)

¥ A complete list of adverse reactions as classified by individual Preferred Terms is available on request.
* Selected reported adverse events reported during Jan-Dec 2015. Note: for injection site reaction, rash and convulsions, PTs were grouped as described below.
** Injection site reaction includes the following MedDRA PTs: injection site reaction, injection site swelling, injection site pain, injection site mass, injection site erythema, injection site cellulitis, injection site rash, injection site induration, injection site abscess, injection site pruritus, injection site nodule, injected limb mobility decreased, injection site urticaria, injection site inflammation, injection site bruising, injection site infection, and injection site warmth.
*** Rash includes the following MedDRA PTs: rash, rash generalised, rash erythematous, rash pruritic, rash maculo-papular, rash macular, rash vesicular, rash papular, rash morbilliform, and rash pustular.
**** Convulsion includes the following MedDRA PTs: febrile convulsion, and convulsion, grand mal convulsion, and partial seizures.
† AEFI records where only one reaction was reported.
§ 'Serious' outcomes are defined in the Methods section.
‡ Includes only AEFI records where an age or date of birth has been reported.
|| Percentages relate to the number of AEFI records in which the specific reaction term was listed.

Two deaths were reported as temporally associated with receipt of vaccines in 2015.

- A 76-year-old male who had been unwell for a week prior to influenza vaccination. He also had history of chronic obstructive pulmonary disease (COPD), diabetes and acute respiratory failure.
- A 73-year-old male with history of severe COPD, diabetes, high cholesterol and lung cancer received influenza vaccine more than two weeks prior to hospitalisation. The causes of death were pneumonia, severe COPD and squamous cell carcinoma of the lung.

In both of these cases, a clear causal relationship with vaccination was unable to be determined due to confounding factors.

Discussion

This report uses a similar methodology of analysis to that used in the previous two annual reports.[2,15] As per the previous report, this method allows for clearer reporting of adverse events using MedDRA PTs, as used in the DAEN. This change in methodology needs to be taken into account when comparing with data on specific reaction terms and categories from annual reports prior to 2013.

In 2015, there appeared to be an overall decline in AEFI reporting rate compared with the previous year. The decline was likely due to it being the third year of the extension of National HPV Vaccination Program to males and also that the HPV male catch-up component ceased in 2014. There is usually an increase in reporting of adverse events when a program is newly rolled out. Previous data have shown that an early increase in AEFI reporting occurred each time a new vaccine was introduced, as immunisation providers are more likely to report milder, less serious AEFIs for vaccines with which they are not as familiar. A reduction and stabilisation of reporting rates over time occurs thereafter.[2,4,5,7,10,12-15,37]

The drop in number of adverse events could also partially be attributed to very few reports of adverse events following administration of individual pathogen vaccines such as varicella, MenC and Hib in this reporting period. This was anticipated as the combined Hib–MenC vaccine replaced the respective monovalent MenC and Hib vaccines in July 2013. Also, from July 2013, the 2nd dose of MMR vaccine was brought forward to 18 months of age and delivered as a combination MMRV vaccine.

From 2015, the seasonal influenza vaccine was provided free for all Aboriginal and Torres Strait Islander children aged 6 months to 5 years.[38] During this first year of the program's implementation, an adverse event following seasonal influenza vaccine was reported in only one Aboriginal and Torres Strait Islander child aged 6 months to 5 years and was not serious.

The dTpa vaccine was recommended and funded for women during the third trimester of pregnancy in this reporting period. As well, a booster dose of DTPa was recommended (though funded only from March 2016) at 18 months of age. In 2015, there had been no impact of this recommendation on numbers of AEFI.

Overall, in Australia, injection-site reaction, pyrexia and rash were the most commonly reported reactions in 2015. Vaccines such as DTPa-containing vaccines, pneumococcal conjugate (13vPCV), MMR and rotavirus had higher reporting rates than other vaccines for children aged <7 years in the current reporting period. However, these rates were not significantly higher than for the previous reporting period.

Conclusion

The reported AEFIs decreased in 2015 compared with 2014. The majority of AEFIs reported to the TGA were mild, transient events. The data reported here are consistent with an overall high level of safety for vaccines included in the NIP schedule.

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Appendix 1: Changes in immunisation policy and the National Immunisation Program (2005–2015)[2,4,5,7,10,12-14,39]

Year	Intervention
2015	From March 2015, seasonal influenza vaccine funded for Aboriginal and Torres Strait Islander children aged 6 months to less than 5 years. From March to June 2015, the dTpa vaccine for women during the third trimester of pregnancy was funded by New South Wales, South Australia, Western Australia, the Australian Capital Territory, Victoria and Tasmania. The Northern Territory had funded it since September 2013 and Queensland since July 2014. In March 2015, a booster dose of DTPa recommended at 18 months of age (funded in March 2016). In April 2015, new immunisation requirements for family assistance payments were announced by the federal government (the 'No Jab, No Pay' policy), to come into effect on 1 January 2016. Only parents of children (aged less than 20 years) who are 'fully immunised' or on a recognised catch-up schedule remain eligible to receive the Child Care Benefit, Child Care Rebate, and/or the Family Tax Benefit Part A end-of-year supplement.
2014	4vHPV catch-up program for males aged 14–15 years ceased in December 2014. In July 2014, dTpa was funded by Queensland for women during the third trimester of pregnancy.
2013	From 1 February 2013, 4vHPV was extended to males aged 12–13 years, delivered through a school-based program, with a catch-up program for males aged 14–15 years in 2013 and 2014. From July 2013, the 2nd dose of MMR vaccine, previously given at 4 years, was brought forward to 18 months of age and delivered as a combination MMRV vaccine. From July 2013, combined Haemophilus influenzae type b (Hib) and meningococcal serogroup C (MenC) vaccine, Menitorix®, was funded for infants aged 12 months. This combination vaccine replaced the single dose of monovalent meningococcal C conjugate vaccine (MenCCV) and booster dose of monovalent Hib vaccine previously scheduled at 12 months of age. At the end of December 2013, the secondary school Year 7 hepatitis B vaccine catch-up program ceased, as all younger age cohorts were eligible for infant immunisation under the NIP (commenced 2000). In September 2013, dTpa was funded by NT for women during the third trimester of pregnancy and for parents of infants aged <7 months under cocoon strategy
2012	From 1 October 2012, a fourth dose of Prevenar 13®, (13vPCV, a 13-valent pneumococcal conjugate vaccine) was listed on the National Immunisation Program (NIP) for Aboriginal and Torres Strait Islander children, aged 12-18 months, residing in Queensland, South Australia, Western Australia and the Northern Territory. This replaced the booster dose of Pneumovax23®, (23vPPV, a 23-valent pneumococcal polysaccharide vaccine) administered between 18 and 24 months of age for Aboriginal and Torres Strait Islander children from these jurisdictions.
2011	From 1 July 2011, Prevenar 13® replaced Prevenar® on the NIP for children at 2, 4 and 6 months of age in all states and territories, except the Northern Territory which adopted 13vPCV from 1 October 2011. 1 October 2011 to 30 September 2012 – all children aged between 12 - 35 months who had completed a primary pneumococcal vaccination course with 7vPCV, were eligible to receive a free, supplementary dose of Prevenar 13® On 25 March 2011, TGA issued a recall of Batch N3336 of the 23 valent pneumococcal polysaccharide vaccine 23vPPV, Pneumovax® 23. April 2011 - health professionals were advised not to administer a second or subsequent dose of Pneumovax 23 vaccine. December 2011 - Revised recommendations regarding which patients should be re-vaccinated under the NIP were provided.
2010	Annual vaccination with seasonal trivalent influenza vaccine (TIV, containing 3 influenza strains: A/H1N1, A/H3N2 and B) was funded under the NIP for people aged ≥6 months with medical risk factors (previously subsidised through the Pharmaceutical Benefits Scheme) and all Aboriginal and Torres Strait Islander Peoples aged ≥15 years (previously all Aboriginal and Torres Strait Islander Peoples ≥50 years and 15–49 years with medical risk factors). On 23 April 2010, the use of the 2010 seasonal TIV in children <5 years of age was suspended by Australia's Chief Medical Officer due to an increased number of reports of fever and febrile convulsions post vaccination. A subsequent investigation identified that Fluvax® and Fluvax junior® (CSL Biotherapies), but neither of the other two available brands registered for use in young children, were associated with an unacceptably high risk of febrile convulsions. The recommendation to resume the use of seasonal influenza vaccine in children aged 6 months to 5 years, using brands other than Fluvax® and Fluvax junior®, was made in August 2010.

Year	Intervention
2009	By late 2009, all states and territories were using the single hexavalent DTPa-IPV-Hib-HepB (Infanrix hexa®) vaccine for all children at 2, 4 and 6 months of age, due to an international shortage of Haemophilus influenzae type b (Hib) (PedvaxHib® [monovalent] and Comvax®[Hib-HepB]) vaccines. Pandemic H1N1 2009 influenza vaccine (Panvax®) was rolled out across Australia from 30 September 2009 for people aged ≥10 years. From December 2009, the pandemic vaccine was made available to children aged 6 months to 10 years.
2008	Western Australia commenced a seasonal influenza vaccination program for all children aged 6 months to <5 years (born after 1 April 2003). In March 2008, Queensland, South Australia and Victoria changed from using two combination vaccines (quadrivalent DTPa-IPV and Hib-HepB) to the single hexavalent DTPa-IPV-HepB-Hib vaccine.
2007	From April 2007, funded immunisation against human papillomavirus for all Australian girls aged 12–13 years was delivered through a school-based program, with a temporary catch-up program through schools or primary care providers for females aged 13–26 years, until December 2009. From July 2007, immunisation against rotavirus at 2 and 4 months of age (Rotarix®) or at 2, 4 and 6 months of age (Rotateq®) was funded.
2005	From January 2005, universal funded infant 7-valent pneumococcal conjugate vaccine (7vPCV) program replaced the previous targeted childhood program, with a catch-up program for children aged <2 years. Universal 23-valent pneumococcal polysaccharide vaccine (23vPPV) for adults aged ≥65 years replaced previous subsidy through the Pharmaceutical Benefits Scheme. From November 2005, universal funded immunisation against varicella at 18 months of age, with a school-based catch-up program for children at 10–13 years of age not previously vaccinated and without a history of varicella infection (no funded catch-up for children 2–10 years of age). IPV was funded to replace OPV, in combination vaccines.

Annual report

Paediatric Active Enhanced Disease Surveillance (PAEDS) annual report 2015: Prospective hospital-based surveillance for serious paediatric conditions

McRae J, Quinn HE, and Macartney K on behalf of the PAEDS network

Abstract

Keywords: paediatric, surveillance, child, hospital, vaccine preventable diseases, adverse event following immunisation, acute flaccid paralysis, encephalitis, influenza, intussusception, pertussis, varicella zoster virus

Abstract

Introduction: The Paediatric Active Enhanced Disease Surveillance (PAEDS) network is a hospital-based active surveillance system employing prospective case ascertainment for selected serious childhood conditions, particularly vaccine preventable diseases and potential adverse events following immunisation (AEFI). PAEDS data is used to better understand these conditions, inform policy and practice under the National Immunisation Program, and enable rapid public health responses for certain conditions of public health importance. PAEDS enhances data available from other Australian surveillance systems by providing prospective, detailed clinical and laboratory information on children with selected conditions. This is the second of the planned annual PAEDS reporting series, and presents surveillance data for 2015.

Methods: Specialist surveillance nurses screened hospital admissions, emergency department records, laboratory and other data, on a daily basis in 5 paediatric tertiary referral hospitals in New South Wales, Victoria, South Australia, Western Australia and Queensland to identify children with the selected conditions. Standardised protocols and case definitions were used across all sites. Conditions under surveillance in 2015 included acute flaccid paralysis (a syndrome associated with poliovirus infection), acute childhood encephalitis (ACE), influenza, intussusception (IS; a potential AEFI with rotavirus vaccines), pertussis and varicella-zoster virus infection (varicella and herpes zoster). Most protocols restrict eligibility to hospitalisations, ED only presentations are also included for some conditions.

Results: In 2015, there were 674 cases identified across all conditions under surveillance. Key outcomes of PAEDS included: contribution to national AFP surveillance to reach WHO reporting targets; identification of signals for *Mycoplasma pneumoniae* and parechovirus-related outbreaks (ACE surveillance); and demonstration of high influenza activity with vaccine effectiveness (VE) analysis supportive of vaccination. Surveillance for IS remains ongoing with any identified AEFIs reported to the relevant State Health Department; varicella and herpes zoster case numbers decreased slightly from previous years in older children not eligible for catch-up. Pertussis case numbers increased in early 2015 and analysis of cases in children aged <1 year demonstrated the importance of timely childhood and maternal immunisation.

Conclusions: PAEDS continues to provide unique policy-relevant data on serious paediatric conditions using hospital-based sentinel surveillance.

Introduction

This is the second annual report of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and summarises data collected in 2015. PAEDS historical data for 2007–2014, including impacts and outcomes, were reported in the PAEDS 2014 inaugural report.[1]

PAEDS is a hospital-based active surveillance system for serious childhood conditions of public health importance, particularly vaccine preventable diseases (VPDs) and adverse events following immunisation (AEFI). PAEDS, through prospective case identification and ascertainment, collects timely and detailed clinical data on children requiring hospitalisation for select conditions. In some instances, emergency department (ED) presentations are also included. PAEDS data is used to better understand these conditions, inform policy and practice under the National Immunisation Program (NIP) and enable rapid public health

responses for certain conditions of public health interest. PAEDS is well positioned compared to other passive surveillance programs that are usually less able to adequately capture such timely and comprehensive data.[2]

During 2015, the PAEDS network consisted of 5 participating hospitals: The Children's Hospital at Westmead (CHW), Sydney, New South Wales (NSW); Royal Children's Hospital (RCH), Melbourne, Victoria; Women's and Children's Hospital (WCH), Adelaide, South Australia; Princess Margaret Hospital (PMH), Perth, Western Australia; and Lady Cilento Children's Hospital (LCCH), Brisbane, Queensland. PAEDS is coordinated by the National Centre for Immunisation Research and Surveillance (NCIRS) based at CHW in Sydney.

PAEDS activities are supported through funding by the Australian Government Department of Health and the 5 participating states' health departments. In addition, the Australian Paediatric Surveillance Unit (APSU) and the Influenza Complications Alert Network (FluCAN) collaborate with PAEDS on specific conditions. PAEDS produces monthly data reports for all funding bodies and collaborators.

Methods

Active case ascertainment

Under PAEDS, specialist surveillance nurses in each hospital identified children diagnosed with the conditions under surveillance, as defined in Table 1, by reviewing admission and emergency department databases, clinical records, laboratory logs and through liaison with medical and nursing staff.[1]

For 2015, all 5 of the PAEDS participating hospitals were approved by their respective Human Research Ethics Committees to operate under a waiver of consent model for surveillance of all conditions. Surveillance nurses collected detailed clinical information from the medical records and vaccination history from the Australian Childhood Immunisation Register (ACIR). Information not available in the medical record was obtained by contacting the child's parent/guardian; participation was voluntary. In some cases, the parent/guardian was approached for consent to their child's participation in additional research studies, involving elements such as long-term follow-up or non-routine specimen collection. In this instance, a patient information sheet and consent form was provided to facilitate participation (Figure 1).

Conditions under surveillance

In 2015, there were 6 conditions under surveillance at all PAEDS sites: acute flaccid paralysis (AFP), acute childhood encephalitis (ACE), intussusception (IS), pertussis, and varicella-zoster virus infection (VZV; varicella and herpes zoster). Surveillance for influenza (in collaboration with FluCAN) was undertaken at 2 PAEDS sites: CHW (Sydney) and PMH (Perth).

In addition, in 2015, data collected from surveillance of 2 select PAEDS conditions in children aged <5 years, AFP and ACE, were analysed monthly to identify any serious acute neurologic events (SANE) that occurred within 6 weeks of receipt of a seasonal influenza vaccine.

Collection of biological samples

Surveillance nurses facilitated collection of samples in line with public health requirements and condition protocols. For example, children hospitalised with AFP require collection of 2 stool samples for enteric virus identification by the National Enterovirus Reference Laboratory (NERL) in Melbourne as part of the Global Polio Eradication Initiative (GPEI).[3,4] For other conditions, samples are collected for virus genotyping (e.g. VZV) or for additional pathogen testing (e.g. ACE).

Quality assurance and ICD-10-AM audits

To check for completeness of case ascertainment, PAEDS nurses at each site conducted regular retrospective audits of medical records by searching for primary and secondary ICD-10-AM codes describing the relevant conditions (e.g. K56.1 for IS). Cases ascertained through the medical records audits were compared with the cases ascertained prospectively by PAEDS for the same period. Additional cases identified by the ICD-10-AM audit process were retrospectively included into PAEDS.[1] As an additional quality assurance measure, periodic audits were undertaken by investigators of case medical records to assess accuracy of data collected.

Data management

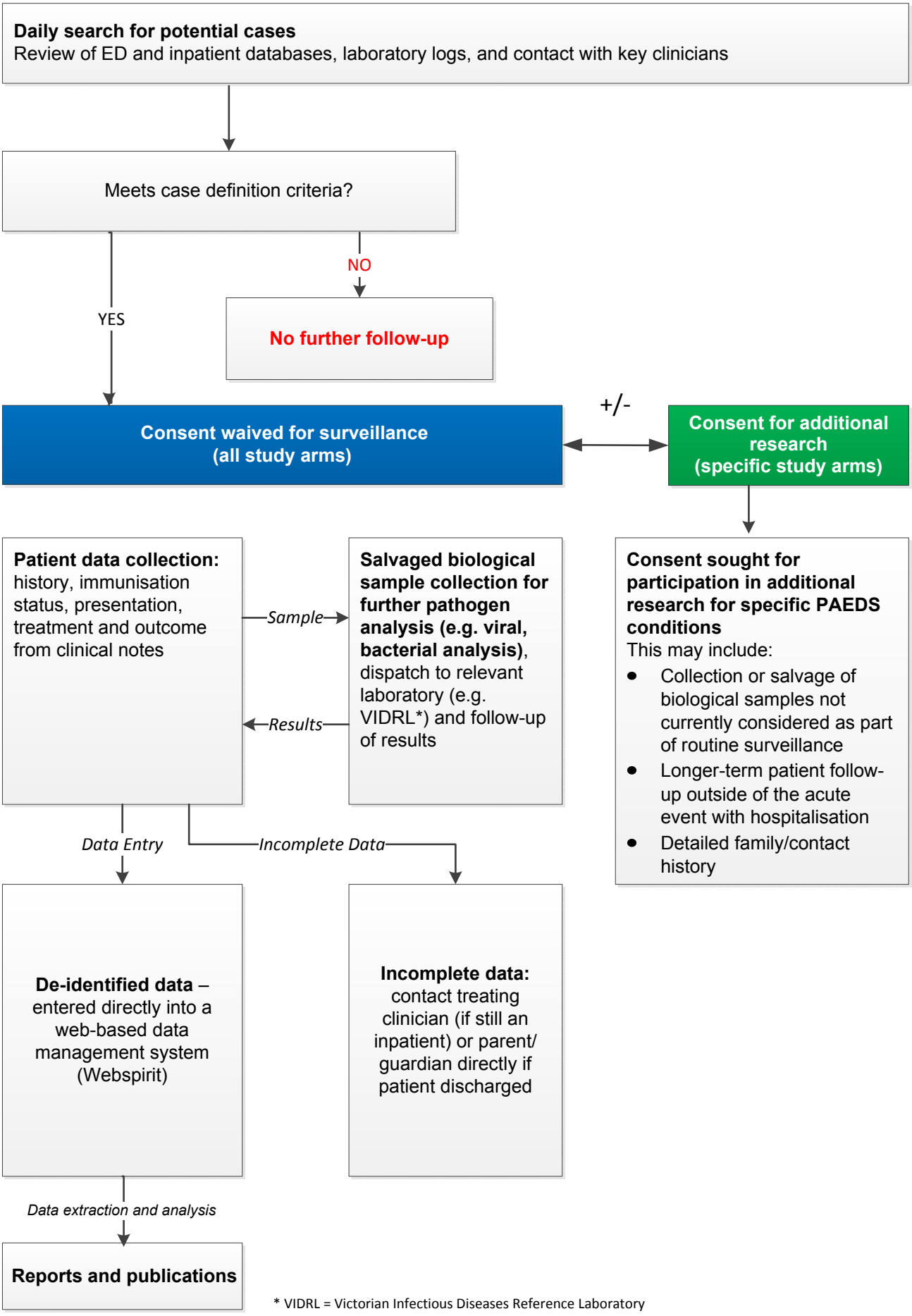
PAEDS utilises a web-based data management system called 'WebSpirit'[5] which enables online data entry by surveillance nurses at each site and centralised data extraction. Data is held securely and exported on a regular basis by staff at the PAEDS coordinating centre for clinical review, monthly quality checks, analysis and reporting.[1]

Table 1: PAEDS conditions under surveillance, case definitions and rationale, 2015

Condition and case definition	Rationale
Acute flaccid paralysis (AFP) *Case definition:* Any child aged birth to <15 years and presenting with acute flaccid paralysis: onset of flaccid paralysis in one or more limbs or acute onset of bulbar paralysis.	WHO requires active national surveillance for cases of AFP in children aged <15 years in order to monitor for potential cases of paralytic poliomyelitis. PAEDS collaborates with the APSU in nationwide surveillance in an effort to meet the target enrolment of 1/100,000 cases per year. Data collected on AFP also contributes to separate analysis for SANE*.
Acute childhood encephalitis (ACE) *Case definition:* Any child aged birth to <15 years **AND** hospitalised with acute encephalopathy **AND** who has one or more of the following: fever, seizures, focal neurological findings, at least one abnormality of cerebrospinal fluid, or EEG/ neuroimaging findings consistent with infection-related encephalitis.	Encephalitis is a critical condition that is considered a marker syndrome for emerging infectious diseases. It is most often caused by viruses (including those which are or potentially will be vaccine preventable). It can also be immune-mediated, and uncommonly can be associated with vaccine receipt. As there is limited epidemiologic data on encephalitis, PAEDS is uniquely placed to undertake active, syndromic surveillance and can collect biological specimens. Enrolment of participants into comprehensive follow-up studies to improve understanding of long-term neuropsychological sequelae also occurs.[6] Data collected on ACE also contributes to separate analysis for SANE*.
Influenza – FluCAN *(Seasonally: April–October)* Case definition: Any hospitalised child aged birth to <18 years who presents with suspected influenza (respiratory symptoms +/– fever) who is influenza PCR-positive.	The emergence of H1N1-09 influenza in 2009 demonstrated the importance of enhanced influenza surveillance in children.[7] PAEDS provides unique timely sentinel data from 2 sites (Sydney and Perth) on influenza hospitalisations, including complications and deaths, which can be used to inform public health response and policy. The data on children supplements adult data from 15 other FluCAN sites. Information on influenza test-negative (control) patients with acute respiratory illness (ARI) is also collected and allows calculation of vaccine effectiveness to be performed.
Intussusception (IS) *Case definition:* Any child aged <9 months presenting with a diagnosis of acute intussusception confirmed using the Brighton Collaboration clinical case definition (Level 1 or 2). Includes hospitalised or ED only.[8]	Intussusception is the most common cause of bowel obstruction in infants and young children and was associated with a previous rotavirus vaccine in the USA which was withdrawn in 1999. Timely, active and systematic surveillance of IS cases is important and has identified a temporal but low incidence association with the rotavirus vaccines currently available under the NIP (since July 2007).[9] Surveillance also aims to describe the epidemiology, aetiology and severity of IS.[10,11]
Pertussis *Case definition:* Any child aged birth to <15 years admitted to hospital with laboratory-confirmed pertussis.	Despite immunisation coverage approaching 93%, pertussis continues to cause significant morbidity and mortality, particularly in very young Australian children.[12] The aims of this surveillance are to determine the burden of disease from hospitalised pertussis, with special emphasis on the duration of hospitalisation, use of intensive care, death and disability. Possible sources of infection and co-morbidities to severity of pertussis are examined. This surveillance data will assist in optimising pertussis prevention strategies.
Varicella–Zoster Virus Infection *Case definition:* Any child aged birth to <15 years hospitalised for varicella or herpes zoster with or without complications.	Complications of varicella or herpes zoster requiring hospitalisation provide a measure of disease burden and severity. Ongoing surveillance aims to show trends in incidence and severity of both varicella and herpes zoster related to the varicella vaccination program and allow vaccine effectiveness estimations.[13] The timely collection of vesicle samples and genetic subtyping of varicella-zoster virus infection allows for identification of vaccine failures in immunised children and genotypes associated with severe complications or derived from the live attenuated vaccine.

*SANE – Serious acute neurological event

Figure 1: PAEDS method for surveillance using the waiver of consent model plus opt-in consent for additional research of specific study arms



Results

In 2015, there were 164,932 admissions at the 5 participating PAEDS sites (Table 2). This represents a substantial proportion of all hospitalisations to specialist paediatric centres in Australia.[1]

There were 674 cases identified across all PAEDS conditions under surveillance and sites in 2015 (Table 3). Data on an additional 215 control cases (influenza test-negative ARI cases) were collected under FluCAN surveillance. Thus, the total number of PAEDS-reported cases (excluding influenza test-negative controls) between the network's inception in 2007 and 31 December 2015 was 4,897.

Surveillance results for 2015

Table 3 shows case numbers for all 6 conditions in 2015 and details of auditing and ICD-coded hospital discharge data.

Acute flaccid paralysis

PAEDS reported 46 cases of AFP to the NERL in 2015, meeting the 1/100,000 surveillance target in children aged <15 years (estimated Australian population in this age group is 4.48 million[14]). Stools could not be collected from 2 of 46 cases due to *Clostridium botulinum* infection. Of the remaining 44 cases, at least 1 stool sample was collected within 2 weeks of onset of paralysis for 29 cases (66%), and 2 stool samples were collected for 11 cases (25%). The most common diagnoses associated with AFP were Guillain-

Table 2: Total hospital admissions and ED presentations (inclusive of admitted patients) for the 5 hospitals participating in PAEDS in 2015

PAEDS site	Hospital admissions	ED presentations	Total cases all conditions (% hospital admissions)*
CHW, Sydney	32,224	57,562	213 (0.67)
RCH, Melbourne	45,427	86,842	89 (0.20)
WCH, Adelaide	21,343	46,004	52 (0.24)
PMH, Perth	27,510	64,935	211 (0.77)
LCCH, Brisbane	38,428	64,345	109 (0.28)
Total	164,932	319,688	674 (0.41)

*Denominator used is hospitalisations, some intussusception, or more infrequently AFP cases, may not be included as they may be treated in ED only.

Table 3: Number of cases captured by PAEDS in 2015 by condition and method of case ascertainment

Condition	Case identification methods			
	Total cases captured by active surveillance	Number captured by PAEDS only, not ICD-coded*	Number captured retrospectively following ICD-10 audit	Total captured cases (surveillance and ICD-10 audit combined)
Acute flaccid paralysis†	45	21	1	46
Acute childhood encephalitis	209	125	15	224
Influenza‡	219	–	–	219
Intussusception	53	7	14	67
Pertussis	73	4	5	78
Varicella or Herpes Zoster	34	10	6	40
Total	633	167	41	674

* These cases did not have an ICD-10 code for this hospitalisation that was consistent with the condition diagnosed.
† AFP numbers may differ from those published in APSU and/or VIDRL reports due to differences in surveillance systems.
‡ Influenza – an additional 215 control cases were captured at CHW (Sydney) and PMH (Perth). No ICD audit was carried out on this condition.

Barré syndrome (GBS; 39%), acute demyelinating encephalomyelitis (ADEM; 17%) and transverse myelitis (13%).

Acute childhood encephalitis

PAEDS identified 224 cases of suspected ACE in 2015. Among these cases was a cluster of *Mycoplasma pneumoniae* encephalitis in NSW that was reported to local public health authorities. A subsequent outbreak investigation was undertaken with the Western Sydney local public health unit and the NSW Ministry of Health rapid surveillance team to which NSW ACE investigators contributed (manuscript under review). Additionally, a signal of increased suspected encephalitis associated with parechovirus was identified in NSW during October 2015. This was communicated to public health authorities in 3 states (NSW, Queensland and Victoria) showing increased case numbers and included advice for clinicians regarding case management. The majority of children with ACE were recruited to follow-up studies and have had biological specimens salvaged for future analysis.

Serious acute neurological events (SANE) following immunisation

Vaccine data from AFP and ACE surveillance was reviewed in combination and included an additional 29 children aged <2 years hospitalised with ICD-coded febrile seizures (FS) from CHW (ascertained through separately funded FS surveillance). During 2015, 68 SANE in children aged <5 years were identified (24 confirmed and 9 probable encephalitis, 5 GBS and 1 ADEM). Only 4 of the 68 children (6%) had received an influenza vaccine; one had been vaccinated within 42 days of symptom onset. This was a previously well child who developed acute encephalitis 18 days following an influenza vaccine but was found to have a viral infection (HHV6) as a likely cause of the encephalitis.

Influenza

There were 219 children with confirmed influenza admitted to CHW (n=98) and PMH (n=121) in the 2015 season (April – October), and 215 influenza test-negative controls were enrolled. Of the cases, 16 (7.3%) were admitted to the intensive care unit, and 108 (49%) had chronic co-morbidities. Of the 202 children with influenza where vaccination status was ascertained, 24 (12%) were vaccinated.

Intussusception

Of the 67 cases of IS identified, 37 (55%) met level 1 Brighton Criteria.[8] Of the affected children, 9 (24%) had received a rotavirus vaccine in the previous 21 days: none had IS within 21 days after their first dose of vaccine, 3 had IS within 21 days after their second dose, and 6 had IS within 21 days after their third dose. Three (33%) of the 9 children required surgery to correct the IS and 6 (67%) children were successfully treated with air enema. Among all 37 cases of level 1 IS, 13 (35%) children required surgery and 24 (65%) resolved following air enema.

Pertussis

There were 78 children hospitalised with laboratory-confirmed pertussis in 2015. Nine children (12%) required admission to the intensive care unit. Of all children, approximately 42% (n=33) were under 3 months of age. A preliminary analysis of data from 2012 (when surveillance commenced) to 2015 showed that, among children aged <1 year (n=180), 37% (n=66) of cases were in infants <6 weeks of age (vaccine ineligible), 30 (16.7%) children required ICU admission, and 11 children (6.1%) required assisted ventilation. One death occurred in an infant <1 month old.[15]

Varicella and Herpes Zoster

In 2015, 40 cases of varicella-zoster virus infection were identified (27 varicella; 13 herpes zoster). Of these, vesicular fluid or vesicle scraping samples were obtained from 14 (35%); in many children sampling was difficult as vesicles had crusted over by the time the child was identified. Of the 40 children, 18 (45%) were eligible for NIP-funded varicella vaccination but only 14 had been vaccinated.

Discussion

PAEDS provides novel and unique data on hospitalisations due to selected uncommon serious childhood conditions, particularly VPDs and potential AEFI. Active case finding by specialist surveillance nurses and collection of detailed clinical and laboratory information provides comprehensive and timely data not available from other surveillance systems. The waiver of consent framework for surveillance allows vitally important information to be captured from otherwise hard-to-reach groups, such as those who are critically ill, lost to follow-up, or from a non-English speaking background (NESB), thereby obtaining more complete data from the broader population. Quality assurance processes such as ICD-10-AM audits, periodic case reviews and improved data management have enhanced both the yield and quality of the data captured.

PAEDS surveillance for AFP continues to provide the majority of cases for national surveillance, enabling Australia to meet the WHO AFP surveillance target for 2015.[3] Achieving the WHO stool collection target of 2 stool samples within 2 weeks remains challenging in the context of a modern health system where a non-polio AFP diagnosis is rapidly available[16]; however, PAEDS nurses facilitated collection of at least 1 stool sample in 64% of PAEDS AFP cases ascertained in 2015.

PAEDS encephalitis surveillance is realising its potential to support early detection of epidemic infectious diseases in children. In addition, arising out of the surveillance is the largest cohort of all-cause childhood encephalitis cases in the world that will be used to define the contemporary causes and consequences of this challenging condition. To date ACE surveillance has identified the importance of emerging infectious pathogens such as parechovirus and enterovirus 71,[17,18] defined the contribution of seasonal influenza to ACE,[19] and contributed data to support the development of clinical guidelines for encephalitis in Australia and New Zealand.[20,21]

Table 4. Table of Acronyms

ACE	Acute Childhood Encephalitis
ACIR	Australian Childhood Immunisation Register
ADEM	Acute Demyelinating Encephalomyelitis
AEFI	Adverse events following immunisation
AFP	Acute Flaccid Paralysis
APSU	Australian Paediatric Surveillance Unit
ARI	Acute Respiratory Illness
CHW	The Children's Hospital at Westmead
ED	Emergency department
FluCAN	Influenza Complications Alert Network
FS	Febrile Seizures
GBS	Guillain Barre Syndrome
GPEI	Global Polio Eradication Initiative
ICD	International Classification of Diseases
IS	Intussusception
LCCH	Lady Cilento Children's Hospital Brisbane
NCIRS	National Centre for Immunisation Research and Surveillance
NERL	National Enterovirus Reference Laboratory
NESB	Non-English Speaking Background
NHMRC	National Health and Medical Research Council
NIP	National Immunisation Program
NSW	New South Wales
PAEDS	Paediatric Active Enhanced Disease Surveillance
PMH	Princess Margaret Hospital Perth
RCH	The Royal Children's Hospital Melbourne
SANE	Serious Acute Neurological Event
VE	Vaccine Effectiveness
VIDRL	Victorian Infectious Diseases Reference Laboratory
VPD	Vaccine Preventable diseases
VZV	Varicella Zoster Virus
WCH	The Women's and Children's Hospital Adelaide
WHO	World Health Organisation

Surveillance of serious acute neurological events following influenza vaccination offers confidence in the influenza vaccines of 2015. Although case numbers were small, there was no indication of an association between influenza vaccine and the onset of serious neurologic disease. Data from multiple influenza seasons could strengthen this preliminary finding, and future studies could potentially include examination of such events temporally associated with other vaccines, such as pertussis booster vaccination.

PAEDS contributes important paediatric data to national influenza surveillance in collaboration with FluCAN.[22] PAEDS data highlights the need for improved uptake of influenza vaccination in children, particularly those who have predisposing chronic conditions.[22] The influenza season of 2015 saw an increase in cases of influenza type B disease.[23] Availability of quadrivalent vaccines under the NIP schedule from 2016[24] may help to address this burden. With influenza vaccines changing each year to provide optimal coverage against new strains, ongoing surveillance is critical to understanding disease burden and how vaccination strategies can be best targeted. A limitation of the PAEDS FluCAN surveillance was that only two sites (WA and NSW) were included in 2015. The future aim is to include all jurisdictions in paediatric influenza surveillance.

PAEDS data has been instrumental in identifying an association between IS and rotavirus vaccine when given as the first dose to children aged 1–3 months.[9] In light of this documented but low vaccine-associated risk, IS surveillance continues. Analysis of the >500 IS cases for which PAEDS holds detailed clinical data is underway to compare the clinical characteristics of vaccine proximate cases with non-vaccine proximate cases.

Pertussis continues to be one of the least well controlled VPDs in Australia.[15] Infants too young for vaccination, or those for whom vaccination is delayed, are at the highest risk of severe morbidity and mortality.[12,25] Sole reliance on cocooning strategies is no longer the primary recommendation for prevention of pertussis transmission to young infants. Since 2015, early infant protection via maternal vaccination during each pregnancy has been recommended.[25-27]

PAEDS data for 2007–2014 showed that 78% of children hospitalised with varicella or herpes zoster were unimmunised.[13] In 2015, vaccine uptake in the eligible age group was slightly increased (78% vs 64%).[1] This surveillance provides the only nationally consistent, verified source of data for severe varicella and herpes zoster, enabling ongoing evaluation of varicella vaccination under the NIP. Analysis of this data to determine varicella vaccine effectiveness is underway.

Currently, PAEDS operates in 5 tertiary paediatric hospitals based in large metropolitan centres, limiting surveillance coverage to populations served by these hospitals. Despite this, we estimate that a substantial proportion of all paediatric admissions to tertiary paediatric services are covered by PAEDS.[1] From late 2016, PAEDS, under an NHMRC partnership grant (ID1113851), expanded to include two new hospital sites, Royal Darwin Hospital in the Northern Territory and Monash Children's Hospital in Victoria. Under the grant, PAEDS activity also expanded to use captured cases to conduct detailed research into vaccine uptake, vaccine effectiveness, and knowledge and attitudes of families of children hospitalised with influenza and pertussis, with the aim of developing improved strategies to better protect young infants.

PAEDS continues to be an important capacity-building initiative to enhance existing public health surveillance for serious childhood conditions, particularly VPDs and AEFIs, with the overarching aim of improving child health outcomes. This unique surveillance platform also has the potential to be used for other urgent or research-focused studies for which active surveillance is optimal. More information on PAEDS is available at www.paeds.edu.au.

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Annual report

Australian Paediatric Surveillance Unit Annual Report, 2016

Marie Deverell, Amy Phu, Yvonne Zurynski, Elizabeth Elliott, and all chief investigators of APSU surveillance studies

Abstract

This report summarises the cases reported to the Australian Paediatric Surveillance Unit (APSU) of rare infectious diseases or rare complications of more common infectious diseases in children. During the calendar year 2016, there were approximately 1500 paediatricians reporting to the APSU and the monthly report card return rate was 90%. APSU continued to provide unique national data on the perinatal exposure to HIV, congenital rubella, congenital cytomegalovirus, neonatal and infant herpes simplex virus, and congenital and neonatal varicella. APSU contributed 10 unique cases of Acute Flaccid Paralysis (a surrogate for polio) – these data are combined with cases ascertained through other surveillance systems including the Paediatric Active Disease Surveillance (PAEDS) to meet the World Health Organisation surveillance target. There was a decline in the number of cases of juvenile onset Recurrent Respiratory Papillomatosis which is likely to be associated with the introduction of the National HPV Vaccination Program. The number of cases of severe complications of influenza was significantly less in 2016 (N=32) than in 2015 (N=84) and for the first time in the last nine years no deaths due to severe influenza were reported to the APSU. In June 2016 surveillance for microcephaly commenced to assist with the detection of potential cases of congenital Zika virus infection and during that time there were 21 confirmed cases – none had a relevant history to suspect congenital Zika virus infection, however, these cases are being followed up to determine the cause of microcephaly.

Introduction

The APSU was established in 1993 to facilitate national active surveillance of uncommon diseases of childhood including selected communicable diseases. This report includes data on the following conditions: acute flaccid paralysis (AFP) – a surrogate condition for poliovirus infection, congenital cytomegalovirus (cCMV), congenital rubella, perinatal exposure to HIV and paediatric HIV infection, neonatal and infant herpes simplex virus (HSV), congenital varicella, neonatal varicella and juvenile onset recurrent respiratory papillomatosis (JoRRP). Surveillance of severe complications of influenza was undertaken during the influenza season (July to September 2016). In addition, surveillance for Microcephaly began in June 2016 to detect potential cases of congenital Zika virus infection.

Methods

Australian Paediatric Surveillance Unit

Each month approximately 1500 paediatricians and other child health clinicians nationally are sent the APSU report card (Figure 1). The majority of clinicians (>90%) report via email, responding each month whether or not they have seen cases of any of the conditions listed on the report card (Figure 2).[1] APSU study protocols and case definitions are developed with collaborating study investigators who provide clinical expertise for each condition listed. All study protocols and case report forms are available for download on the APSU website (www.apsu.org.au).

For surveillance of AFP, the APSU collaborates with the Paediatric Active Enhanced Disease Surveillance (PAEDS) system. PAEDS is a hospital-based surveillance system reliant on active case ascertainment by specialist surveillance nurses and operates in five tertiary hospitals around Australia.[2] Data collected from the APSU is provided in this report. For data on AFP collected through PAEDS please refer to the PAEDS Annual Reports via the *Communicable Diseases Intelligence* website.[3]

Results

In 2016, the response rate to the APSU monthly report card was 90%, and completed questionnaires containing detailed clinical data were received for 81% to 100% of notifications (Table 1). The numbers of confirmed cases and the relevant reported rate estimates for 2016 as well as for the whole study period for each condition, are presented in Table 1. These estimates are accurate at the time of publication, however, should any additional cases be reported later, the estimates will be adjusted accordingly.

Figure 1: Example APSU Email Report Card

Dear xxx, *(APSU Dr code xxx)*

REMINDER: APSU REPORT CARD APRIL 2016A

NOTHING TO REPORT? PLEASE HIT REPLY AND TYPE 'NTR' IN THE SUBJECT LINE OF THIS EMAIL

DO YOU HAVE A CASE TO REPORT? HIT REPLY AND TYPE THE NUMBER OF CASES IN THE SPACE PROVIDED BELOW

If you report a case, please record patient details for later reference

NEWLY DIAGNOSED CASES ONLY - *Please report cases diagnosed within study period only*

Study case report forms are available through the hyperlinks below or via the APSU website www.apsu.org.au

 # See your protocol sheet for details regarding stool/serum specimens.

No of Cases	Study Case Report Forms (paper form for fax/email)	Web links for completion of Case Report Forms online
[ ]	EOED Case Report Form	EOED Online Questionnaire
[ ]	22q11.2 Deletion Syndrome	22q Online Questionnaire
[ ]	Chronic Fatigue Syndrome	CFS Online Questionnaire
[ ]	Fetal Alcohol Spectrum Disorders	FASD Online Questionnaire
[ ]	Childhood Interstitial Lung Disease	chILD Online Questionnaire
[ ]	MECP2 Duplication Syndrome	
[ ]	Juvenile onset Recurrent Respiratory Papillomatosis	
[ ]	Congenital varicella	Vcon Online Questionnaire
[ ]	Neonatal varicella	Vneo Online Questionnaire
[ ]	Rett syndrome	
[ ]	Congenital cytomegalovirus infection – NSW – Other States	
[ ]	Newborn and infant herpes simplex virus infection	HSV Online Questionnaire
[ ]	Acute flaccid paralysis +#	
[ ]	Paediatric HIV infection OR perinatal exposure to HIV – Mother – Child	
[ ]	Vitamin K deficiency bleeding (includes haemorrhagic disease of the newborn)	VitK/HDN Online Questionnaire
[ ]	Congenital rubella	RUB Online Questionnaire

Please ALSO report cases of acute flaccid paralysis immediately by telephone to the National Enterovirus Reference Laboratory on (03) 9342 9607 or email enterovirus@mh.org.au.

Please send all CMV and HIV Completed questionnaires directly back to the APSU.

If you have notified a previous case and are yet to complete a case report form, please forward via email SCHN-APSU@health.nsw.gov.au or fax 02 9845 3082 as soon as possible

CHANGED YOUR CONTACT DETAILS? CONTACT THE APSU ON 02 9845 3005 OR EMAIL SCHN-APSU@health.nsw.gov.au

Kind regards,

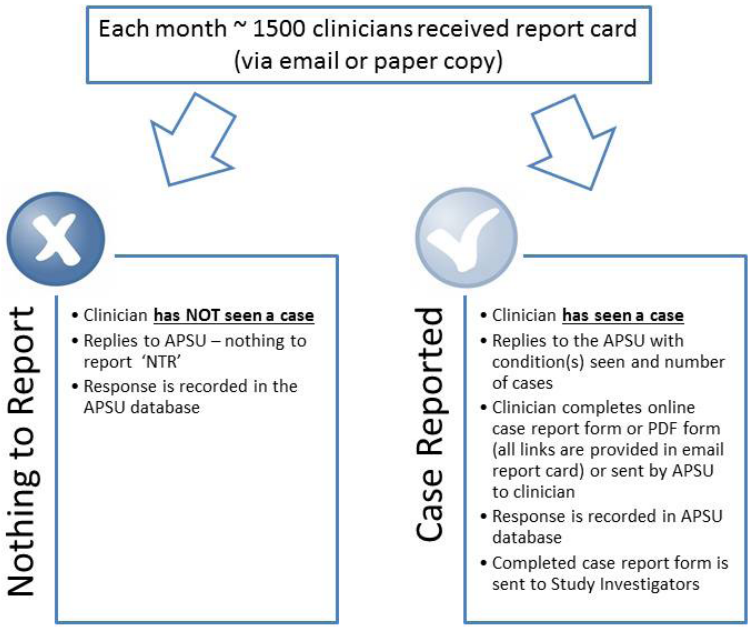
The APSU Team

Australian Paediatric Surveillance Unit (APSU)

t: (02) 9845 3005 | f: (02) 9845 3082 | e: SCHN-APSU@health.nsw.gov.au | w: www.apsu.org.au

kids research Institute the children's hospital at Westmead

Figure 2: Schematic of APSU Methodology



All reported rates are based on child population estimates published by the Australian Bureau of Statistics.[4]

Acute flaccid paralysis

Paediatricians are instructed to report all cases of AFP immediately as they are identified to the APSU and the National Polio Reference Laboratory. Data from the APSU are submitted regularly to the Polio Expert Panel (PEP). In 2016, there were 10 confirmed cases of AFP notified to the APSU. Of the 10 confirmed cases, 4 were reported from New South Wales, 4 from Victoria and 2 from Tasmania. All cases were reviewed by the PEP, and classified as non-polio AFP. The main diagnoses associated with AFP were transverse myelitis (30%) and Guillain-Barre syndrome (20%). Other diagnoses included acute disseminated encephalomyelitis, conversion disorder, encephalomyelitis, anterior horn cell disease and neuromyelitis spectrum disorder. APSU contributes to the national AFP surveillance efforts to reach the World Health Organisation surveillance target of 1/100,000 children aged <15 years per annum.[5]

Table 1: Confirmed cases identified Australian children aged < 16 years in 2016 and for the total study period, and reported rates per 100,000 of the relevant child population, by condition

Condition	Date study commenced	Questionnaires returned (%)	Number of confirmed cases 2016	Reported rate for 2016 (per 100,000)	Number of confirmed cases for total study period	Reported rate for total study period (per 100,000 per annum)
Acute flaccid paralysis	Mar 1995	100	10*	0.22§	953	0.98‖
Congenital cytomegalovirus	Jan 1999	84	13	4.26§	306	6.47§
Congenital rubella (with defects)	May 1993	100	Nil	Nil	54	0.06§
Perinatal exposure to HIV	May 1993	98	40	13.10§	704	11.25§
HIV Infection	May 1993		Nil	Nil	87	0.09‖
Neonatal - herpes simplex virus infection	Jan 1997	89	6	1.96§	186	3.56§
Infant - herpes simplex virus infection	Jan 2012		1	0.33¶	16	1.04¶
Congenital varicella	May 2006	Nil	0	Nil	2	0.07§
Neonatal varicella	May 2006	100	1	0.09§	27	0.07§
Juvenile onset recurrent respiratory papillomatosis (JoRRP)**	Oct 2011	100	1	0.02†	15	0.07†
Severe complications of influenza††	Influenza season each year since 2008	100	28	0.62†	516	1.33†
Microcephaly	June 2016	81	21	6.67¶	21	6.67¶

* Includes all cases of acute flaccid paralysis (AFP) reported via the APSU. All cases have been classified by the Polio Expert Panel (PEP) as 'non-polio AFP' according to World Health Organization criteria. The number of confirmed cases for the total study period includes both the APSU and PAEDs data.
† Based on population of children aged < 15 years.
§ Based on number of births.
‖ Based on population of children aged < 16 years.
¶ Based on population < 12 months.
** Includes both confirmed (visualisation via endoscopy and histology report) and probable cases (visualisation via endoscopy but no histology report).
†† Influenza surveillance was conducted each year since 2008 during the influenza season, July to September except in the pandemic year (2009) when surveillance occurred from June to October.

Congenital cytomegalovirus

In 2016, 13 confirmed cases were reported to the APSU, with 306 confirmed cases reported during the entire study period 1999 - 2016. Of the 13 confirmed cases, 7 were from Queensland, 2 were reported from New South Wales, 2 from Tasmania, 1 from Western Australia and 1 from the Northern Territory. All of the 13 children were born in Australia, none identified as Aboriginal or Torres Strait Islander.

Congenital rubella

There were no notifications of congenital rubella reported to the APSU during 2016. During the entire study period (1993 – 2016) there have been 59 cases of congenital rubella (54 confirmed and 5 probable) reported to the APSU. It is important to continue surveillance and vaccination as imported and locally acquired cases, especially among immigrant unvaccinated women, still occur. [6]

Perinatal exposure to HIV and HIV infection

There were 40 confirmed cases of perinatal exposure to HIV reported to the APSU in 2015, but no cases of HIV infection in children. Of the 40 confirmed cases, 21 were from Victoria, 13 were from New South Wales, 5 from Queensland and 1 from the Australian Capital Territory. No child with perinatal exposure to HIV was of Aboriginal or Torres Strait Islander descent.

The majority of mothers of these children were receiving antiretroviral therapy (n=38, 92%). Women most frequently gave birth by vaginal delivery (n=21, 51%) or by elective caesarean section (n=7, 17%) and emergency caesarean (n=4, 9%).

Neonatal and infant herpes simplex virus

Of 19 notifications, there were 7 confirmed cases of neonatal or infant HSV reported to the APSU in 2016. There were 6 neonatal cases (aged <1 month) and 1 was an infant onset case (aged between 1 month and 1 year). The 1 case of infant onset was reported from New South Wales, with HSV-1 and skin, eye, mouth (SEM) disease.

Of the 6 neonatal cases, 4 cases were reported from Queensland, 1 from New South Wales and 1 from Victoria. One had SEM disease, 1 had HSV CNS disease alone and 4 had disseminated disease (all 4 involving CNS symptoms). Five neonatal cases had HSV-1; 1 had HSV-2. There was 1 death in 2016 of a newborn infant with disseminated HSV disease.

Congenital and neonatal varicella

There was 1 notification of a case of congenital varicella reported during 2016, however, we were unable to obtain any further information about this case from the reporting clinician who was not the primary clinician caring for this child. The last case of congenital varicella reported to the APSU was in 2007. There was one case of neonatal varicella reported from Victoria. The the child required hospitalisation for 6 days and was treated with aciclovir.

Juvenile onset recurrent respiratory papillomatosis

There was 1 probable case of JoRRP reported in 2016 from Queensland; this case is currently awaiting confirmation via histopathology. During the total study period (2011 – 2016) there have been 21 notifications, with detailed clinical data available for 20 (95%) cases. Of the 20 completed case reports there were four duplicate reports and one error. Of the remaining 15 notifications there were 10 confirmed and 4 probable cases: 6 confirmed and 1 probable case in 2012; 2 confirmed and 1 probable 2013; 1 confirmed and 1 probable case in 2014; and 1 confirmed and 1 probable case in 2015. The data suggest a decline in JoRRP cases seen in Australia likely associated with the introduction of the National HPV Vaccination Program in 2007, and these results have been published in the The Journal of Infectious Diseases together with an expert editorial[7,8].

Severe complications of influenza

There was a decrease in the number of notifications of children admitted to hospital with serious complications of influenza reported to the APSU in 2016 (n=32) compared to 2015 (n=84). In 2015 the majority of cases were due to influenza B while influenza A was the most common strain detected in 2016. Of the 32 case reports, 3 were duplicates and 1 was an error. Of the 28 confirmed cases, 14 were from New South Wales, 8 from Queensland, 4 from Victoria, 1 from Western Australia and 1 from South Australia. Half of the children identified as Caucasian (54%), 1 child identified as Aboriginal or Torres Strait Islander.

The most commonly reported strain in 2016 was Influenza A (n=27), 1 child had Influenza B. Serious complications included pneumonia (n=11), seizures (n=2), laboratory proven bacterial co-infection (n=2) and encephalitis (n=2).

In 2016, 17 (61%) children required an ICU admission and no deaths were reported. Of the 28 children, 12 were previously healthy, while 16

had chronic pre-disposing conditions including asthma, chronic lung disease, neuromuscular conditions and congenital heart disease.

Only 1 of the 28 children was vaccinated for influenza within the last 12 months. Of the children with a chronic pre-disposing condition, who are recommended and eligible for a free vaccine under the National Immunisation Program, only 1 child was vaccinated. An increased awareness among parents and clinicians of the importance of influenza vaccination in this high risk group is required.

Microcephaly

Microcephaly surveillance commenced in June 2016. APSU clinicians were asked to report any child < 12 months of age with microcephaly when the occipito-frontal head circumference (OFC) is more than two standard deviations (<3rd percentile) below the mean for age and gender according to standard growth charts, with adjustment for gestational age. There were 37 notifications from June to December 2016. Of the 37 notifications there were 21 confirmed cases (57%), eight outside case definition (22%), 1 administrative error (2%) and 7 (19%) case report forms were not returned. Of the confirmed cases, 14 were from New South Wales, 3 from Victoria, 2 from Queensland, 1 from Western Australia and 1 from the Northern Territory. A third of children (29%) identified as Caucasian, one third identified as Asian (29%) and 1 child identified as Aboriginal or Torres Strait Islander.

In half of the children (n=10) were diagnosed with microcephaly was detected during the neonatal period (<30 days old), in another 10 it was detected later (>31 days old) and 1 child was diagnosed with microcephaly in-utero. In most cases (67%) the definitive cause of microcephaly was unknown and children were undergoing investigations to determine the cause. Identified causes included single gene defects (20%), congenital cytomegalovirus (5%), severe CNS trauma, ischaemic or haemorrhagic stroke (5%) and severe deprivation including malnutrition, or placental insufficiency (5%). A follow-up of confirmed cases at six months is currently being undertaken to obtain a confirmation of the cause of microcephaly where available. No children were identified as having Zika virus-associated microcephaly.

We conducted a 10-year retrospective medical record audit of microcephaly cases that presented to the Children's Hospital at Westmead. Using the ICD-10AM code for microcephaly (Q02) we identified 102 potential cases which had Q02 assigned as the primary ICD-10AM code. Of the 102 cases, 78 met case definition criteria, 22 were coded inappropriately as the OFC was not less than the 3rd percentile. Ten (12.8%) had a confirmed congenital infection – nine CMV and one had both CMV and HSV. The microcephaly was attributed to a chromosomal anomaly or a single gene defect in 24(30.7%). This current analysis is limited to the primary ICD-10 code and will be expanded to cases for which the Q02 ICD-10AM code had been assigned as one of the first three codes for each case.

Conclusions and future directions

The APSU has been facilitating active surveillance of uncommon rare childhood diseases for twenty-four years. Last year, the Department of Health requested that APSU introduce surveillance for microcephaly. This rare condition is often associated with symptoms of neurological impairment including seizures and may also be associated with developmental delay, intellectual impairment, problems with vision, hearing and feeding. Microcephaly is of current interest due to the proven relationship between maternal Zika virus infections during pregnancy and certain congenital abnormalities including microcephaly.

The APSU continues to lead the way in rare disease epidemiological research and provides valuable data on diagnosis, treatment and outcome for infectious and vaccine preventable conditions in Australian children. The APSU continues to be a vital resource to gather information on new and emerging conditions such as congenital Zika virus infection, through microcephaly surveillance. The data collected through the APSU contribute significantly to the national surveillance effort, providing valuable information for clinicians, policymakers and the community.

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