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The contribution of PCR testing to influenza and pertussis notifications in Australia

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SUMMARY

Influenza and pertussis are the two most common vaccine-preventable infections notified in Australia. We assessed the role of polymerase chain reaction (PCR) diagnosis in influenza and pertussis cases notified to the Australian National Notifiable Diseases Surveillance System (NNDSS). There were a total of 2 10 786 notified influenza cases (2001–2013) and 2 55 866 notified pertussis cases (1991–2013). After 1 January 2007, the majority of influenza and pertussis notifications were PCR-based (80·5% and 59·6%, respectively). Before 31 December 2006, PCR-based notifications were limited (29·1% and 11·7%, respectively). By 2013, PCR-based notifications had largely replaced all other diagnostic methods, with the exception of serology-based notifications in pertussis cases in adults aged $\geqslant$25 years.

Key words: influenza, PCR, pertussis, serology.

INTRODUCTION

Influenza and pertussis are the two most common vaccine-preventable infections notified in Australia [1]. The clinical illness for both influenza and pertussis infections range from mild to severe, and asymptomatic cases can occur across all age groups, and may not be uncommon [2, 3].

Both influenza and pertussis are nationally notifiable in Australia according to State and Territory legislation. For notification, cases must meet the case definitions which require laboratory evidence of infection, with acceptable testing methods including polymerase chain reaction (PCR), culture, antigen detection, and serology [4, 5].

Compared to culture and serology, PCR testing is more sensitive and has a faster turn-around time for results [6]. In Australia, the availability of PCR for diagnosis of influenza and pertussis has increased over the last decade. Public funding for laboratories to test specimens using PCR commenced under the Australian Government-funded Medicare Benefits Schedule in 2005 [7]. Additionally, public funding was provided for laboratories to purchase equipment, primarily for PCR, during the 2009 H1N1 influenza pandemic [8].

Since 2007, increased influenza and pertussis incidence has been associated with a pertussis epidemic (2009–2012) caused in part by waning immunity, and an influenza pandemic (2009) caused by the circulation of a novel virus strain [1, 9]. The role of

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improved availability of PCR testing has been hypothesized to have led to improved case ascertainment and improved detection of disease activity [1, 10].

With this study, we describe patterns of notified pertussis and influenza cases in Australia, and explore the role of newer laboratory diagnostic methods in any changes.

METHODS

All available pertussis and influenza notifications were obtained from the National Notifiable Diseases Surveillance System (NNDSS). Both are notifiable conditions under Public Health legislation in each State and Territory in Australia, and all cases that meet the case definition are required to be notified to the State and Territory Health Departments [5]. The Australian Government Department of Health aggregates state notification data in the NNDSS.

Influenza has been nationally notifiable since 2001 and a confirmed case of influenza requires a laboratory diagnosis. Definitive laboratory evidence for notification consists of isolation of influenza virus by culture, detection of influenza virus by nucleic acid testing, or laboratory detection of influenza virus antigen. Alternatively, serology for notification requires IgG seroconversion, a significant increase in antibody level or a $\geqslant$fourfold rise in titre to influenza virus, or a single high titre by complement fixation testing or haemagglutination inhibition assay to influenza virus [5].

Pertussis was made nationally notifiable in 1991, and a case meets the definition if there is either laboratory definitive evidence or a combination of laboratory suggestive evidence with clinical evidence. Laboratory definitive evidence includes isolation of *Bordetella pertussis* by culture, detection of *B. pertussis* by nucleic acid testing, or seroconversion in paired sera for *B. pertussis* using whole cell or specific *B. pertussis* antigen(s) in absence of recent pertussis vaccination. Laboratory suggestive evidence required for notification, in absence of recent vaccination, includes a significant change (increase or decrease) in antibody level (IgG, IgA) to *B. pertussis* whole cell or *B. pertussis* specific antigen(s), or a single high IgG and/or IgA titre to pertussis toxin, or a single high IgA titre to whole cell *B. pertussis* antigen. Clinical evidence requires coughing illness lasting $\geqslant$2 weeks or paroxysms of coughing, inspiratory whoop or post-tussive vomiting [4].

Line listed data were provided for each notification, rather than each individual case, as cases could be notified in duplicate following different diagnostic tests. Duplicate notifications, where a case was diagnosed using more than one diagnostic method and therefore notified more than once, were combined into a single record. Notifications with laboratory testing methods of histopathology, microscopy, 'other' or 'unknown' were excluded, as the former two no longer meet the case definition and it is uncertain whether the latter two meet the case definition. During analysis, data were aggregated by diagnostic method, year and age groups (<1, 1 to <5, 5 to <10, 10 to <15, 15 to <25, $\geqslant$25 years). Annual age-group specific incidence rates per 1 00 000 population were calculated using Australian Bureau of Statistics population estimates [11]. For simplicity, duplicate notifications were grouped into 'Multiple methods (PCR)' if PCR was one of the diagnostic methods used, or 'Multiple methods (other)' if any combination of tests not including PCR were used. Data were also aggregated into the pre-PCR era ($\leqslant$31 December 2006) and PCR era ($\geqslant$1 January 2007). Although funding became available in late 2005 for PCR testing [7], the PCR era was defined as beginning 1 January 2007 as it took time for laboratories to purchase equipment and liaise with clinicians to change sample collection protocols. Total PCR-based notifications (PCR-only notifications combined with duplicate notifications where PCR was one of the methods used) were compared with all other single and duplicate non-PCR notifications ('All non-PCR methods').

Ethics approvals for this study were obtained from the ACT Health Human Research Ethics Committee and The University of Queensland School of Population Health Research Ethics Committee.

RESULTS

A total of 2 10 786 influenza cases and 2 55 866 pertussis cases were notified over the study period (influenza: 1 January 2001 to 31 December 2013; pertussis: 1 January 1991 to 31 December 2013). Of these, 12 666 (6·0%) influenza and 64 438 (25·2%) pertussis notifications were excluded, predominantly because they had an 'unknown' diagnosis method (85·5% and 99·4%, respectively (Table 1). Excluded notifications were approximately equally distributed across all age groups but primarily occurred in the pre-PCR era rather than the PCR era (influenza: 18·8% *vs.* 4·8%; pertussis: 48·2% *vs.* 25·2%,

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Table 1. *Influenza and pertussis notifications, by diagnostic method and time period, to 31 December 2013, Australia*

	Influenza (from 1 January 2001), *n* (%)			Pertussis (from 1 January 1991), *n* (%)		
	⩽31 December 2006	⩾1 January 2007	Total	⩽31 December 2006	⩾1 January 2007	Total
Total single diagnostic method used	13 219 (88·5)	1 70 589 (93·1)	1 83 808 (92·8)	49 175 (98·3)	1 38 515 (98·0)	1 87 690 (98·0)
PCR only	3442 (23·0)	1 35 620 (74·0)	1 39 062 (70·2)	5052 (10·1)	81 404 (57·6)	86 456 (45·2)
Culture only	2061 (13·8)	5527 (3·0)	7588 (3·8)	1309 (2·6)	283 (0·2)	1592 (0·8)
Serology only	5395 (36·1)	22 495 (12·3)	27 890 (14·1)	41 537 (83·0)	56 466 (39·9)	98 003 (51·2)
Antigen detection only	2321 (15·5)	6947 (3·8)	9268 (4·7)	1277 (2·6)	362 (0·3)	1639 (0·9)
Total multiple diagnostic methods used	1715 (11·5)	12 597 (6·9)	14 312 (7·2)	841 (1·7)	2897 (2·0)	3738 (2·0)
Multiple methods: PCR*	907 (6·1)	11 897 (6·5)	12 804 (6·5)	787 (1·6)	2818 (2·0)	3605 (1·9)
Multiple methods: Other†	808 (5·4)	700 (0·4)	1508 (0·8)	54 (0·1)	79 (0·1)	133 (0·1)
Total included notifications	**14 934 (100·0)**	**1 83 186 (100·0)**	**1 98 120 (100)**	**50 016 (100·0)**	**1 41 412 (100·0)**	**1 91 428 (100)**
Total PCR-based notifications‡	4349 (29·1)	1 47 517 (80·5)	1 51 866 (76·7)	5839 (11·7)	84 222 (59·6)	90 061 (47·0)
Excluded§	3462	9204	12 666	46 564	17 874	64 438

* Includes all notifications where polymerase chain reaction (PCR) was used in combination with culture, serology and/or antigen detection.
† Includes any combination of culture, serology and/or antigen detection-based notifications, without PCR testing.
‡ Includes all 'PCR only' and 'Multiple methods: PCR' notifications.
§ Excluded notifications include those with a laboratory method of histopathology, microscopy, 'other' or 'unknown'.

respectively). The majority of influenza and pertussis cases were notified following a single diagnostic test (92·8% and 98·0%, respectively). From 2007 (the 'PCR era'), the majority of influenza and pertussis notifications were PCR-based (80·5% and 59·6%, respectively), with serology largely responsible for the remainder of notifications (12·3% and 39·9%, respectively).

There was variation in the median age of notifications, with individuals whose notification was based on PCR methods consistently younger than individuals whose notification was based on non-PCR methods (Table 2). The age difference between individuals with PCR and non-PCR-based notifications increased in the PCR era for both influenza and pertussis cases. The incidence rate of influenza and pertussis notifications (per 100 000 age group-specific population) increased in all age groups (Figs 1 and 2).

Between the pre-PCR era and PCR era there was a 3·1-fold increase [95% confidence interval (CI) 3·0–3·1] in the proportion of influenza PCR-based notifications and an 8·7-fold increase (95% CI 8·5–9·0) in the proportion of pertussis PCR-based notifications (Table 3). The proportion of all non-PCR-based notifications decreased 0·4-fold for influenza notifications and 0·5-fold for pertussis notifications. The highest increases in the proportion of PCR-based notifications were in children aged 1 to <5 years (influenza) and 5 to <10 years (pertussis).

Diagnostic methods varied by age group over the study period (Figs 3 and 4). From 2001, there was a gradual increase in the proportion of PCR-based notifications in all age groups; however, from 2007 a marked increase was observed in all age groups for influenza and younger age groups (<15 years) for pertussis. Although the proportion of PCR-based pertussis notifications also increased in individuals aged ⩾15 years, a large proportion of notifications in the 15 to <25 and ⩾25 years age groups remained serology-based in the PCR era. The proportion of culture, serology and antigen detection-based notifications in influenza cases and younger pertussis cases declined over the study period.

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Table 2. *Median and mean age of influenza and pertussis notifications, by diagnostic method and time period, to 31 December 2013*, Australia*

	⩽31 December 2006		⩾1 January 2007		Total	
Age, years	PCR†	All non-PCR methods‡	PCR†	All non-PCR methods‡	PCR†	All non-PCR methods‡
Influenza median (mean)	18 (25·4)	19 (27·6)	25 (28·8)	34 (35·7)	24 (27·8)	31 (33·8)
Pertussis median (mean)	13 (19·9)	28 (30·5)	10 (19·1)	46 (44·7)	10 (19·1)	38 (36·9)

PCR, Polymerase chain reaction.

* Influenza reporting period: 1 January 2001 to 31 December 2013; pertussis reporting period: 1 January 1991 to 31 December 2013.

† 'PCR' includes all notifications where PCR was used as diagnostic method (irrespective of whether the sole method or in combination with other methods).

‡ 'All non-PCR methods' includes all culture, serology and/or antigen detection-based notifications, including any combination of these diagnostic methods, without PCR testing.

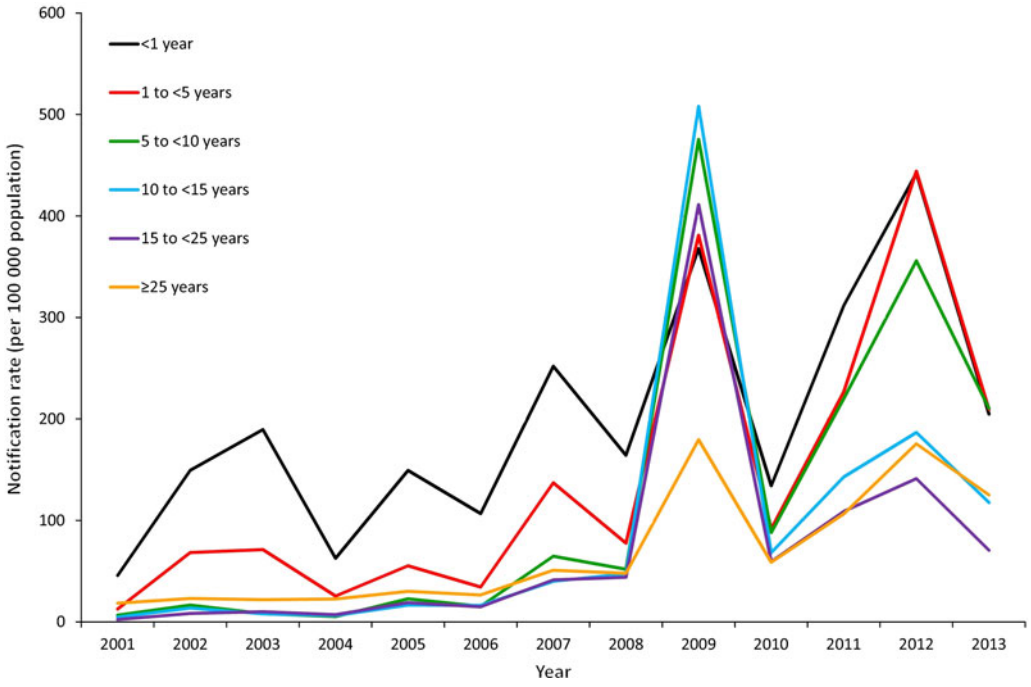

Fig. 1. Annual influenza notification rate per 1 00 000 age-specific population, 1 January 2001 to 31 December 2013, Australia.

DISCUSSION

PCR-based influenza and pertussis notifications have increased substantially in Australia over the study period. In the PCR era (⩾2007), the proportion of notifications that were PCR-based for influenza and pertussis was 3·1- and 8·7-fold higher, respectively, compared to the pre-PCR era. The largest increase in the proportion of PCR-based notifications was in children aged 5 to <10 years. By 2013, the majority of notifications were PCR-based and PCR had largely replaced all other diagnostic methods, other than in pertussis cases aged ⩾25 years, which remain predominantly serology-based (68·5% in 2013).

PCR has provided an opportunity to increase testing due to its advantages over previously available diagnostic methods. In Australia in the pre-PCR era, culture, antigen detection, and serology were the primary methods for diagnosing influenza and pertussis. Serology is generally rejected for younger age groups who are more likely to present during acute illness,

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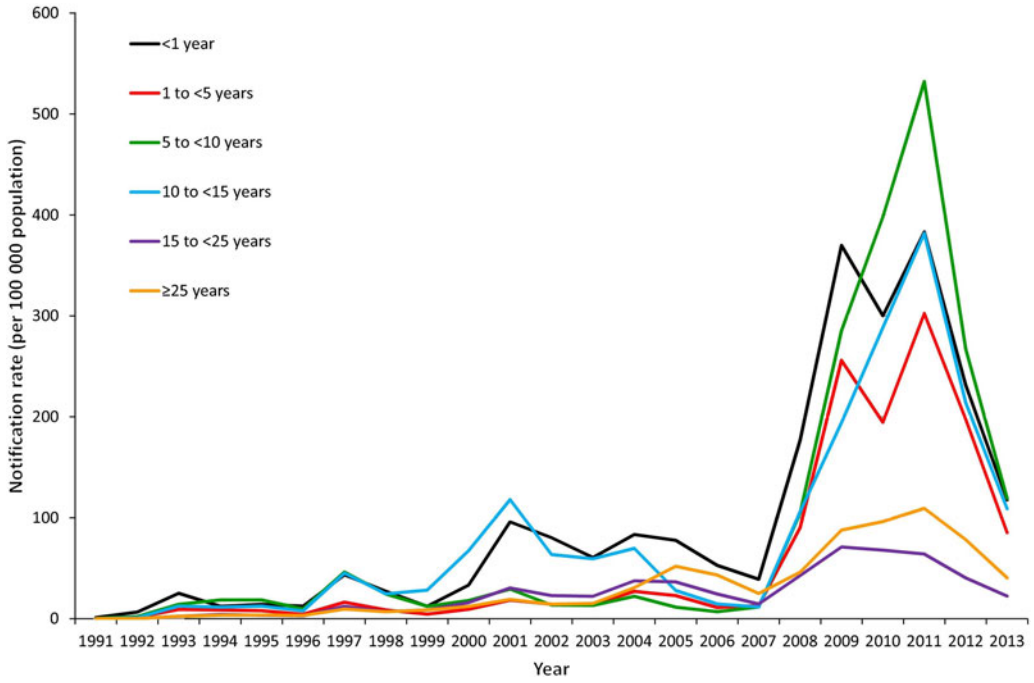

Fig. 2. Annual pertussis notification rate per 1 00 000 age-specific population, 1 January 2001 to 31 December 2013, Australia.

and has primarily been (and continues to be) used in older age groups for retrospective diagnosis, especially for pertussis [12, 13]. Culture and antigen detection can be used during acute illness; however, both of these methods have limitations. Culture (particularly for pertussis) requires high-quality specimens, is time consuming, difficult, costly, and has been increasingly rarely offered over time [12–14]. Antigen detection is generally not available for pertussis, while for influenza, it has lower sensitivity than culture or PCR, is not routinely used in Australia, and can be expensive [14]. By contrast, PCR provides highly sensitive and specific, rapid, inexpensive diagnostic testing, with fewer specimen collection, quality or transport requirements [12, 14]. It is therefore not surprising that the use of PCR has increased markedly over time, or that it has replaced other diagnostic methods.

The expansion of PCR-based testing and the impact on notifications seen in our study may, at least in part, explain changes in the observed epidemiology of pertussis and influenza that occurred over the study period. In the pre-PCR era, both pertussis and influenza had different age distributions, with incidence rates highest in very young children [15]. During the PCR era, a growing proportion of notifications have occurred in older children [1]. Our results highlight that PCR has provided the opportunity to test and notify cases in age groups (particularly 5 to <10 years) that have previously had low notification rates. Increasing incidence of influenza and pertussis notifications may also be partially attributed to changes in diagnostics, with PCR providing the opportunity to test more broadly. Previous Australian studies have observed an increase in the total number of pertussis and influenza diagnostic tests performed since 2007, and a sevenfold rise in the likelihood of having a pertussis diagnostic test ordered in the primary-care setting between 2000–2004 and 2010–2011 [10, 16].

However, expanding availability and use of PCR did not occur in isolation, and there are other factors that are likely to have contributed to increased PCR-based notifications. In recent years, Australia has experienced a pertussis epidemic (2009–2012) and influenza pandemic (2009) [1]. The pertussis epidemic has in part been attributed to waning immunity in older children who received complete courses of acellular vaccine, while the impact of the influenza pandemic was due to a novel strain to which children and younger adults were more susceptible [1, 9]. While the pathogen–host interactions were responsible for changes in incidence and demographics, we argue that without the increased availability of PCR, it would have been more difficult to detect these changes. Additionally, there was substantial media

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Table 3. *Influenza and pertussis notifications, by age group, diagnostic method and time period, to 31 December 2013, Australia*

Age group, years	⩽31 December 2006		⩾1 January 2007		Total	Fold difference in number of PCR tests*†	Relative difference in % PCR*† (95% CI)	Relative difference in % all non-PCR methods*‡ (95% CI)	Absolute difference in % PCR*‡ (95% CI)
	PCR†	All non-PCR methods‡	PCR†	All non-PCR methods‡					
Influenza (from 1 January 2001)									
<1	507 (22·5%)	1742 (77·5%)	4500 (76·2%)	1408 (23·8%)	8157	8·9	3·4 (3·1–3·6)	0·3 (0·3–0·3)	53·6 (51·2–55·7)
1 to <5	849 (23·5%)	2765 (76·5%)	15 664 (82·6%)	3309 (17·4%)	22 587	18·4	3·5 (3·3–3·7)	0·2 (0·2–0·2)	59·1% (57·6–60·5)
5 to <10	355 (27·1%)	956 (72·9%)	18 176 (86·1%)	2932 (13·9%)	22 419	51·2	3·2 (2·9–3·5)	0·2 (0·2–0·2)	59·0 (56·6–61·5)
10 to <15	293 (27·3%)	779 (72·7%)	13 275 (82·9%)	2746 (17·1%)	17 093	45·3	3·0 (2·7–3·3)	0·2 (0·2–0·2)	55·5 (52·8–58·2)
15 to <25	534 (27·1%)	1439 (72·9%)	21 822 (77·4%)	6358 (22·6%)	30 153	40·9	2·9 (2·7–3·1)	0·3 (0·3–0·3)	50·4 (48·3–52·4)
⩾252	1824 (22·3%)	6354 (77·7%)	74 187 (65·7%)	38 638 (34·3%)	1 21 003	40·7	2·9 (2·8–3·1)	0·4 (0·4–0·4)	43·4 (42·5–45·0)
Total	**4362 (23·7%)**	**14 035 (76·3%)**	**1 47 624 (72·7%)**	**55 391 (27·3%)**	**2 21 412**	**33·8**	**3·1 (3·0–3·1)**	**0·4 (0·3–0·4)**	**49·0 (48·4–49·6)**
Pertussis (from 1 January 1991)									
<1	956 (24·7%)	2913 (75·3%)	4675 (93·6%)	320 (6·4%)	8864	4·9	3·8 (3·6–4·0)	0·1 (0·1–0·1)	68·9 (67·4–70·4)
1 to <5	693 (13·2%)	4554 (86·8%)	12 520 (88·8%)	1583 (11·2%)	19 350	18·1	6·7 (6·3–7·2)	0·1 (0·1–0·1)	75·6 (74·5–76·6)
5 to <10	503 (4·9%)	9799 (95·1%)	21 962 (87·7%)	3067 (12·3%)	35 331	43·7	18·0 (16·5–19·6)	0·1 (0·1–0·1)	82·9 (82·3–83·4)
10 to <15	1066 (6·8%)	14 583 (93·2%)	14 945 (77·1%)	4435 (22·9%)	35 029	14·0	11·3 (10·7–12·0)	0·2 (0·2–0·2)	70·3 (69·6–71·0)
15 to <25	734 (6·5%)	10 643 (93·5%)	5452 (49·0%)	5665 (51·0%)	22 494	7·4	7·6 (7·1–8·2)	0·5 (0·5–0·5)	42·6 (41·6–43·6)
⩾25	1889 (3·8%)	48 247 (96·2%)	24 674 (29·1%)	59 988 (70·9%)	1 34 798	13·1	7·7 (7·3–8·1)	0·7 (0·7–0·7)	25·4 (25·0–25·7)
Total	**5841 (6·1%)**	**90 739 (93·9%)**	**84 228 (52·9%)**	**75 058 (47·1%)**	**2 55 866**	**14·4**	**8·7 (8·5–9·0)**	**0·5 (0·5–0·5)**	**46·8 (46·5–47·1)**

PCR, Polymerase chain reaction; CI, confidence interval.

* Comparison between ⩽31 December 2006 and ⩾1 January 2007

† 'PCR' includes all notifications where PCR was used as diagnostic method (irrespective of whether the sole method or one of a combination).

‡ 'All non-PCR methods' includes all culture, serology and/or antigen detection-based notifications, including and combination of these diagnostic methods, without PCR tests.

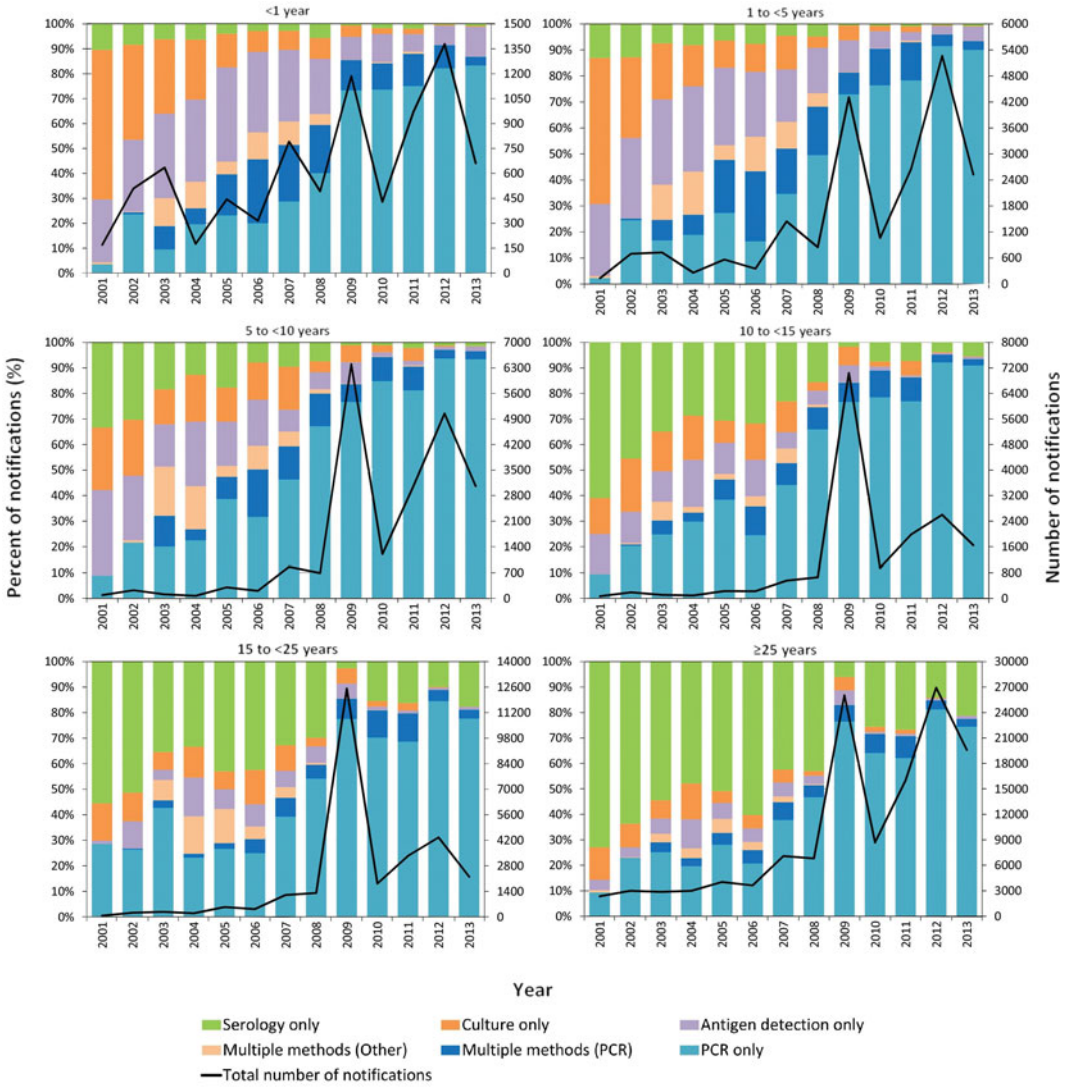

Fig. 3. Notifications of influenza by diagnostic method and year, 1 January 2001 to 31 December 2013, Australia, with percent of notifications on the left axis and total number of notifications on the right axis.

attention about pertussis and influenza during peak periods of activity and following deaths in young infants. Improved awareness, whether following media attention or training, has been found to increase diagnostic testing, through changed patient and clinician behaviour [17–20]. Moreover, the combination of improved PCR availability, better awareness and increased circulation of pathogens is likely to have created a positive feedback loop, ultimately leading to more testing over time.

Overall, increasing PCR use has probably improved case detection for notifiable infections such as influenza and pertussis. The purpose of infectious disease surveillance is to monitor trends, detect outbreaks, and both guide and evaluate public health responses. While at a national level the NNDSS functions very well to achieve these goals, as a passive surveillance system it is prone to case under-ascertainment and has lower sensitivity than an active surveillance system. Over our study period, the changes in the use of PCR, along with increased awareness of the illnesses, would have improved NNDSS case ascertainment, sensitivity, and representativeness. There would also have been a reduction in ascertainment bias, as PCR allows more widespread testing (and therefore notification) of cases across the population. Although it is unlikely that PCR use will decline in the near future, we hypothesize that the increase in testing will eventually plateau and set a new higher background

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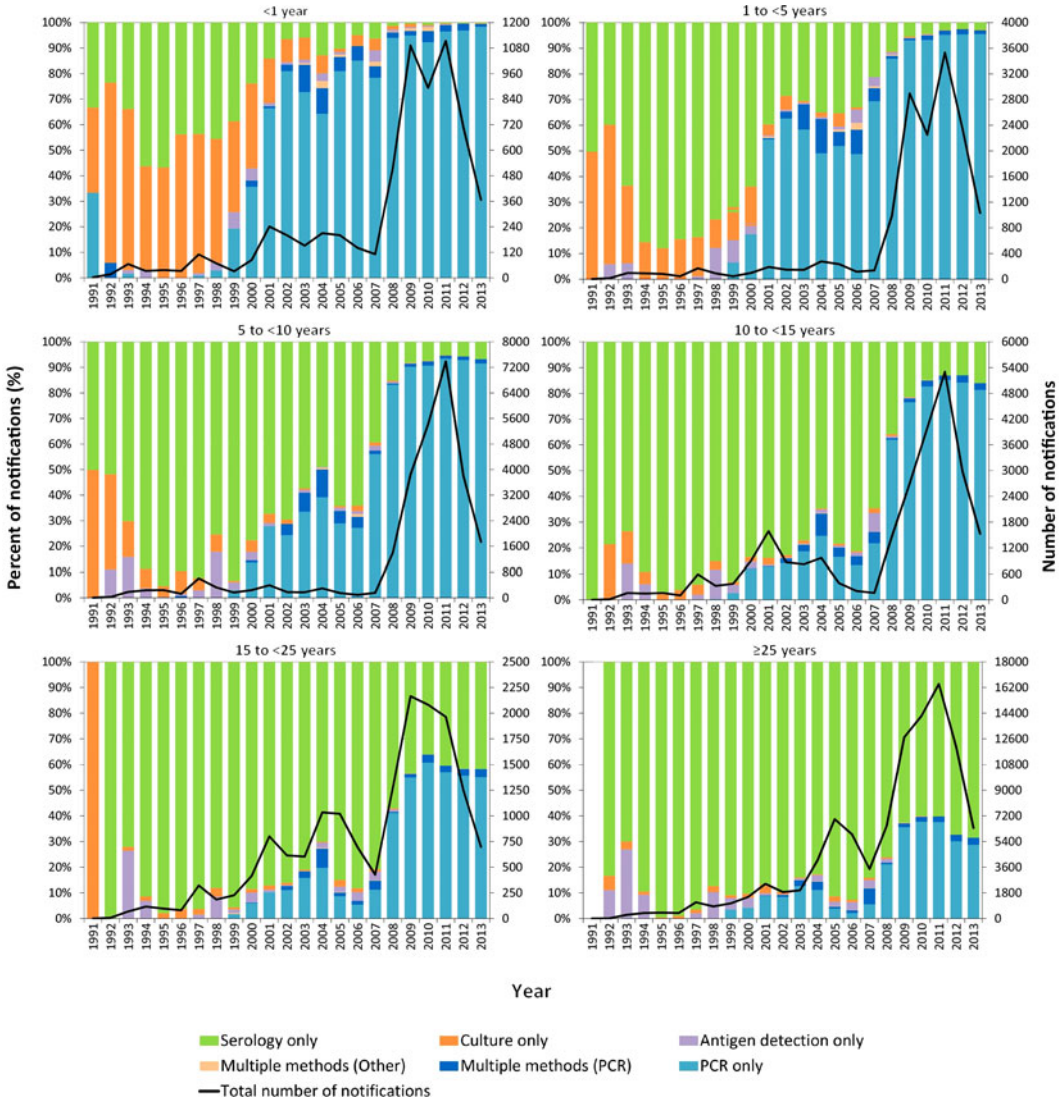

Fig. 4. Notifications of pertussis by diagnostic method and year, 1 January 2001 to 31 December 2013, Australia, with percent of notifications on the left axis and total number of notifications on the right axis.

incidence for pertussis and influenza. At this time it will be easier to identify true increases in incidence without the influence of changes in testing and awareness.

We have demonstrated the role that increased PCR use has had on observed pertussis and influenza epidemiology; however, this phenomenon is not limited to Australia. Globally, other countries with increasing PCR use have reported similar changes to observed pertussis incidence and demographics [21, 22]. As PCR testing is expanded to other pathogens, such as those that cause gastrointestinal infections [23, 24], changes to the infection epidemiology are likely to be observed. When relying on a laboratory-based surveillance system, any changes in disease epidemiology need to be interpreted in conjunction with knowledge of underlying testing patterns.

CONCLUSION

In Australia, PCR-based influenza and pertussis notifications have been increasing since 2001 across all age groups. By 2013, PCR-based notifications had largely replaced all other diagnostic methods, with the exception of serology-based notifications in older pertussis cases.

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DECLARATION OF INTEREST

None.

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