Taiwan Epidemiology Bulletin
Biweekly
April 6 , 2010 / Vol.26 / No.7

Pertussis Outbreak in a Junior High School－Yunlin County, 2009

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Abstract

In June 2009, the largest outbreak of pertussis in campus occurred in Yunlin County. Taiwan Centers for Disease Control started to investigate the outbreak that finally ended on July 28. There were total 24 confirmed cases, including 20 students, 3 teachers, and 1 parent. Symptomatic students in six different classes were found, with the index case occurred in early April. Initially, the index case in the 2nd grade only had minor symptoms that were easily overlooked; but subsequently, many students and faculty members also started coughing. To prevent further transmission, the Public Health Bureau of Yunlin County gave prophylactic treatment to 251 close contacts. After prophylactic treatments and application of control measures, the number of symptomatic subjects decreased gradually and we successfully prevented it from spreading into communities.

Investigation revealed the major causes that led to this outbreak. First, immunity against pertussis in teenagers who had received DTP vaccination in the past decayed. Second, close contacts via mixed classes, post-curricular activities, and sharing diets occurred frequently in these students. Third, teachers and school nurses were not vigilant enough to notice the unusual increased number of students with prolonged cough in the non-influenza season. Finally, health care workers could be more cautious so that the late reporting would not delay effective control measures. In response to this pertussis outbreak, we should remind health care providers and school authorities to be more vigilant and suggest re-evaluating the vaccination policy.

Keywords: pertussis, outbreak, azithromycin

Introduction

Pertussis is a highly contagious disease caused by inspiration of infectious droplet containing the bacterium *Bordetella pertussis* which mainly attacks upper airway and can induce acute respiratory illness. Human is the

The Taiwan Epidemiology Bulletin series of publications is published by Centers for Disease Control, Department of Health, Taiwan (R.O.C.) since Dec 15, 1984.
Publisher : Hsu-Sung Kuo
Editor-in-Chief : Min-Ho Lai
Executive Editor : Li-Gin Wu, Hsiu-Lan Liu
Telephone No : (02) 2395-9825
Address : No.6,Linshen S. Road, Taipei,Taiwan 100(R.O.C.)
Website : http://teb.cdc.gov.tw/
Suggested Citation :
[Author].[Article title].Taiwan Epidemiol Bull 2010;26:[inclusive page numbers]

only reservoir. The typical presentations include prolonged cough up to two weeks, paroxysms of cough, inspiratory whoop, and post-tussive vomiting. Newborns and younger children are more vulnerable, with a higher risk of death and other complications such as pneumonia or encephalopathy. Symptoms in adolescents and adults are relatively minor, also with fewer complications. Therefore, the bacterium is often transmitted from infected parents, elder brothers or sisters to younger children at home.

Many countries started vaccinating infants and younger children decades ago. Because of the generally high coverage of the effective vaccine, deaths and admissions associated with pertussis in newborns has been dramatically decreasing. However, the immunity from vaccination only lasts for a few years. Decreasing immunity acquired from the vaccines had lead to an increased number of cases in adults and adolescents [1], and posed newborns again at risk of exposure to pertussis. In recent years, outbreaks could be heard worldwide [1-5]. Considering the frequent interactions and intensively contacts in school and extra-curricular activities of adults and adolescents, a good surveillance system, notifying cases on time, age-appropriate vaccination and adequate control measures are of paramount importance to prevent clustering in schools or even outbreaks in communities.

Origin

The index case, a junior high school student in his second grade, visited a local hospital in Yunlin County because of prolonged cough in mid May, 2009. The attending physician was vigilant and reported the case that was later confirmed to be positive in polymerase chain reaction (PCR) of pertussis. Clustering in his class was suspected since several classmates and teachers had similar symptom. After notifying the Public Health Bureau of Yunlin County and the 4th branch of Taiwan Centers for Disease Control (CDC), outbreak investigation has begun on June 3, 2009. Purposes of investigation included estimation of the number of affected subjects, figuring out the source of infection, clarification of transmission route, and offering recommendation on preventive measures.

Investigation

1. Background

The school located in Douliou City, Yunlin County, with 5 to 6 classes in each grade. There were total 526 students and 46 faculty members. The authority does not offer school bus or dormitories. All students were separated in their own classes but mixed up when attending English or mathematics lessons. They were divided into

three groups (A, B, and C) according to their ability.

2. Investigation of suspected cases

We used a questionnaire, retrospectively investigated all students and faculty members, focused on those who had had cough for more then a week since early April, 2009. We tried to identify the presence of clinically compatible symptoms (cough for more then 2 weeks, paroxysm of cough, post-tussive vomiting, etc.), the date of onset, history of seeking medical attention, history of recent traveling, extra-curricular activities (cram schools or student societies), compositions and health conditions of families in those suspicious cases.

Thirty-one students were in the same class with the index case; 24(75%) had cough one after another and some of them also had other upper airway symptoms. Because the students were mixed up with other classes during certain lessons and they shared extra-curricular activities together, we also investigated students and faculties in other classes of second grade simultaneously. Among the total 160 persons underwent investigation, 84 of them had presented with cough by June 5, 2009, including 3 teachers (faculty: 46 persons), 18 students in grade 2 class 1 (classmates: 32 persons), 15 students in grade 2 class 2 (classmates: 31 persons), 10 students in grade 2 class 3 (classmates: 33 persons), 24 students in grade 2 class 4 (classmates: 32 persons), and 12 students in grade 2 class 5 (classmates: 32 persons). In addition to students in grade two, 20 students in grade 1 class 4 (classmates: 30 persons) also had similar symptoms. Overall, the cases surged from late May to early June (Figure 1). Twenty-one persons (3 teachers, 2 students in grade 2 class 1, 1 students in grade 2 class 2, 2 students in grade 2 class 3, 9 students in grade 2 class 4, 2 students in grade 2 class 5 and 2 students in grade 1 class 4) had presentations fulfilling the clinical diagnostic criteria, defined by prolonged cough for more then 2 weeks associated with at least one of the following signs, including paroxysm of cough, post-tussive vomiting or flushing, inspiratory whoop.

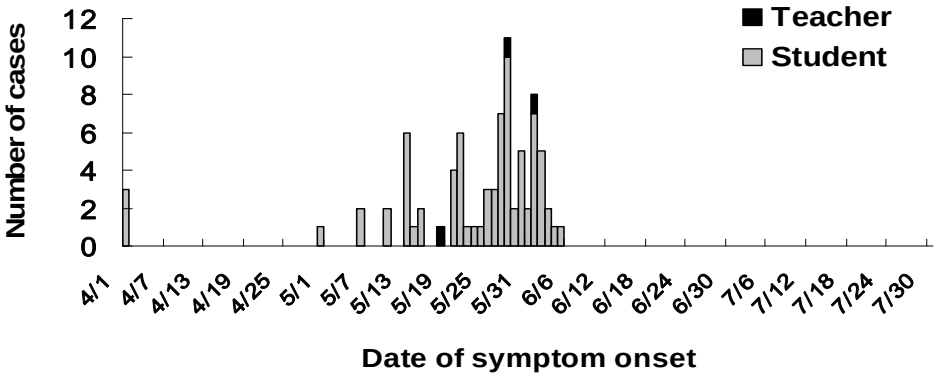

Figure 1. Number of cough cases in a junior high school, by onset date－Yunlin County, 2009

3. Follow-up

Follow-up of the clustering started from the date of the first case reported (June 2) and ended on the date when 2 incubation periods of the last confirmed case has passed (July 28). Three additional cases were reported, including the mother of a student in grade 2 class 4 who started cough on May 26, a student in grade 1 class 4 who started cough on May 25, and another student in grade 2 class 2 who started cough on June 18. Monitoring in campus started since June 5; the number of cough cases decreased gradually since June 10 (Figure 2). Monitoring of family members started since June 12, and the number of persons with cough also decreased since June 16. Monitoring in cram schools and coworkers of confirmed case was done but no case has been found. Through daily surveillance, combination of drug prophylaxis and other control measures were found to be effective in control of the disease.

4. Laboratory examination

We use nasal swab designated to use in pertussis to collect nasopharyngeal discharge. The specimens were sent to Research and Diagnostic Center of Taiwan CDC for bacterial culture and PCR. Subjects who received laboratory diagnostic examinations included 21 reported cases from the campus (2 cases from grade 2 class 1, 1 case from grade 2 class 2, 2 cases form grade 2 class 3, 9 cases from grade 2 class 4, 2 cases from grade 2 class 5, 2 cases from grade 1 class 4, and 3 teachers), 3 additional cases reported

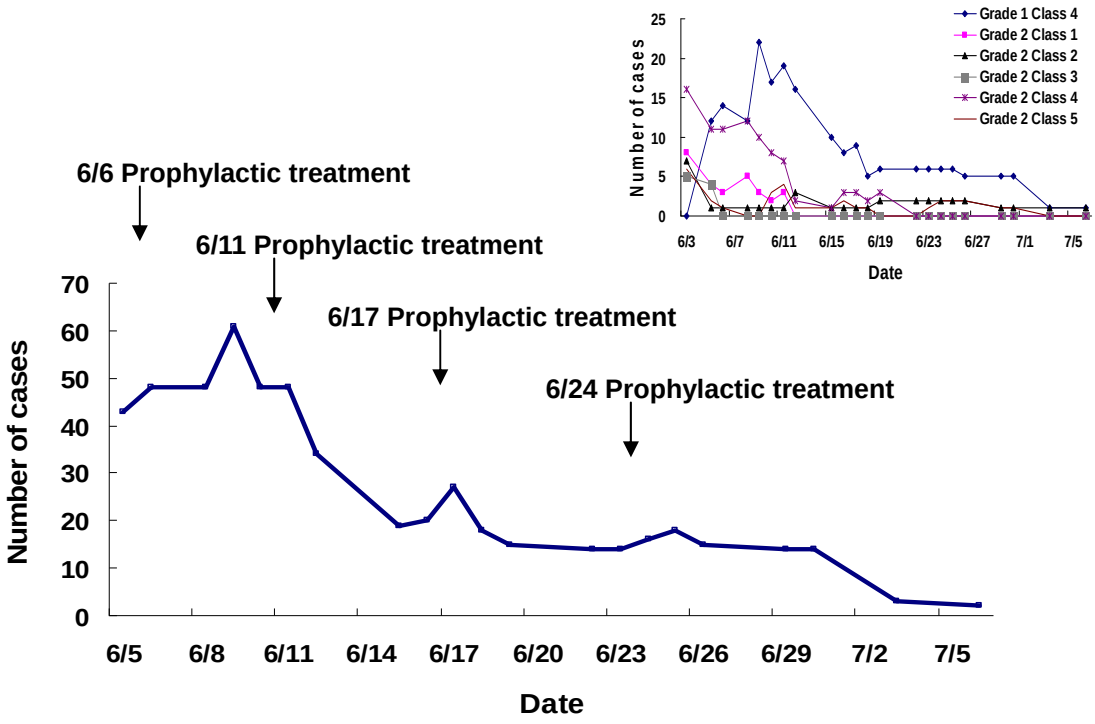

Figure 2.Number of cases with cough under daily surveillance in a junior high school－Yunlin County, 2009

(Daily surveillance was discontinued on July 3, 2009 due to summer vacation.)

during follow-up (the mother of index case, a student from grade 1 class 4, and a case from grade 2 class 2), and 6 contacts of reported cases.

5. Results of examinations

According to Research and Diagnostic Center of Taiwan CDC, of all the suspected cases, both bacterial culture and PCR were positive in 3 and 5 had positive PCR results. But in another lab of a hospital, 9 cases were positive in PCR; only 2 of them had consistent results with Research and Diagnostic Center of Taiwan CDC. The results in either examination were negative in close contacts.

6. Confirmed Cases

There were two definitions of confirmed cases according to Communicable Disease Control Workbook published by Taiwan CDC: cases compatible with clinical diagnostic criteria and confirmed by laboratory exams (bacterial culture or PCR) or cases compatible with clinical diagnostic criteria and epidemiologic association with confirmed cases. Twenty-four confirmed cases were found in this outbreak; 5 were laboratory-confirmed, and 19 were epidemiologically associated with confirmed cases. The epidemic curve of confirmed case was shown in Figure 3. Six close contacts of symptomatic students was neither positive in laboratory exams nor fulfilling clinical diagnostic criteria; they were not included in the list of confirmed cases.

Of the 24 confirmed cases, 3 were teachers in the junior high school, 20 were students in grade 2 and grade 1, and 1 was the mother of a confirmed case who works in a factory in Douliou City. Ten patients were male and 14 patients were female. Twenty cases were between 10 to 19 years old; 4 cases were beyond 20 years old （Table 1）. Twenty cases had received pertussis vaccination. All of them denied history of traveling abroad or attending student societies. Three cases attended to three different cram schools.

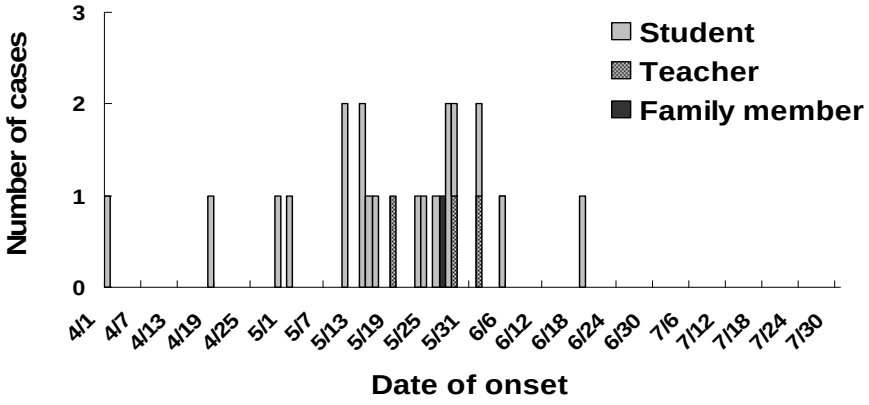

Figure 3.Number of confirmed pertussis in a junior high school, by date of illness onset－Yunlin County, 2009

7. Control and preventive measures:

（1）Reinforcement of surveillance and reporting system

First, in order to evaluate the effectiveness of control measures as well as medical prophylaxis, we asked the school authorities to perform daily surveillance of the health conditions in all students and faculties to intensively monitor the number of suspected cases. Reporting the number of persons with cough to the Public Health Bureau of Yunlin County was required everyday.

Second, strongly recommend symptomatic cases seek medical attention as early as possible and ask the Public Health Bureau of Yunlin County to strengthen health education in schools.

Third, the Public Health Bureau of Yunlin County informed local health care providers the outbreak and reminded them to report suspected patients.

Table 1.Selected characteristics of confirmed pertussis cases in Yunlin County, 2009

Characteristic	**Number of patients (%)**
Number of confirmed cases	24
Male	10（42）
Female	14（58）
Age (years)	
0-9	0
10-19	20（83）
≥ 20	4（17）
Clinical presentations	
Fever	3（13）
Prolonged cough for more then 2 weeks	13（54）
Paroxysm of cough	15（63）
Post-tussive vomiting	5（21）
Laboratory examinations	
Positive result of Pertussis PCR	5（21）
Positive bacterial culture	3（13）
Group identity	
Students in grade 2	17（70）
Class 1	2
Class 2	2
Class 3	2
Class 4	9
Class 5	2
Students in grade 1 class 4	3（13）
Teachers	3（13）
Family members of students	1（4）

（2）Health education

Urge school students to put respiratory hygiene and cough etiquette into practice.

（3）Prophylaxis in close contacts

As recommended by Communicable Disease Control Workbook, we gave prophylactic treatment with erythromycin to close contacts of confirmed cases in accordance to the health conditions of the subjects. Because 9 suspected cases in this outbreak were found to be positive in pertussis PCR in a hospital lab and the unavoidable latency to culture confirmation, it was decided to give prophylactic treatment to close contacts of these suspected cases before the final laboratory results were available. By June 6, 2009, 141 subjects were willing to accept erythromycin prophylaxis and the recommended dose for erythromycin was 500mg (2 capsules) four times a day for 14 days. However, 85 subjects (60%) stopped this medication in three days due to adverse effects, such as gastrointestinal upset (Figure 4). The local health departments informed schools authorities to stop using erythmycin and give azithromycin instead on June 8. On June 11, 17, and 24, azithromycin was given to total 251 subjects, including 124 students in the second grade, 45 students in the first grade, 11 faculty members in the school, 69 family members, and 2 public health coworkers. Among them, only 0.8% of them had mild diarrhea.

（4）Disinfection

School authorities were asked to perform disinfection control measures, maintain good ventilation in the classrooms and offer soaps at washbasin.

（5）Vaccination against pertussis

Students and faculties were investigated for if there were young

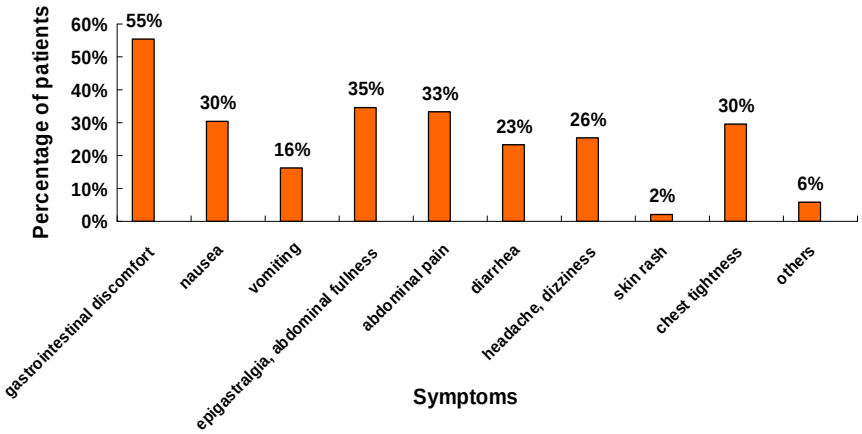

Figure 4. Adverse reactions occurred after use of erythromycin in Yunlin County, 2009.

children less than 7 years old at home and if their vaccination were completed. The health bureau reinforced vaccination against pertussis in infants and children in the county. According to available records, the coverage rate for Tdap in first grade students of elementary schools was 100% in Douliou City; the coverage rates of the 3rd and 4th dose in Yunlin County was 98% and 96% respectively. The un-vaccinated children were asked to booster and the unregistered children were updated the immunization status as soon as possible.

8. The possible infection source and routes of infection

The suspected infection source in this outbreak was the case in grade 2 class 4 presenting with cough earliest in the course, whose PCR result was positive in a hospital lab. Students in the same class and different classes also developed similar symptoms in mid April. The younger brother of a confirmed case in grade 2 class 3 also had cough from May 28 to June 2; he was supposed to be the infection source in grade 1 class 4. Mixed-up English and meth classes were supposed to be the key transmission route.

Discussion

This pertussis outbreak was the largest one in Taiwan in recent years, with 24 confirmed cases in teenagers and adults. It began in students of grade 2 class 4 and spread to other classes and one family member of a confirmed case. Luckily, Infants and young children were not infected. Investigation revealed four major causes that led to an expansion of this outbreak. First, immunity in teenagers who had received DTP vaccination against diphtheria toxoid, tetanus toxoid, and pertussis in the past decayed. Second, close contacts via mixed classes, post-curricular activities, and sharing diets occurred frequently in these students. Third, teachers and school nurses were not vigilant enough to notice the unusual increased number of students with prolonged cough in the non-influenza season. Finally, health care workers could be more cautious so that the late reporting would not delay effective control measures.

The incidence and mortality rate of pertussis in Taiwan declined gradually in the past 40 years. However, the numbers of both imported and indigenous cases rebound recently, from 6 cases in 2001, 38 cases in 2005, a transient decline in 2006 with 14 cases, to 43 cases in 2007, 41 cases in 2008, and 35 cases in the first 5 months in 2009. In addition, the number of teenager cases also increased from 3 in 2007, 19 in 2008 to 16 in the first 5 months in 2009. We found the increase of pertussis patients occurred in different age groups including infants, young children, teenagers and adults; the similar epidemiological trends were seen in western countries [3, 4]. There were 3 outbreaks of pertussis in campus since 2008, with 3-20 confirmed cases for each and most of the patients aged between 13-15 years. This could contribute to immunity against pertussis in teenagers who had received DTP vaccination in the past decayed, the group living lifestyle, and delayed diagnosis.

Several cases in this outbreak had sought medical attention several times when they

were sick, but health care workers were unable to diagnosis on time and give adequate antibiotics due to minor clinical symptoms of pertussis in teenagers and adults. In contrast to infants and young children presenting with paroxysm cough, inspiratory whoop, post-tussive vomiting, and cyanosis [1], they only presented with mild cough, protracted cough to more then 2 weeks, or night-time cough. Because the infected teenagers and adults with minor symptoms still could affect infants and young children at home [5], clusters in campus often evolved into community outbreak according to reports from the US [2-4]. To keep health care workers and school authorities more alert, we should reinforce the education in diagnosis and management of pertussis.

Laboratory confirmation tests in pertussis, including bacterial cultures, PCR, and serology examinations, are not without difficulties. Traditional culture which takes at least a week to reveal the result is the most important diagnostic method but with sensitivity easily influenced by antibiotic treatment, delayed cases reporting, or incorrect collection and transmission of specimen. New laboratory diagnostic methods that use PCR to detect bacterial DNA were under development. Compared to traditional methods, it takes less time to make diagnosis, does not require live bacteria from fresh specimens and the sensitivity was higher. Using PCR might lead to some false positive results, but could help health departments to intervene earlier [1]. Because teenagers often delayed in seeking medical attention due to minor symptoms and bacterial culture alone may result in false negative results, Taiwan CDC have applied PCR methods in making diagnosis in 2009. Considering the advantages and disadvantages of serology test, although it can detect antibody against pertussis late in the course, the methodology is not standardized and we cannot use it to differentiate recent infection from remote infection. Therefore the serology method is not yet to be included in making definite diagnosis.

As recommended by Communicable Disease Control Workbook, clinicians can give prophylactic treatment with erythromycin to close contacts of confirmed cases within 3 weeks after their onset of symptoms. In this outbreak, 141 people had received prophylactic treatment. Because 60% of them had stopped using erythromycin due to adverse effects, all medication was replaced by azithromycin. According to previous studies, the generally-used prophylactic treatment is 500mg erythromycin four times a day; but 30-60% of those who received this prescription presents with gastrointestinal discomfort, nausea, vomiting, or diarrhea [8]. In another outbreak in junior high school in Taipei County last year, 30% of students who had been commenced with prophylactic treatment with erythromycin complained about side effects and used azithromycin instead. These experiences proved that prophylactic treatment in pertussis often fails due to adverse effects. Besides, lack of knowledge in pertussis and the medication also leads to poor compliance in teenagers and hidden breach in controlling the disease. Compared with erythromycin, azithromycin was known to have similar bactericidal effect, better drug compliance (subjects take the pill

once daily for a total course of 5 days) [8-12], and less adverse effects (2-5%), Taiwan CDC, following the steps of Centers for Disease Control and Prevention, USA, has listed it into prophylactic medication for pertussis [9].

The most effective preventive measure against pertussis is vaccination. In Taiwan, infants receive DPT vaccines in 2, 4, and 6 months after birth, followed by a booster in age one and half years [13]. After four doses of vaccination, the vaccine efficacy reaches 70 to 90% and the immunity lasting for 5-10 years. Considering pertussis outbreaks in teenagers, Food and Drug Administration, USA has approved using a new Tdap vaccination containing tetanus toxoid, reduced diphtheria toxoid, and acelluar pertussis in teenagers between 11 to 18 years old and adults between 19 to 64 years old in 2005 [9,14]. It is believed that regular vaccination in teenagers and adults could achieve the best cost-effectiveness and improve public health [15]. Advisory Committee on Immunization Practices in the United States had recommended a booster of Tdap in teenagers above 11 years old and adults in 2006 [9] and the vaccine efficacy has been proven to reach 62 to 92% in teenagers and adults [16]. Tdap had also been used in a large outbreak in a senior high school in the US in 2006. All faculties and students had received vaccination and the result was fairly impressive [4]. In Taiwan, the vaccine was approved in 2007 in those between 4 to 64 years old and booster of Td in the first grade of elementary school has been replaced by Tdap since 2009 [13]. Because these measures may not be effective soon in controlling increase of pertussis outbreak in schools, we could consider a booster of Tdap once a cluster occurs in a school or the possibility of re-boost to all school-aged children.

Conclusion

It is fortunate that all control measures taken by public health departments, hospitals, school authorities, students, and parents for this pertussis clustering in the campus were effective and therefore prevent it from spreading in the community. The control measures included taking specimens from suspected cases and helping them to seek medical attention, implementation of personal hygiene and cough etiquette, raising vaccine coverage, prophylactic treatment in close contacts, reminding local health care providers to report suspected patients and daily surveillance of the health conditions in all students and faculties. Hopefully this experience can be helpful in management of outbreaks in the future.

Acknowledgement

We deeply thank the school nurses and staff members of Public Health Bureau of Yunlin County for their assisting in offering records of daily surveillance. We would also like to thank Research and Diagnostic Center for their help in diagnosis and the Second Division of Taiwan Centers for Disease Control for their generous support in arrangement of prophylactic treatment.

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Evaluating the Choice of Prophylactic Antibiotics for Stockpiling against Pertussis

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Abstract

This article discussed the current policy of the use of prophylactic antibiotics against pertussis in Taiwan. It is recommended that all close contacts of patients with pertussis receive antibiotics for prophylaxis. However, the choice of antibiotics should not only consider the cost and effectiveness of prophylaxis, but also compliance towards medication. If the preventive effect and patient compliance of the selected antibiotics are poor, not only medical resources may be wasted, the bacteria may also develop resistance against antibiotics due to abuse. As a result, in addition to regulate the type of antibiotics to be prescribed and how they should be administered, it is also

necessary to choose an appropriate antimicrobial agent for preventive stockpiling in order to improve the quality of infection control and medical care.

Key words: pertussis, antimicrobial agent, prophylactic antibiotics

Background

Pertussis becomes a notifiable disease in Taiwan since 1999. Erythromycin was stockpiled for the purpose of controlling pertussis outbreaks and preventing high-risk close contacts of patients from contracting pertussis. The benefits of using erythromycin for the treatment and prophylaxis of pertussis have been widely documented and accepted. However, the low patient compliance due to the side effect of erythromycin has somewhat hindered the efforts in disease control.

During the outbreaks of pertussis at middle schools in Taipei County and Yunlin County in 2008 and 2009, 75.6% (28/35) and 60% (85/141) of the close contacts of patients with pertussis developed some forms of side effect after taking erythromycin for prophylaxis, respectively. During the outbreak in Taipei County, 37.8% (14/37) of close contacts reported non-compliance to prophylactic erythromycin. Due to the side effect and non-compliance to erythromycin during the two outbreaks, the local health authorities have replaced erythromycin with azithromycin for more adequate disease control.

Currently, the Centers for Disease Control, Taiwan (Taiwan CDC) stockpile erythromycin for the prophylaxis of pertussis. The purpose of this article is to compare the relevant guidelines and research from other countries, to discuss the appropriateness of the current use of prophylactic agents against pertussis, and to offer suggestions on the choice of medications for stockpiling.

Comparison of various types of antibiotics

Macrolide antibiotics are the most commonly used antimicrobial agents for the treatment of patients with pertussis and the prophylaxis of their close contacts. The most frequently prescribed macrolides include erythromycin, clarithromycin, and azithromycin. Trimethoprim-sulfamethoxazole (TMP-SMX) may be used as an alternative medication in patients with contraindication to macrolides [1].

Erythromycin is the preferred drug of choice for the treatment of patients with pertussis and the prophylaxis of their close contacts according to guidelines in many countries [1-4]. Clarithromycin and azithromycin may be used as substitutes in those who have developed severe discomfort or low tolerance to erythromycin [1, 5, 6]. Both in vitro and in vivo pharmacological studies have confirmed that the therapeutic effect in patients taking 14 days of erythromycin is comparable to that in patients taking five days of azithromycin or seven days of clarithromycin [7]. All three medications are effective in eliminating the nasopharyngeal pathogens in the upper respiratory tract [8-11]. The following paragraphs summarize the side effect and patient compliance of these medications mentioned above using information from the relevant literature review, which may be used as references for the choice of proper prophylactic agent for public health stockpiling.

Side effect

Research reports indicate that the most common side effect caused by macrolide antibiotics is gastrointestinal discomfort, such as nausea, vomiting, diarrhea, abdominal pain, abdominal cramps, and reduced appetite. Skin rash may also develop in some patients [12]. The occurrence and severity of side effect is more pronounced in patients taking erythromycin [1, 6].

Halperin et al. [13] indicated that the incidence of gastrointestinal side effect is significantly higher in patients taking erythromycin compared with those taking placebo (34% vs 16%, RR=2.17, 95% CI=1.43 to 3.31). Another study by Lebel et al. [14] suggested that the proportion of patients who developed side effect after taking 14 days of erythromycin is somewhat higher than that in those taking seven days of clarithromycin (44% vs 32%). Langley et al. [9] also reported that the proportion of gastrointestinal side effect in patients taking five days of azithromycin is lower than that in those taking ten days of erythromycin (18.8% vs 41.2%). The reported incidence of side effect caused by azithromycin and erythromycin are as follows: nausea (2.9% vs 8.4%), vomiting (5.0% vs 13.0%), diarrhea (7.1% vs 11.8%).

Compliance

The success of treatment and prevention of pertussis is significantly associated with the frequency of side effect as a result of medication [6, 15-17]. Results from the studies mentioned above all indicated that the incidence of side effect is unequivocally higher in patients taking erythromycin compared with those taking clarithromycin and azithromycin.

Other studies also suggested that the compliance of patients taking azithromycin and TMP-SMX reached 99% and 90%, respectively, while the compliance of patients taking erythromycin was only 73% [1]. Halperin et al. [13] indicated that 65.1% and 54.2% of patients finished the treatment course with erythromycin and placebo, respectively. Lebel et al. [14] also suggested that compliance of patients taking clarithromycin is higher than those taking erythromycin. Langley et al. [9] reported that the compliance in children taking azithromycin was 90%, while for erythromycin the compliance was only 55% (RR=1.63, 95% CI=1.45 to 1.85).

Table 1 and table 2 below compare the cost, side effect, drug resistance, compliance, and recommended dose of macrolide antibiotics and TMP-SMX:

Recommendation for the choice and use of prophylactic antibiotics for stockpiling

From the public health perspective, choosing the proper prophylactic agent for infectious disease prevention needs to consider not only the therapeutic and preventive effect of the agent, but also the proportion of patients that may develop side effect and patient compliance. The summary from table 1 showed that the cost of azithromycin is lower than clarithromycin, but slightly higher than erythromycin. However, because azithromycin has lower incidence of side effect and higher compliance in patients, it is a more appropriate drug of choice for stockpiling for prophylactic purposes compared with erythromycin and clarithromycin.

Table 1.Comparison of cost, side effect, and compliance among macrolide antibiotics and TMP-SMX

Class / Type	Macrolide			TMP- SMX
	Erythromycin	Clarithromycin	Azithromycin	
Cost / Per person per course (according the estimated payment schedule of National Health Insurance [18])	$280 / 14 days (112 tablets)	$280 / 14 days (112 tablets)	1. Adults (tablet): $336 / 5 days (6 tablets) 2. Children (≤ 20 kg / suspension / bottle): $391/ 5 days	$42 / 14 days (28 tablets)
Frequency of side effect [1, 6]	High	Low	Low	Low
Common side effect [12]	Allergic reaction: dyspnea, urticaria, rash Gastrointestinal system: reduced appetite, diarrhea, nausea, vomiting, etc. Neurological system: headache, dizziness, etc.	Gastrointestinal system: abdominal discomfort or pain, diarrhea, nausea, vomiting, etc. Neurological system: headache, dizziness, etc.	Gastrointestinal system: abdominal discomfort or pain, diarrhea, nausea, vomiting, etc. Neurological system: headache, dizziness, etc.	Skin: rash Gastrointestinal system: reduced appetite, diarrhea, nausea, vomiting, etc. Neurological system: headache, dizziness, etc.
Rare side effect [12]	Liver: abnormal liver function Gastrointestinal system: may develop infantile hypertrophic pyloric stenosis (IHPS) in children less than one year old Cardiovascular system: arrhythmia (Torsade de pointes) Gastrointestinal system: pseudomembranous colitis	Liver: liver toxicity Allergic reaction: dyspnea, pruritus, rash Gastrointestinal system: pseudomembranous colitis Hematological system: thrombocytopenia	Genitourinary system: acute interstitial nephritis Allergic reaction: dyspnea, urticaria, rash Gastrointestinal system: pseudomembranous colitis	Fever Skin: rash, Steven-Johnson syndrome Hematological system: hemolytic anemia (in patients with G6PD deficiency), leucopenia, neutropenia, thrombocytopenia, anemia Genitourinary system: nephritis, renal tubular necrosis Neurological system: aseptic meningitis Liver: cholestatic hepatitis Thyroid: abnormal thyroid function
Drug resistance identified in Taiwan [19]	No	No	No	No
Compliance to medication [1, 9, 13, 14]	Lower than clarithromycin, erythromycin	Higher than erythromycin	Higher than erythromycin	Higher than erythromycin

Table 2.Recommended dose of macrolide antibiotics and TMP-SMX by age

Age	Recommended drug			Alternative drug
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX
Less than 1 month old	10 mg/ kg/ day, once a day for 5 days*	40 – 50 mg/ kg /day, 4 times a day for 14 days	No recommendation	Contraindicated in infants less than 2 months old
1 to 5 months old	Same as above	Same as above	15 mg/ kg /day, 2 times a day for 7 days	Infants 2 months and older: TMP: 8 mg/ kg/ day; SMX: 40 mg/ kg/ day, 2 times a day for 14 days
6 months and older and young children	1. Day 1: 10 mg/ kg/ day, once a day (maximum dose 500 mg) 2. Day 2 – 5: 5 mg/ kg/ day, once a day (maximum dose 250 mg/ day)	Same as above (maximum dose 2 g/ day)	Same as above (maximum dose 1 g/ day)	Same as above
Adolescents and adults	1. Day 1: 500 mg/ day, once a day 2. Day 2 – 5: 250 mg/ day, once a day	2 g/ day, 4 times a day for 14 days	1g/ day, 2 times a day for 7 days	TMP: 300 mg/ day; SMX: 1600 mg/ day, 2 times a day for 14 days

Note:
1. TMP: trimethoprim; SMX: sulfamethoxazole
2. *: Macrolides are the preferred drug of choice for the treatment of pertussis; however, erythromycin might cause infantile hypertrophic pyloric stenosis (IHPS) in this age group

To conclude, we recommend replacing erythromycin with azithromycin as the preferred drug of choice for stockpiling for pertussis prophylaxis in Taiwan:

1. Start purchasing and stockpiling appropriate quantity of azithromycin. When macrolide antibiotics are contraindicated in the targeted patients, use TMP-SMX as an alternative drug of choice. From our previous experience, patients who have contraindications to macrolides are very rare in Taiwan. In the future, when we identify that the close contacts of pertussis patients have contraindications to macrolide antibiotics, the local health departments will refer these contacts to hospitals for further evaluation. Appropriate medications will be prescribed by the physicians from the hospitals, and the associated cost of treatment will be paid for by the public health authorities.
2. The existing supply of erythromycin in the stockpile that has not yet passed their expiration date will be prescribed primarily to individuals 18 years and older, since it may be easier to monitor the presence of side effect and communicate concerns regarding the adverse effect among these groups of patients. When the side effect due to erythromycin can not be tolerated, azithromycin will then be prescribed as a substitute. For individuals under 18 year of age or in the event of mass prophylactic treatment (such as in schools), azithromycin will be the preferred drug of choice.
3. When the existing supply of erythromycin in the stockpile is exhausted or has passed their expiration date, azithromycin will be used as the preferred drug of choice for stockpiling for pertussis prophylaxis.

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