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Original Article

# Resurgence of pertussis in Taiwan during 2009–2015 and its impact on infants

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**KEYWORDS**
Epidemiology;
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**Abstract** *Background/purpose:* Pertussis incidence markedly decreased due to universal vaccination, but outbreaks had been noted worldwide in recent decade. This study was conducted to know the epidemiology of pertussis and its impact on infants in Taiwan.
*Methods:* Epidemiologic parameters for confirmed pertussis cases were collected from the Taiwan Centers for Disease Control. The incidence of each age group over years was calculated using population data. We also did retrospective reviews of laboratory-confirmed pertussis cases in NTUH to analyze clinical characteristics and disease severity.
*Results:* A total of 668 confirmed pertussis cases were obtained from the Taiwan CDC open database between 2003 and 2017. There was higher incidence during the period 2009–2015, with a mean incidence of 0.27 cases per 100,000 population, about 2-fold increase compared with mean incidence of 0.12 cases per 100,000 population during the period 2003–2008. Infants accounted for the highest proportion of all cases (49.8%), with mean incidence of 16.1 cases per 100,000 people per year during 2009–2015, and a trend of increase was found from 2003 to 2015. In NTUH, a total of 17 laboratory-confirmed pertussis cases were diagnosed during 2012–2016, and 14 cases were young infants. Among them, 9 infants had been admitted to intensive care unit and 2 infant needed invasive ventilator support.
*Conclusion:* There was a resurgence of pertussis during 2009–2015 and it had significant impact on infants. Young infants with pertussis may be severe and need intensive care, so preventive strategy may be advocated for them.


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## Introduction

Pertussis, a highly contagious and acute coughing illness was a major cause of infant and children death in pre-vaccine era. The incidence of pertussis markedly decreased due to universal vaccination. In Taiwan, incidence of reported pertussis had decreased significantly, from 77 per million population in 1955 to less than 1 per million population in 1970, due to full implementation of whole-cell pertussis vaccination program since 1954, and then a low incidence is maintained.[1]

However, resurgences were noted in 1992 and from 1997 to 2000.[1] Disease burden was shift from young children to infants and adolescents, and the incidence of pertussis in infants remained high (120–650 reported cases per million during the period from 1993 to 2004).[1] In the recent decade, disease outbreaks had been noted in North America (2010 and 2012),[2,3] the United Kingdom (2011–2012),[4] Australia and New Zealand (2008–2011),[5,6] and Japan (2008–2011).[7] Thus, this study was conducted for epidemiology of pertussis in Taiwan in the recent decade and to understand more clinical characteristics and disease severity of pertussis, especially in infants.

## Methods

### Epidemiology of pertussis in Taiwan

We collected data of confirmed pertussis cases from 2003 to 2017 from the Taiwan Centers for Disease Control (Taiwan CDC) Open Data Portal and annual surveillance reports of communicable diseases to analyze epidemiologic parameters.[8,9] According to Taiwan CDC, the confirmed case met the clinical definition (coughing illness lasting for at least 2 weeks with paroxysms of coughing, inspiratory whoop, or post-tussive vomiting without other apparent cause) plus laboratory confirmation by either culture or polymerase chain reaction (PCR) of *Bordetella pertussis* or epidemiological link to a laboratory-confirmed case. The crude incidence rate and incidence of each age group were calculated using population data from statistical information released by Ministry of the Interior.

### Pertussis cases in National Taiwan University Hospital (NTUH)

Pertussis is a mandatory notifiable disease in Taiwan and confirmation tests (culture and PCR of *B. pertussis*) are conducted at the Taiwan CDC Laboratory. We collected the laboratory-confirmed cases at NTUH during the period of 2012–2016. We collected the demographics, contact history, vaccination history, clinical manifestations, laboratory data, management and complications via medical chart review. Positive contact history was defined as contacting with people who had persistent cough symptoms 7–14 days prior to index case, according to the incubation period of pertussis. Infant cases were divided into 2 groups, severe disease and non-severe disease groups. Severe disease was defined as the need of intensive care, the need of ventilator support or with any pertussis-related complications. Based on previous literatures, pertussis-related complications were defined as having apnea, pneumonia, respiratory failure, seizure, encephalopathy, or apparent life-threatening event.[10–12] Clinical variables, including age, gender, pertussis vaccination status, symptoms, white blood cell count, lymphocyte count were compared between severe disease and non-severe disease groups. Leukocytosis was defined as the white blood cell (WBC) count over 17,000/μL,[13] and lymphocytosis was defined as the lymphocyte count over 8000/μL in infancy.[14] Normal C-reactive protein (CRP) was defined as lower than 1 mg/dL.[15] Respiratory syncytial virus was identified via antigen detected in nasopharyngeal aspirate by direct immunofluorescence assay. *Chlamydia pneumoniae* was detected in sputum via polymerase chain reaction. Approval for this study was obtained from the Institutional Review Board of NTUH (IRB number: 201806031RINC).

### Statistical analysis

The annual incidence rates of confirmed pertussis were calculated by dividing the number of confirmed pertussis cases by the population number and were expressed as per 100,000 people in the given year. The incidence trend was estimated using linear regression by Pearson correlation approach and $R^2$ was calculated. Regarding comparisons of clinical variables between severe disease and non-severe disease groups, descriptive variables including gender, acellular pertussis vaccination dose and symptoms were analyzed by Fisher's exact test (two tailed) and continuous variables including age, white blood cell count, lymphocyte count and duration (days) from cough to admission were compared by Mann–Whitney U test. A p-value $<0.05$ was considered statistically significant. SPSS version 22 was used for statistical analyses.

## Results

### Epidemiology of pertussis

A total of 668 confirmed pertussis cases were obtained from the Taiwan CDC database from 2003 to 2017. The mean pertussis case number was 45 cases per year (range: 17–75 cases per year) and the mean incidence was 0.19 cases per 100,000 population (range: 0.07–0.32 cases per 100,000 population) as Fig. 1 shows.

Higher incidence was noted during the period 2009–2015, with a mean incidence of 0.27 cases per 100,000 population (range: 0.2–0.32 cases per 100,000 population), about 2-fold increase compared with the mean incidence of 0.12 cases per 100,000 population during the period 2003–2008.

#### Incidence of pertussis in infants

Infants accounted for the highest proportion of all cases (49.8%), with a mean incidence of 11.1 cases per 100,000 infants (range: 2.4–20 cases per 100,000 infants). During the period of 2009–2015, the mean incidence was 16.1 cases per 100,000 infants, around 2.5-fold higher than the mean incidence during period of 2003–2008 (6.6 cases per 100,000 infants) as Fig. 2 shows. In addition, Fig. 3 shows a significant trend of increase from 2003 to 2015 in annual

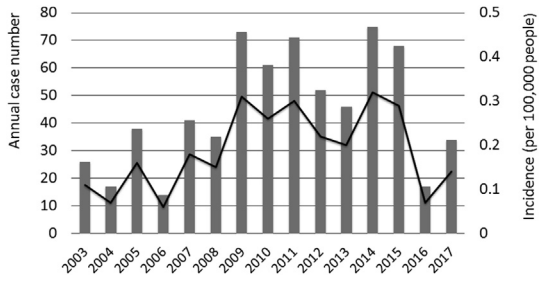


**Figure 1.** Number and incidence of confirmed pertussis in Taiwan, 2003—2017. Each column represented the annual confirmed case number and the line represented the annual incidence of confirmed pertussis.

incidence in infants ($p < 0.001$). Among infant cases, 2-month-old infants accounted for the highest proportion (109/313, 35%), followed by 1-month-old infants (93/313, 30%) as Fig. 4 shows.

### Incidence of pertussis in other age groups

The incidence rates of age groups other than infants were low as Fig. 2 shows. The mean incidence rates of 1—4 years, 5—9 years, 10—14 years, 15—39 years, and ≧40 years people were 0.46, 0.14, 0.39, 0.09, and 0.03 cases per 100,000 population, respectively. There were related higher incidence in 10—14-year-old and 1—4-year-old people among these age groups and accounted for 12.4% and 8.3% of all cases, respectively.

## Pertussis cases in NTUH

A total of 17 laboratory-confirmed pertussis cases were collected from 2012 to 2016. Fourteen cases were infants aged less than 1 year, 2 cases were adolescents, and 1 case was young adult. The demography, clinical symptoms, laboratory data and supportive management of these 14 infant patients are listed in Table 1.

Two patients had comorbidity. One female 6-month-old infant was a premature baby (gestational age 24 weeks and 5 days, birth body weight 640 gm) with bronchopulmonary dysplasia. Another 3.5-month-old male infant was found to have ventricular septal defect during this illness episode.

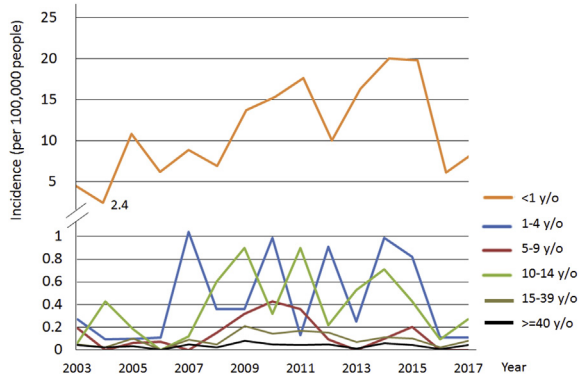


**Figure 2.** Incidence of confirmed pertussis by age groups in Taiwan, 2003—2017.

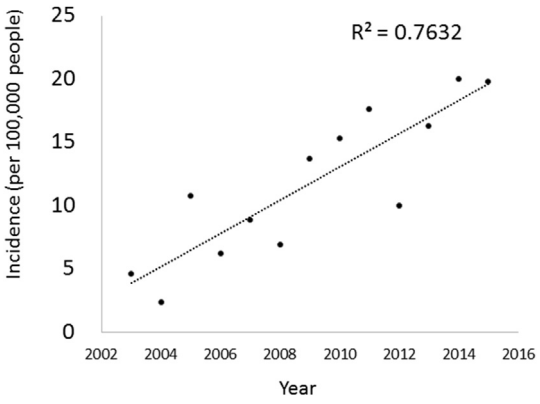


**Figure 3.** Increased trend of annual incidence of confirmed pertussis in infants, 2003—2015 ($R^2 = 0.7632$, adjusted $R^2 = 0.742$, $p < 0.001$).

They both missed pertussis vaccination due to repeated illness.

Seven cases (50%) had positive household contact history and 2 cases' father had positive nasopharyngeal culture for *B. pertussis*.

All patients presented with coughing symptoms (paroxysmal cough 36%, inspiratory whoop 21%, post-tussive vomiting 57%). Twelve (84%) patients had episodes of cyanosis. The median duration from cough to admission was 5.5 days (range 1—21 days) and 10 (71%) patients was admitted within one week after the initial symptoms.

Twelve (84%) patients had lymphocytosis (>8000/μL) and 3 (21%) patients had positive respiratory syncytial virus (RSV) antigen detected in nasopharyngeal aspirates. One patient presented with prominent cough, elevated CRP (2.3 mg/dL) and infiltration on chest roentgenogram had positive *C. pneumoniae* PCR in sputum (bacterial load: $1.4 \times 10^7$ cp/mL buffer solution).

### Cases of severe disease

Nine (64%) severe cases requiring ICU admission were listed in Table 2. Their median age was 1.8 months (range: 0.6—6.0 months). They were admitted to ICU mostly due to cyanosis and tachypnea, and under diagnosis of pertussis, bronchiolitis or pneumonia. The median days of ICU stay

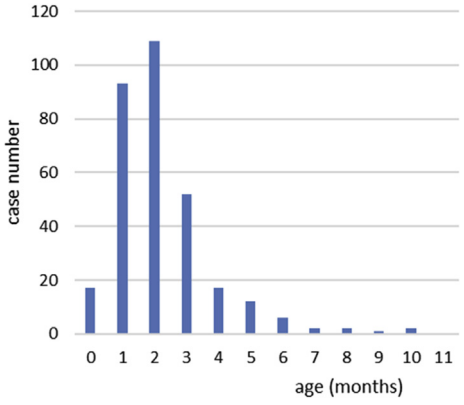


**Figure 4.** Age distribution of confirmed pertussis in infants, 2005—2017.

**Table 1** Demographic, clinical and laboratory information of 14 infants of confirmed pertussis in NTUH, 2012–2016.

| Characteristics | Case number (%); median (range) |
|---|---|
| Gender (M:F) | 7:7 |
| Age (months) | 1.85 (0.62–6.03) |
| 0–1 m/o | 8 (57%) |
| 2–3 m/o | 5 (36%) |
| 6 m/o | 1 (7%) |
| Acellular pertussis vaccination status | |
| 0 dose | 10 (71%) |
| 1 dose | 4 (29%) |
| Positive contact history | 9 (64%) |
| Parent and/or sibling | 7 (50%) |
| Cousin | 2 (14%) |
| Symptoms at presentation | |
| Fever | 1 (7%) |
| Cough | 14 (100%) |
| Vomiting | 8 (57%) |
| Tachypnea | 7 (50%) |
| Cyanosis | 12 (86%) |
| Chest retraction | 9 (64%) |
| Days from cough to admission | 5.5 (1–21) |
| Laboratory data | |
| Leukocytosis (>17,000/uL) | 5 (36%) |
| Lymphocytosis (>8000/uL) | 12 (86%) |
| Elevated C-reaction protein (>1 mg/dL) | 1 (7%) |
| Pertussis confirmation test | |
| Positive culture | 2 (14%) |
| Positive polymerase chain reaction | 14 (100%) |
| Pathogen co-detected | |
| Respiratory syncytial virus | 3/14 (21%) |
| Chlamydia pneumoniae | 1/1 |
| Need intensive care unit | 9 (64%) |
| Supportive care procedures | |
| Nasogastric tube feeding | 4 (29%) |
| Oxygen therapy | 13 (93%) |
| Continuous positive airway pressure | 1 (7%) |
| Invasive mechanical ventilator | 2 (14%) |

was 8 days (range: 3–55 days). Five (36%) patients had pertussis-related complications, 2 (14%) patients needed invasive ventilator support, and no mortality. There was no significant difference in following clinical variables between severe disease and non-severe groups: age ($p = 0.69$), gender ($p = 0.26$), fever ($p = 1.0$), cyanosis ($p = 1.0$), tachypnea ($p = 1.0$), WBC count ($p = 0.60$), absolute lymphocyte count ($p = 1.0$) and the duration (days) from cough to admission ($p = 0.51$) but acellular pertussis vaccination status had borderline statistical significance ($p = 0.095$).

### Complications of pertussis

Five patients had pertussis-related complications. One 0.9-month-old patient presented with apneic episodes and cyanosis. One 1.1-month-old patient coinfected with *C. pneumoniae* had pneumonia at presentation. One 1.2-month-old patient coinfected with RSV developed complications of respiratory failure with hypercapnia, pneumonia (sputum culture yielded *Escherichia coli*) and seizures after one week of admission. Marked leukocytosis and lymphocytosis (white blood cell count: 67,520/μL, lymphocyte count: 39,836/μL) were noted at the time of clinical deterioration. He received invasive ventilator support and was discharged home after 55 days of ICU stay. His white blood cell and lymphocyte counts normalized after 2 months. One 3.4-month-old patient presenting with respiratory distress and paroxysmal cough developed heart failure and needed mechanical ventilator. After echocardiographic exam, ventricular septal defect (VSD) was found and his heart failure was controlled after VSD repair. One 6-month-old patient with prematurity and bronchopulmonary dysplasia presented with fever, cough and cyanosis suffered from an episode of bradycardia (pulse rate decreased to 50 bpm) on the second day of admission and was recovered after 30 s of cardiopulmonary resuscitation.

### Adolescent pertussis

Three of 17 laboratory-confirmed cases were adolescents and young adult and their age were 11, 12 and 19-year-old. They sought the doctor mainly for prolonged and severe cough. The mean duration of cough from onset to diagnosis was 4 weeks. All patients complained of being unable to stop coughing and disrupted sleep. One patient had spasmodic cough and another had facial flushing at the end of paroxysm.

## Discussion

Surveillance from 2003 to 2017 showed a 2-fold resurgence in the period 2009–2015 despite of persistent high pertussis vaccine coverage. The mean vaccine coverage rates for 3rd dose DTaP-Hib-IPV, 4th dose DTaP-Hib-IPV and Tdap-IPV(2011-2017.9)/DTaP-IPV(2017.10-) booster at pre-elementary school age were 97%, 93% and 94%, respectively, from 2014 to 2017.[16] There were epidemics of pertussis in recent decade worldwide,[17] but the resurgence in Taiwan was not as noticeable as some foreign countries.[4,7,18] High immunization rate in Taiwan may play an important role on less severity of the resurge.

Possible explanations for the resurgence of pertussis are as followings. Immunity has waned in vaccinated individuals, so pertussis might circulate among them.[19–21] In addition, pathogen adaptation, including antigenic divergence with vaccine strains had been reported worldwide and decreased the effective period of vaccines.[22] In Taiwan, Yao SM et al. analyses the genotypes of important antigens (*ptxP*, *prn*, *ptxA1* and *fim3*) of 376 isolates from 1992 to 2014 and found the proportion of *fim3-1* reversely increased from 0% in 2006 to 82% in 2011.[23] This change may indicate adaptation of these specific strain to the host factors and environment and cause resurgence since 2009. The introduction of polymerase chain reaction (PCR) for *B. pertussis* as a diagnostic tool in Taiwan CDC laboratory since 2009 may contribute to the increased capacity of laboratory-confirmed cases. Finally, in some countries, cyclic epidemics of pertussis every 3–5 years were noted.[7,24,25] Therefore, long-term surveillance is warranted.

In our study, infants accounted for the highest proportion (49.8%) of confirmed pertussis cases and a trend of

**Table 2** Nine severe pertussis cases[a] in National Taiwan University Hospital, 2012–2016.

| Age (month) | Gender | Pertussis vaccination status | Indications for ICU admission | Initial diagnosis | Complications | Co-infection | Respiratory support |
|---|---|---|---|---|---|---|---|
| **0.6** | F | No | Cough to cyanosis | Pertussis | – | | Oxygen therapy |
| **1.8** | F | No | Cough to cyanosis | Pertussis | – | RSV | Oxygen therapy |
| **1.9** | F | No | Cough to cyanosis | Pertussis | – | | Oxygen therapy |
| **2.4** | M | One dose | Cough to cyanosis | Acute bronchiolitis | – | | Oxygen therapy |
| **0.9** | F | No | Apnea, cyanosis | Pertussis | **Apnea** | | Oxygen therapy |
| **1.1** | F | No | Easily choking while feeding | Pneumonia | **Pneumonia** | Chlamydia | Oxygen therapy |
| **1.2** | M | No | Cough to cyanosis | Acute bronchiolitis | **Pneumonia with respiratory failure, Seizure** | RSV | **Invasive mechanical ventilation** |
| **3.4** VSD[b] | M | No | Respiratory distress, cough to cyanosis | Acute bronchiolitis | **Heart failure** | | **Invasive mechanical ventilation** |
| **6.0** BPD[c] | F | No | Cyanosis | Pneumonia | **Pneumonia, Apparent life-threatening event** | | **Nasal CPAP**[d] |

[a] Definition of severe disease is written in the text.
[b] VSD: Ventricular septal defect.
[c] BPD: Bronchopulmonary dysplasia.
[d] CPAP: Continuous positive airway pressure.

increase in infant pertussis incidence was significant. In the worldwide outbreaks of pertussis, the disease burden strikes on infants and causes morbidity and mortality.[3,4,6,26] In our study, infants of age less than or equal to 2 months old accounted for 70% of all infant cases as Fig. 4 shows. Case numbers decreased stepwise from age group of 3 months or older, indicating that the first dose of acellular pertussis vaccine at the age of 2 months may provide some protection. Young infants not eligible for vaccination were most affected and the peak age of hospitalized infants was one month old.[6,26] In our study, infants aged 0–1 months accounted for more than half of total hospitalized cases. Nine (64%) cases were admitted to intensive care unit, and 2 cases (14%) needed invasive ventilator support. In Japan, 2006–2008, 25% of total 660 infants hospitalized for pertussis had pertussis-related complications and 1 infant died.[26] In our study, 5 (36%) patients had pertussis-related complications and no mortality case was found. In fact, there were 3 infants who died of pertussis during 2003–2014 in Taiwan, and all were young than two months old.[27] Currently, the solution for infant pertussis is maternal immunization.[3,28,29] In Taiwan, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) for pregnant woman has been recommended since November 2012. However, the exact vaccine rate was unknown. A cross-sectional questionnaire survey for prenatal pertussis vaccination was conducted in one medical center in Taiwan: 65% of the 53 recruited women were being informed of the vaccine by their obstetricians, and only 33% of them actually received the vaccination.[30] Clinicians in Taiwan need to provide information of and recommend the maternal pertussis vaccine to increase the success of this important vaccination program.

Early identification and early treatment can help prevent transmitting the disease.[31] However, in a previous study, the sensitivity of clinical diagnosis of pertussis in infants based on WHO definition was low, only 30%.[32] Based on our study and previous literature, some clinical characteristics, including age less than 2 months, no prior pertussis vaccination or only one dose immunization, afebrile, cyanosis and lymphocytosis can be added in criteria of diagnosis or disease notification to help identify infants with pertussis.[32,33] Apneic episodes, including in clinical criteria of pertussis by European Centre for Disease Prevention and Control (ECDC),[34] was presented in only one case of our 9 severe cases (Table 2).[34] In our study, typical evolution of three phase symptoms in pertussis were not noted in infants and the progression from cough to admission, which might be due to cyanosis, tachypnea or dehydration, was rapid with median duration of 5.5 days. In our study, 13 of 14 (94%) cases had normal CRP and the only case with elevated CRP was coinfected with *Chlamydia*, so normal CRP may be a clue to diagnosis. In our study, we compared the clinical variables between severe disease group and non-severe group and tried to find out the parameters that can predict severe disease. Among these parameters, no acellular pertussis vaccination seems associated with sever disease (8 in 9 severe disease cases versus 2 in 5 non-severe cases) but failed to show the statistical significance ($p = 0.095$). In previous studies, young age, no pertussis vaccination, higher WBC count, higher lymphocyte count were risk factors for infant mortality.[35] In our study, the case number might be too small to show significance.

In adolescents, there were small peaks of incidence (0.7–0.9 cases per 100,000 population) in 2009, 2011 and 2014. In the 2012's outbreak in the United Kingdom, the

incidence of laboratory-confirmed pertussis in adolescents was around 25 cases per 100,000 population and the most increased trend among all age groups.[4] In Japan's outbreak, 2008—2011, adolescent and adult cases accounted for 56—62% of the reported cases.[7] Previous seroepidemiologic studies in Taiwan showed that pertussis continues to circulate in adolescents and adults.[21,36] In addition, a seroprevalence study in adults from southeast Asian countries showed the incidence of pertussis in adults with coughing more than 2 weeks was 5%.[37] Mild or atypical symptoms in adolescents and adults and being underrecognized may be attributed to the low incidence in these age groups.[37] In previous published data in Taiwan, there were 17 pertussis clusters in 2014, and 94% of these clusters were household clusters.[27] The main infection sources for infants were adults or children in the same household.[27] Therefore, early identification of pertussis in adolescents and adults can prevent transmission to infants at home. In our study, prolonged and prominent cough (mean duration 4 weeks) was the main symptoms in adolescents and adults. In previous study, symptoms such as paroxysm, breathlessness and chest pain can help diagnosis and early notification.[37]

There were also small peaks of incidence in children aged 1—4 years (0.8—1.0 cases per 100,000 population) in 2007, 2010, 2012, 2014 and 2015. The proportion of cases in this age group was similar in Japan and the USA.[7,18]

Co-infection of pertussis and the other pathogens was found in several cases of this study. Three of 14 (21%) cases were coinfected with RSV. In previous literature, the RSV co-infection rate in infants hospitalized for *B. pertussis* was 2—5%.[10,26,32,38] During the seasonal RSV epidemics in some countries, pertussis-RSV co-infection is more common in young infants with co-infection rate of 60—70% in previous studies of bronchiolitis in the winter and spring seasons.[39,40] Although there is no definite RSV season in Northern Taiwan, RSV circulated in the community throughout the year.[41] Therefore, pertussis-RSV co-infection in young infants may not be uncommon. Diagnosis of pertussis could not exclude RSV infection and vice versa. Aoyama et al. reported 2 infants with pneumonia caused by both *B. pertussis* and RSV who suffered from respiratory failure.[42] In one study for severe pertussis, 8 out of 55 (14.5%) patients admitted for pertussis were co-infected with RSV, and mortality was more associated with RSV co-infection (3 in 6 dead cases versus 5 in 49 survived cases).[43] However, the differences in clinical severity between infants with B. pertussis infection alone and those with RSV coinfection were not known due to small case number in this study. *C. pneumoniae* can cause pertussis-like syndrome.[44] Pertussis co-infected with *C. pneumoniae* had been reported in adults.[45]

There are some limitations in this study. First, the maternal acellular pertussis vaccination status of these 14 infants was not recorded in the medical chart, indicating lack of awareness of this vaccination program in clinician in the past few years. Second, in our study, lack of control (non-*B. pertussis* respiratory tract infection cases) for comparison to analyze pertussis characteristics. Besides, lab-confirmed case number was small. We could use National Health Insurance Research Database to collect nationwide pertussis clinical information to understand the disease burden in Taiwan.

In conclusion, there was resurgence of pertussis during 2009—2015 and it had significant impact on infants. Young infants with pertussis may be severe and need intensive care, so preventive strategy such as maternal and household immunization may be advocated for them.

## Conflicts of interest

All the authors have no conflicts of interest to disclose.

## Acknowledgement

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.06.002.