Articles

THE EPIDEMIOLOGY OF PERTUSSIS IN THE AUSTRALIAN CAPITAL TERRITORY, 1999 TO 2005—EPIDEMICS OF TESTING, DISEASE OR FALSE POSITIVES?

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Abstract

The increase in pertussis notifications since the 1990s in many countries, including Australia, has been attributed to improved diagnosis. This study aimed to describe the epidemiology of pertussis in the Australian Capital Territory from 1999 to 2005, determine whether the apparent changes could be accounted for by greater recognition and testing, and explore the impact of false positive serology results associated with faulty test kits. The Australian Capital Territory resident notification, laboratory and separation data from 1999 to 2005 were examined and the proportions of positive tests across time periods and age groups compared. Notification rates increased in the years 2000, 2003 and 2005. There was a shift in the age distribution of cases, from children and teenagers in 2000, to teenagers in 2003 and adults in 2005. Testing activity and notification activity were closely related. Comparing the epidemic periods to the preceding inter-epidemic periods, the proportion of positive tests was maintained or increased for all age groups combined and for adults and children (e.g. statistically significant increase from 7.8% to 14.0% in the 2005 epidemic in adults). During each epidemic the proportion of positive tests was statistically significantly higher in the age group with the highest notification activity. Despite similar testing rates in adults in 2003 and 2005, greater disease activity was reported in 2005. Although the numbers were small, polymerase chain reaction and culture positive test results increased in 2003 but not in 2005. The proportion of positive polymerase chain reaction results increased in 2003, providing strong evidence that the apparent epidemic of 2003 was due to a true increase in underlying disease activity. Because of the uncertainty surrounding the timing of the false positive serology results, the study provides weaker support for a true epidemic of pertussis in 2005. *Commun Dis Intell* 2007;31:383–391.

Keywords: whooping cough, *Bordetella pertussis,* epidemiology

Introduction

Since the 1990s, an increase in pertussis notifications has been reported for many countries, including Argentina, Australia, Canada, Italy, Japan, the Netherlands, Switzerland and the United States of America.[1,2] The increase has been noted particularly in adolescents and adults.[3,4,5]

Proposed reasons for increased incidence of infection include waning natural and vaccine induced immunity[6] and changes in the organism leading to a mismatch between the vaccine and circulating strains.[7] A New South Wales study concluded that the observed increase in pertussis notifications from 1988 to 2002 in adults reflected a true increase in disease.[8] Others have argued that the apparent increase may be due to increased recognition of disease that has been previously undetected.[9,10,11] This may occur through increased testing, particularly in the older age groups; the use of more sensitive tests;[12] or changes in reporting practices.

Disease due to waning immunity following natural infection in adults has certainly been documented at an individual level since the early 1900s[13] and studies of *Bordetella pertussis* infections in adolescents and adults during non-outbreak times suggest that the disease is common and endemic in this population.[14,15]

Many studies have examined trends in notification data, but few have also examined trends in the number and types of tests ordered. A study from British Columbia in Canada examined hospital separations, notifications and laboratory data during successive outbreaks during the 1990s and 2000, and demonstrated an increased incidence in 2000 in pre-teens and teens.[5]

This study examines Australian Capital Territory resident notification, laboratory and separation data from July 1999 to December 2005. There were no major changes in the notification case definition during this period. The use of serology for the diagnosis of pertussis was standard practice before the study period. Polymerase chain reaction

(PCR) became available in 2000 in the Australian Capital Territory and became widely used from 2003 onwards. Serology is thought to be more sensitive than PCR or culture[16] and studies have shown that the sensitivity of PCR compared to serology is around 60%.[11]

Pertussis is a diagnosis that is not easily made on clinical grounds alone, particularly in older children and adults. The typical whoop of whooping cough is generally not as frequent in adults,[9] in whom symptoms are indistinguishable from a viral upper respiratory tract infection in the early catarrhal phase, and a post viral cough in the later phase is common. The characteristic symptom in adults is a persistent cough, and testing for pertussis is often part of the investigation for a chronic cough. There is the potential for greater awareness of the disease among clinicians to cause an increase in the number of pertussis tests ordered.

This study aimed to describe the epidemiology of pertussis in the Australian Capital Territory from 1999 to 2005 and to determine whether the apparent changes could be accounted for by greater recognition and testing.

All three laboratories servicing the Australian Capital Territory used manufacturer A's *Bordetella pertussis* IgA enzyme-linked immunosorbent assay (ELISA) kit. In September 2006, the manufacturer, in consultation with the Therapeutic Goods Administration, issued a 'recall for product correction' for three batches of the kit which had been used in the Australian Capital Territory from mid-December 2005, because the cut-off determination point was set too low resulting in false positive results. We also aimed to explore the impact of this problem on the data.

Methods

Data sources

Notification data

Australian Capital Territory resident pertussis notifications from July 1999 to December 2005 were obtained from the Australian Capital Territory Health Protection Service. Data on cases that were notified, but excluded from the official notification data because they did not meet the surveillance case definition were also obtained. The surveillance case definitions used during the study period are specified in Table 1.

Testing data

Pertussis laboratory data on Australian Capital Territory residents was obtained for the same time period from the three major laboratories that service the region. There was a fourth laboratory that performed testing at the smaller of the two public hospitals from November 1999 to November 2002 but data from this laboratory was not available. As this hospital does not admit paediatric patients and adult pertussis rarely requires hospital admission, the pertussis testing data during this period from this laboratory is expected to only comprise a small proportion of the total tests. Recently, an additional New South Wales private laboratory has begun to service the Australian Capital Territory. A review of the 2005 notifications indicated that only one patient was tested at this laboratory, in December.

Laboratory Z provided the test details grouped by patient encounter (for example, if multiple tests were ordered on the same day for a patient, these were grouped). Laboratory Y was unable to provide culture data. The data provided by laboratory Z showed that during the study period, 1.8% (46 out of 2,506 patient encounters) of patients were tested by culture and no other method. Laboratory Z was not able to provide the results of some of its PCR tests in 2002 and 2003 – the missing results comprised 4.0% of the total PCR data in 2002 and 6.4% in 2003.

Serology was recorded as positive if IgA was detected. Laboratory X used only IgA antibodies to whole cell pertussis antigen, as did laboratory Y from September 2005 onwards. Laboratory Z and laboratory Y (prior to September 2005) used IgA and IgG to whole cell pertussis antigen. All three laboratories used manufacturer A's *B. pertussis* IgA ELISA kit.

Laboratory X sends samples to a reference laboratory for PCR testing – the method used is an in-house conventional PCR with end point fluorescence detection. Laboratory Y sends samples to another inter-state laboratory that uses an in-house real-time PCR assay performed on the Roche LightCycler instrument. Laboratory Z uses the Roche LightCycler real-time PCR.

Separation data

Australian Capital Territory resident hospital separation data for which the principal or other diagnosis was pertussis was obtained from the ACT Health Information Management Section from July 1999 to December 2005.

Analysis

Age-specific yearly and monthly notification rates were calculated using Australian Bureau of Statistics (ABS) mid-year population estimates.

Table 1. Surveillance case definitions

Time period	Probable case	Confirmed case
1997–2003[17]	A cough illness lasting 14 days or more with one or more of the following: paroxysms of coughing; inspiratory whoop or post-tussive vomiting, without other apparent case. OR A cough illness lasting 14 days or more in a patient with *B. pertussis*-specific IgA detected in serum.	*Laboratory confirmed* Isolation of *B. pertussis* from a clinical specimen. OR Positive PCR assay for *B. pertussis* undertaken in a laboratory with established expertise in the area. *Epidemiologically confirmed* A cough illness lasting 14 days or more in a patient who is epidemiologically linked to a laboratory confirmed case.
2003 onwards[18]	A probable case requires clinical evidence only: - a cough illness lasting two or more weeks; AND - paroxysms of coughing OR inspiratory whoop OR post-tussive vomiting.	A confirmed case requires: - laboratory definitive evidence; OR - laboratory suggestive evidence AND clinical evidence; OR - clinical evidence AND epidemiological evidence.* *Laboratory definitive evidence:* - isolation of *B. pertussis*; OR - detection of *B. pertussis* by nucleic acid testing. *Laboratory suggestive evidence:* - seroconversion or a significant increase in antibody level to *B. pertussis*; OR - single high IgA titre to whole cells; OR - detection of *B. pertussis* antigen by immunofluorescence assay (IFA). *Clinical evidence:* - a coughing illness lasting two or more weeks; OR - paroxysms of coughing OR inspiratory whoop OR post-tussive vomiting.

* The criteria for an epidemiologically confirmed case changed slightly to allow for a person with a cough of any duration who was epidemiologically linked to a confirmed case to be classified as a confirmed case.

An epidemic period was defined as one in which the monthly notification rate was greater than or equal to five per 100,000 for three consecutive months.

Age-specific testing rates were calculated using ABS mid-year population estimates as the denominator and an adjusted number of tests performed in each age group for the numerator (a rate based on the estimated number of people tested rather than on the total number of tests performed.) Based on the data provided by laboratory Z, the percentage of patients who received more than one test was calculated for each year of the study period. The adjusted testing rate was then calculated by reducing the total number of tests by these percentages. Less than 1% of patients received three tests in 2003, 2004 and 2005, so this was ignored. For these testing rates, the PCR tests for which the results were unavailable were still included in the number of tests.

The proportion of positive tests was calculated over time and across age groups. For these calculations, the total unadjusted number of tests was used but the PCR data for which results were unavailable were excluded. The number of positive results was used as the numerator rather than the number of notifications. Data from December 2005 were excluded due to the likelihood of false positive results.

As pertussis is a cyclical disease with epidemics occurring every 2–5 years,[10] the likelihood of detecting trends over time is influenced by the stage of the cycle. Therefore, the proportions of tests that were positive during the epidemic periods as defined above were compared to the proportions that were positive in the preceding inter-epidemic periods, and this was repeated for children and adults.

The median age of pertussis hospital separations each year was calculated.

Analysis was performed using Excel and STATA 8. Ninety-five per cent confidence intervals for the proportion of positive tests positive were calculated.

Ethics approval

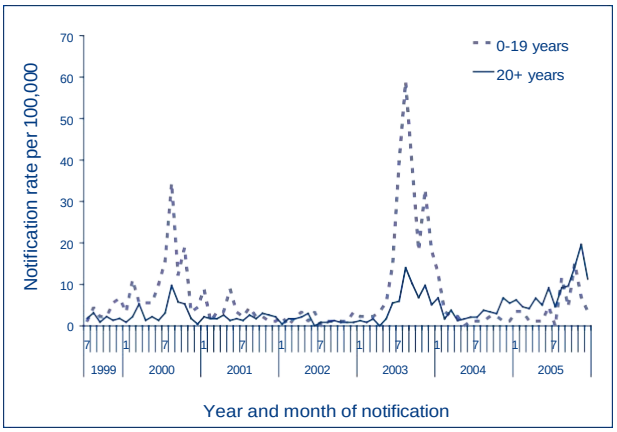
Ethics approval was obtained from the University of Newcastle Health Human Research Ethics Committee and the Australian Capital Territory Health Human Research Ethics Committee in 2005.

Results

Notifications

From July 1999 to December 2005 there were 1,180 pertussis notifications in the Australian Capital Territory. Females comprised 55.7% of the notifications. There were epidemics in 2000, 2003 and 2005. Figure 1 indicates that the peak monthly notification rate for those aged 20 years or greater was higher in 2005 than in 2000 or 2003. The annual notification rate in 2003 in this age group was 62.9 per 100,000 population and this increased to 104.6 per 100,000 population in 2005.

Figure 1. Monthly pertussis notification rate, Australian Capital Territory, July 1999 to December 2005, by age group

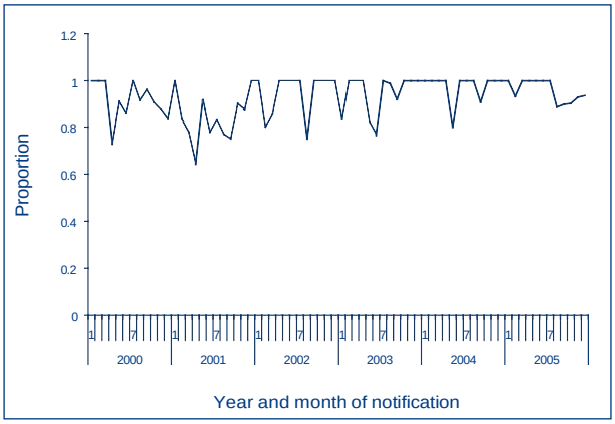


Over these time periods there were changes in the age distribution of cases. During 2000, the highest notification rates were in those aged 10–14 years (294.9 per 100,000) and 5–9 years (108.1 per 100,000). In 2003, the highest notification rates were in those aged 10–14 years (510.9 per 100,000) and 15–19 years (298.9 per 100,000). Those aged 40-49 years had a notification rate of 129.2 per 100,000 population. In 2005 the highest notification rate was in those aged 50–59 years (124.0 per 100,000) and those aged 60 years or greater (123.2 per 100,000). The proportion of cases in those aged greater than or equal to 20 years increased from 41.5% in 2003 to 83.6% in 2005.

Epidemics occurred in July–October 2000, June 2003–January 2004, and August–December 2005. Those aged 0–19 years experienced epidemics in February–October 2000, May 2003–January 2004, and August–November 2005 and those aged 20 years or greater in August–October 2000, June 2003–January 2004, and November 2004–December 2005 (although in those aged 20 years or greater the notification rate dropped to 4 per 100,000 in March 2005).

During the study period, there were very few cases notified that did not meet the surveillance case definition. Figure 2 demonstrates that there was no obvious trend in the proportion that did meet the case definition over time.

Figure 2. Proportion of all notified pertussis cases that met the surveillance case definition, Australian Capital Territory, 2000 to 2005

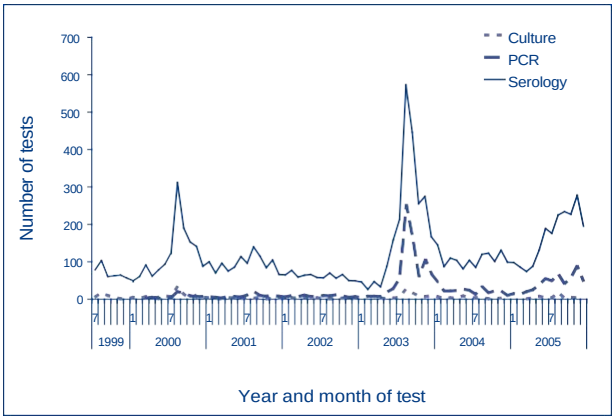


Testing data

Testing rates

During the study period, 11,600 pertussis tests were ordered on Australian Capital Territory residents (not including the missing culture data but including the PCR tests for which results were not available). Figure 3 shows that the number of tests increased during 2000, 2003 and 2005. Most of the total testing was by done by serological methods, with PCR becoming more common from 2003 onwards.

Figure 3. Pertussis tests performed, Australian Capital Territory, July 1999 to December 2005, by method



Based on examination of the data provided by laboratory Z, 1.6% of patients were tested using more than one method in 1999 and this increased over time to 9.7% in 2003 and 9.3% and 13.1% in 2004 and 2005 respectively. The combination was usually PCR and serology. However, the number of patients with at least one positive test result when tested via multiple methods was small. For example, in 2003 only 1.9% of all testing encounters involved a positive test result in a patient who was tested by multiple methods, and this only increased slightly to 2.0% in 2004 and 2.1% in 2005. Of the 196 patients who were tested via more than one method, there were only three instances (one each in 2003, 2004 and 2005) where more than one result was positive.

Figure 4 demonstrates that, excluding the serology data, there was an increase in positive tests in 2000 and 2003, but not in 2005.

Figure 4. Pertussis positive tests, PCR and culture only, Australian Capital Territory, July 1999 to December 2005

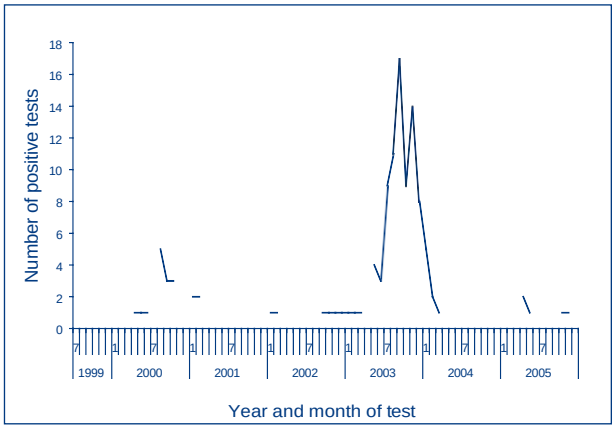


Figure 5 compares the notification and adjusted testing rates. Testing and notification activity were very closely related. Testing activity didn't appear to significantly precede or lag behind the notifications, but was sustained slightly for a period (for example, in 2001 and 2004) after the end of the epidemic.

Adjusted testing rates in adults and children are shown in Figure 6. During the 2003 epidemic the testing rate was higher in all age groups compared to preceding and following years. The testing rate was highest in those aged 10–14 years (192.2 per 10,000) and 15–19 years (157.8 per 10,000). In 2005, the adjusted testing rate in adults (72.4 per 10,000) was similar to the rate in 2003 (72.3 per 10,000). The highest rate in 2005 was in those aged less than one year (142.0 per 10,000), followed by those aged 40–49 years (81.0 per 10,000) and those aged 50–59 years (75.3 per 10,000). The adjusted

Figure 5. Pertussis monthly notification and adjusted testing rates, Australian Capital Territory, July 1999 to December 2005

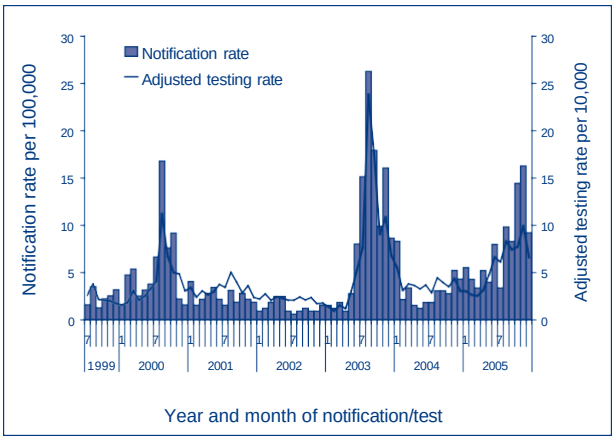
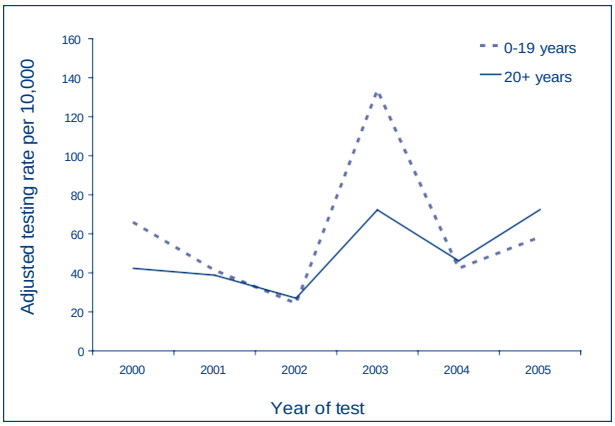


Figure 6. Adjusted yearly pertussis testing rates, Australian Capital Territory, 2000 to 2005, by age group



age specific testing rates were higher in 2003 than in 2005 for those aged 30–39 years, 40–49 years and 50–59 years. In 2005, adjusted age specific testing rates did not increase noticeably in the younger age groups except for those aged less than one year.

Proportion of positive test results

Tables 2 and 3 show the proportion of positive tests during epidemic and non-epidemic periods for those aged 0–19 years and 20 years or greater. Comparing the epidemic periods to the preceding inter-epidemic periods, the proportion stayed the same or increased overall (data not shown) and for both children and adults. The increase in the proportion of positive tests was statistically significant overall for the 2003 epidemic. In children, the increase was statistically significant in the 2003 epidemic, and in adults, was statistically significant in the 2005 epidemic. During each epidemic, the proportion of positive tests was statistically significantly higher in the affected age group, for example, 19.8% in children

Table 2. Proportion of pertussis tests positive in the Australian Capital Territory during epidemic and non-epidemic periods, age 0–19 years

Period	Proportion of tests positive	Percentage of tests positive	95% confidence interval
Jul 99–Jan 00	22/152	14.47	9.30, 21.09
Feb 00–Oct 00*	99/501	19.76	16.36, 23.52
Nov 00–Apr 03	70/751	9.32	7.34, 11.63
May 03–Jan 04*	210/1,293	16.24	14.27, 18.37
Feb 04–Jul 05	28/585	4.79	3.20, 6.84
Aug 05–Nov 05*	15/293	5.12	2.89, 8.30

* Epidemic period.

Table 3. Proportion of pertussis tests positive in the Australian Capital Territory during epidemic and non-epidemic periods, age 20+ years

Period	Proportion of tests positive	Percentage of tests positive	95% confidence interval
Jul 99–Jul 00	63/689	9.14	7.10, 11.55
Aug 00–Oct 00*	47/452	10.40	7.74, 13.59
Nov 00–May 03	134/1,914	7.00	5.90, 8.24
Jun 03–Jan 04*	157/1,789	8.78	7.51, 10.18
Feb 04–Oct 04	68/868	7.83	6.13, 9.83
Nov 04–Nov 05*	278/1,993	13.95	12.46, 15.55

* Epidemic period.

in 2000 versus 10.4% in adults, 16.2% in children in 2003 versus 8.8% in adults and 14.0% in adults in 2005 compared to 5.1% in children. Comparing the 2003 and 2005 epidemics in adults, the proportion of positive tests was statistically significantly higher in 2005 (14.0% versus 8.8%).

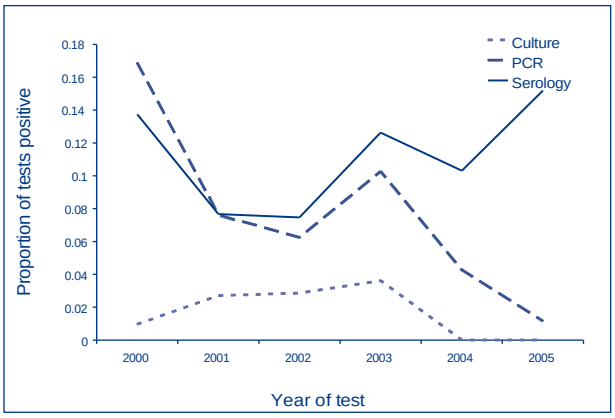
Figure 7 shows the proportion of positive test results by method for each year from 2000 to 2005. The proportion of positive test results via PCR was high in 2000 and 2003, and fell to its lowest level in 2005. The proportion of positive serology results was high in 2000 and 2003, and reached its highest level in 2005. The proportion of positive culture results was fairly steady but fell to its lowest level in 2005.

Children comprised 63.6% of the PCR tests in 1999 and this decreased to 39.0%–52.8% between 2000 and 2005. Overall in this population, serology was more likely to yield a positive test result than PCR or culture.

Hospital separation data

Table 4 summarises the hospital admissions (based on hospital discharge data) for which the primary or secondary diagnosis was pertussis during the study period. During the entire study period, 26% of admissions were in those aged 20 years or greater, and in 2005, this age group accounted for 50% of the admissions.

Figure 7. Proportion of pertussis tests positive, Australian Capital Territory, by test and year, 2000 to 2005



Discussion

Interpretation is complicated by false positive serological results. The product recall in September 2006 was for three batches of manufacturer A's pertussis IgA serology kit, which had been used in the Australian Capital Territory since mid-December 2005. If this was the earliest time at which the faulty kits were used in the Australian Capital Territory, this study does provide evidence that the increases in notifications during the study period were asso-

Table 4. Pertussis hospitalisations in the Australian Capital Territory (ACT residents) from July 1999 to December 2005

Year	Admissions: age less than 1 year	Admissions: age greater than or equal to 1 year (age of cases in years)	Median age of admission	Total
1999	4	1, (73)	0	5
2000	5	6, (2, 6, 10, 38, 46, 75)	2	11
2001	3	3, (29, 30, 64)	15	6
2002	2	1, (58)	0	3
2003	4	4, (1, 12, 17, 28)	1	8
2004	7	0	0	7
2005	2	4, (4, 21, 30, 57)	13	6

ciated with a true increase in underlying disease incidence and not merely the result of increased awareness and testing, for the following reasons:

- Comparing the epidemic periods to the preceding inter-epidemic periods, the proportion of positive tests increased, or at least stayed constant, overall, and in both children and adults.
- The proportion of positive tests during the epidemics was statistically significantly higher in the affected age group.
- The upsurges in notifications were not preceded by increases in testing activity.
- In adults although there was a similar amount of testing in 2005 compared to 2003, the notification rate was considerably higher in 2005 and the proportion of positive tests was statistically significantly higher in the 2005 epidemic, suggesting that the disease that was detected in 2005 was not present in 2003.
- Although the number of hospital separations is small, there was an increase in the proportion of adult separations in 2005.

However, manufacturer A was not able to accurately determine when the false positive issue first arose. If it was at some point earlier in the study period, the apparent changes in disease activity could be the result of a test artifact.

Excluding the serology data, there was an increase in positive tests in 2000 and 2003, but not 2005. The use of PCR in adults increased during the study period. The proportion of positive test results via PCR was highest in 2000 and 2003 and declined to its lowest level in 2005. The proportion of positive culture results was also the lowest in 2005. In contrast, the proportion of positive serology results reached a peak in 2005. These results suggest that the false positive issue arose in 2005 and may have been responsible for the apparent increase in disease in adults during that period. However, conclusions are limited by the small number of positive PCR and culture results. Furthermore, as adults may present and therefore be tested later in the course of their illness than children, resulting in a lower chance of a positive result with these tests, and the sensitivity of PCR has shown to decrease with increasing age,[19] an increase in positive PCRs and cultures may not be expected during an epidemic that predominantly affects adults.

Increases in notifications during the study period are not explained by the greater use of multiple tests on patients. The use of multiple tests on patients did increase during the study period, however, instances of patients having a positive result when tested via more than one method were few.

A study from the Australian Capital Territory showed that information alerts issued by ACT Health in 2003 in response to the increased notifications at the time, were associated with an increase in the proportion of cases notified within the infectious period of 21 days.[20] Potentially, such information alerts could have led to testing of patients with a clinical spectrum that did not previously lead to pertussis testing. For example, testing people whose cough was not protracted at presentation (and therefore may have been due to a variety of causes). However, apart from being slightly elevated following the end of the 2003 epidemic, the testing and notification activity were very closely related, suggesting that the testing that was occurring was discriminate and in response to underlying disease activity.

There were very few notified cases that did not meet the surveillance case definition for pertussis and no obvious trend in the proportion of notified cases that did over time. Even if the false positive issue did arise at some point during the study period, it would appear that the majority of cases detected via the faulty kits did have an illness similar to pertussis. A recent evaluation has showed that the majority of the false positive results were due to non-specific cross-reactions with the filamentous haemagglutinin (FHA) as demonstrated by Western

blot.[21] Cross reactions with the FHA antigen are known to occur in respiratory illnesses such as influenza and *Mycoplasma pneumoniae*.

A study from British Columbia in Canada examined notifications, hospital separations, and laboratory data during successive outbreaks in the 1990s and 2000, and concluded that the incidence of pertussis increased in 2000 in pre-teens and teens and decreased in infants and younger children.[5] The proportion of positive cultures was maintained among pre-teens and teens during the 2000 outbreak compared to earlier outbreaks, despite the rate dropping among young children. In addition, the greatest proportion of positive tests was in the older age group. Our study demonstrates a similar increase in the proportion of positive PCR results during an epidemic year (2003) compared to earlier years.

A New South Wales study also concluded that the observed increase in pertussis notifications from 1988 to 2002 in adults reflected a real increase in disease.[8] There was a significant increase in both pertussis notification and hospitalisation rates among those aged 15 years or more, whereas in other age groups, there was an increase in notification rates only. Although the number of separations in our study is small, and hospitalisations attributable to pertussis may also be over-estimated by false positive serology results, the increase in the proportion of adult separations in 2005 is also suggestive of a true increase in disease activity in this age group.

To our knowledge, this study is the first published analysis of population based pertussis testing data in Australia, and one of only a few in the international literature. This study used testing data from all of the major laboratories that serviced the Australian Capital Territory during the study period, with testing data from only one minor laboratory missing. Although there was some missing culture data (both results and the test request), the quantity of this was estimated to be insignificant. Although some PCR results were missing, the test requests were available for the calculation of testing rates. These PCR tests were not included in the analysis of the proportion of positive test results. Although only one laboratory was able to provide data grouped by patient, these data were used to adjust the testing rates for the combined data to account for the increased use of multiple tests during the study period.

This study highlights the current difficulties in diagnosing pertussis. Diagnosis in Australia is usually based on a single positive serological test for IgA antibody against whole cell *B. pertussis* antigen. Based on comparison with a clinical case definition, this method was previously shown to be highly specific and thought to be more likely to under-estimate rather than over-estimate the true incidence of disease.[22] However, a recent evaluation, prompted by the product recall, has demonstrated that even the new version of manufacturer A's kit has a specificity of only 86.7% compared to a test panel of sera using complement fixation, immunofluorescence and Western blot. In addition, the sensitivity and specificity of all the currently available serology kits were shown to be variable.[23] Our experience demonstrates the importance of continuous review of laboratory testing methods and close laboratory liaison regarding apparent changes in surveillance data.

Were the apparent epidemics of pertussis in the Australian Capital Territory in 2000, 2003 and 2005 the result of real disease activity, increased and less discriminate testing or an artifact of false positive serology results? As conclusions are limited by the uncertainty surrounding when the false positive serology problem began, the combination of an increase in adult notifications, separations and proportion of positive tests in 2005, is only weak evidence of an increase in underlying disease activity. However, the increase in the proportion of positive PCR results during 2003 is strong evidence that this apparent epidemic was due to a real increase in disease rather than increased testing, and provides support for the current policy in Australia of providing a booster dose of the pertussis vaccine to adolescents.

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