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Reinfection of Invasive *Streptococcus pneumoniae* － Analysis of Notifiable Diseases Database in Taiwan

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Abstract

This study describes the epidemiology of invasive *Streptococcus pneumoniae* based on Notifiable Diseases Database between October 15, 2007 and June 30, 2009. There were 1,366 confirmed cases, with 67 % male and 9.7 % mortality. Persons under five years of age and over 64 years old together represented majority of cases. According to 2008 data, the annual incidence was 3.5 per 100,000 populations, and mortality was 0.48 per 100,000 population. Among 27.6% of patients have underlying diseases, the identified top seven serotypes were 14, 23F, 3, 6B, 19F, 19A, 23A, and the disease was more prevalent in spring and winter.

We identified seven patients, 6 were male, with reinfection from the notifiable diseases database. These patients aged 2 to 87 years old, and had one reinfection. They all had underlying diseases which made them more vulnerable to reinfection. The time between the two infections in these patients ranged from 38 to 390 days. Two patients were infected twice with bacteria of the same serotype (23, and 6B). The seven patients all survived. This is the first epidemiological analysis of reinfection of invasive *Streptococcal pneumoniae* in Taiwan, which may provide useful information for clinical practice and public health authorities.

Keyword：invasive *Streptococcus pneumoniae* infection, notifiable diseases database, reinfection

Introduction

Streptococcus pneumoniae is one of the important pathogens that causes invasive infections in the elderly and children by contact with respiratory secretions and droplet spread. The pathogen is normally found in nasopharyngeal cavity of human body, when immunity is decreasing, it colonizes in the body and causes invasive clinical symptoms including bacteremia, meningitis, peritonitis, septicemia, and other respiratory symptoms such as pneumonia, and otitis media [1].

INSIDE

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Based on the epidemiological study in the USA, 40,000 people died annually due to *Streptococcus pneumoniae* infection mainly in the elderly and children less than 2 years old [2].

According to the related research in Taiwan, most patients were children under 5 years old and the elderly 60 years old or above, the highest fatality rate was found in age 75 and older.

In recent years, several medical centers in Taiwan found that drug resistance of *Streptococcus pneumonia* in Taiwan was one of the worst countries in the world [3]. As the result, the government decided to enforce the policy of vaccination. Since October 2007, the Department of Health accepted the 23-valent pneumococcal polysaccharide vaccines donated by Formosa Plastics Group and the vaccines were given in the following three years. In 2007, the vaccines were first given nationwide to residents in senior health-care centers and the elderly 75 years old or above in Yunlin county, Chiayi city, and Chiayi county. In 2008-2009, the elderly nationwide of 75 years old or above received the PPV-23 and flu vaccination at the same time to increase the inoculation rate.

Although there are many therapeutic methods to battle against invasive *Streptococcus pneumoniae* infection, the morbidity and mortality rate were still very high [4], which was a serious threat for people with low immunity. In recent years, even thought lots prevention efforts about the disease were made, there was an increasing number of patients with reinfection [5]. There were few references discussing the issue and no relevant research in the country now.

Taiwan Centers for Disease Control (Taiwan CDC) classified the *Streptococcus pneumoniae* infection as a category 4 notifiable disease since October 15, 2007 and incorporated it in notifiable disease reporting system. The data has been collected for more than one year. This research was based on the database of the system, based on the onset date from October 15, 2009 to June 30, 2009, to analyze the epidemiology of invasive *Streptococcus pneumoniae* infection and it's reinfection. This study could be used as a reference for government when making vaccination policy, this is also a pioneer study on the characteristics of reinfection in epidemiology and clinical presentation in Taiwan.

Material and Methods

A. Notifiable disease reporting system:

According to the case definition announced by Taiwan CDC, all invasive disease, such as septicemia, pneumonia, meningitis, arthritis, osteomyelitis, pericarditis, and peritonitis, caused by *Streptococcus pneumonia*, and isolation of *Streptococcus pneumoniae* from sterile sites, including blood, cerebral spinal fluid, synovial fluid, ascites, or pericardial fluids,

should be reported within one week. The strain should be sent to Research and Diagnostic Center, Taiwan CDC for serotyping. Finally, the data is incorporated into notifiable disease database.

B. Data collection:

We collected data information from confirmed cases of invasive *Streptococcus pneumoniae* infection which reported according to the regulation by doctors from October 15, 2007 to June 30, 2009. The information included name, identification number, date of disease onset, gender, age of disease onset, area of infection, strain type, clinical signs, underlying diseases, and survival. All collected information was established into a database by using Microsoft Excel for epidemiological analysis.

C. Other underlying diseases:

According to the published documents [2,8], the Advisory Committee on Immunization Practices (ACIP) of U.S. suggested that the risk group of the disease is patients with the following underlying diseases including human immunodeficiency virus (HIV) infection, congenital heart diseases, malignant tumors, alcohol intoxication, asthma, immune suppressive or abnormal, steroid or immune suppression usage, neurological diseases, asplenia syndrome or splenectomy, chronic obstructive pulmonary disease (COPD), and other dread diseases. Patients with underlying diseases are those who have at least one of the diseases listed above.

D. The definition of reinfection and selection methods:

Definition: According to the published reference [6] and the treatment period of the disease, patients with reinfection means patient specimen is positive by laboratory culture for the second time at least 30 days after the previous test.

We selected the reinfection cases through checking and comparing identification from the database, which should be with different report numbers and the date of a positive test identified in the laboratory should be different from the other test with at least 30 days interval. Besides, to approve deliberation and completion of the data, the local health department was notified to retrieve files of cases from medical institutions that patients attended for research analysis.

Result

From October 15, 2007 to June 30, 2009, the notifiable disease reporting system received reports of 1,366 confirmed cases (24% are from medical centers and 76% are from other facilities include 14% from clinics, 24% from hospitals, and 38% from regional hospitals). Male patients were about 67%. As to the age distribution and the annual morbidity, the highest was for 64 years old and above and less than 5 years old. The patients of 75 years old and above had the highest mortality (4.61%). As to the case fatality, the highest rate was for 50 years old and above which was 9.7 % on average. The definition of case with underlying diseases is that patient had at least one of the underlying diseases suggested by U.S. ACIP; doctors reported the underlying diseases of cases to notifiable reporting system according to the clinical diagnosis and history of patients. Analyze the rate of underlying diseases in different age group of patients would allow understanding the correlation and realizing the fatality of patients with underlying diseases. Through the study, the number of patients with underlying diseases was about three tenths (27.6%) of all patients and the rate increasing

with age. For example, patients with underlying diseases were about four tenth for those aged 50 years and older. Overall, the case fatality rate of the patients with underlying diseases was about 12.5% (Table 1).

The strain of *Streptococcus pneumoniae* was cultured by reporting medical facilities and was sent to Taiwan CDC Research and Diagnostic Center for serotype identification. The test protocol followed the Manual of Laboratory Testing Standards for Communicable Diseases. Finally, the serotype data of the strain were recorded into the notifiable disease reporting system. The majority serotypes identified were 14, 23F, 3, 6B, 19F, 19A, and 23A, each accounted for more than 50 strains, and the 6A ranked eighth with 36 strains. As to the high risk age groups, the top five serotypes for children

less than 2 years were 19F, 6B, 14, 23F, and 19A; the top five serotypes for the age of 65 years and older were 14, 3, 23F, 6B, and 19F. The 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV-7) has the strain coverage rate of 72.6% and 68.8%, respectively for children less than 2 years old and less than 5 years old. The 23-valent polysaccharide vaccine (PPV-23) contains most of the serotypes for people 65 years and older with strain coverage rate of 79.6% (Table.2).

Table 1. The analysis of patients with invasive *Streptococcus pneumoniae* infection, by age group－Taiwan, October 2007- June 2009

Age group	No. of cases	Male rate (%)	Case-fatality rate(%)	No. of cases with underlying disease (%)	2008 Morbidity* (per 100,000	2008 Mortality* population)
<1	28	64	0	3 (10.7)	9.9	0
1	66	61	1.5	3 (4.5)	17.4	0.48
2-4	207	49	2.4	8(3.9)	17.7	0.61
5-17	71	65	0	7 (9.9)	0.9	0
18-34	82	65	2.4	21 (25.6)	0.7	0.03
35-49	185	81	9.7	54 (29.2)	2	0.23
50-64	210	71	13.3	80 (38.1)	3.3	0.69
65-74	210	68	9	82 (39.0)	9.6	1.34
≥75	307	70	19.5	119 (38.8)	18.9	4.61
Total	1366	67	9.7	377 (27.6)	3.5	0.48

Note 1：The data of Morbidity & Mortality was in 2008 only

Note 2：The death toll of patients with underlying diseases was 47 (case fatality rate 12.5%)

Table. 2 The percentage of *Streptococcus pneumoniae* serotypes in high risk groups covered by marketed vaccines in Taiwan

Age group (yrs)	PCV7-related (%)	PPV23-related (%)
<2	72.6	—
≦5	68.8	—
≧65	—	79.6

Note 1：PCV7 contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F

Note 2：PPV23 contains serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20,22F, 23F, and 33F

According to the month of onset, the infection often occurred in spring and autumn period in 2008; the peak months were in March and December (Figure.1).

Since October 15, 2007, the disease was classified as a category 4 notifiable disease. We analyzed and found 7 reinfection patients by June 30, 2009, which comprised 0.51 % (7/1366) of all cases. The age for these patients ranged 2-87 years old. Six patients were male, one was female. The time interval in the episodes of reinfection was 38-390 days. All of them had

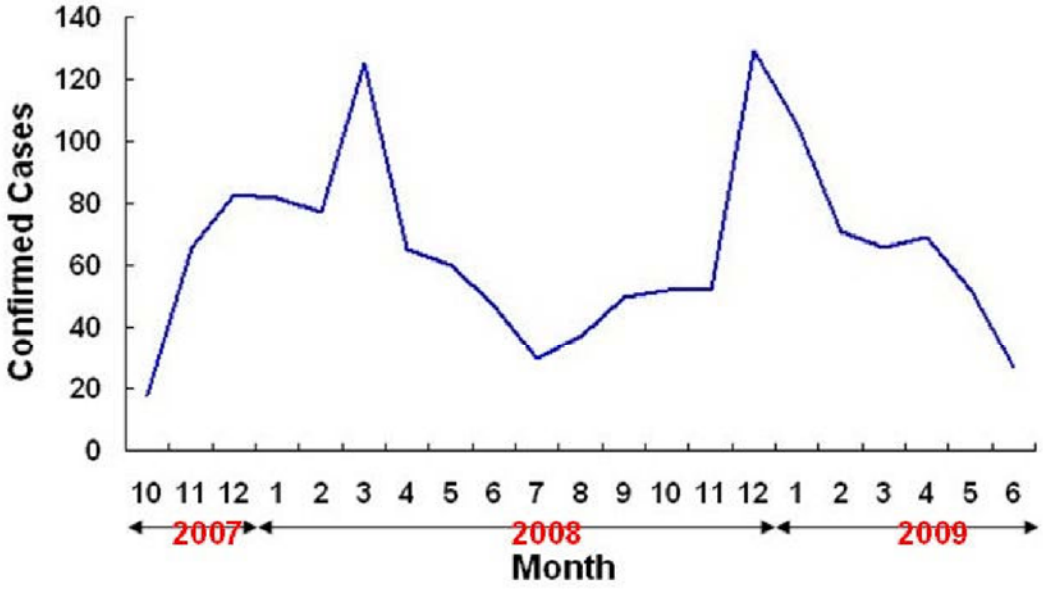

Figure 1. The seasonal distribution of invasive infection of *Streptococcus pneumoniae* —Taiwan, October 2007-June 2009

Table 3. The selected characteristics of patients with reinfection of *Streptococcus pneumoniae* —Taiwan, October 2007-June 2009

Case no.	Age(y)	Sex	Underlying disease	Interval between episodes (days)	Episode (date)	Serotype	Outcome
1	34	M	alcoholism	358	I (20080106)	19F	survived
			gout		II(20081229)	20	survived
2	68	M	alcoholism、COPD	58	I (20071221)	23A	survived
			liver cirrhosis		II(20080217)	23A	survived
3	69	M	—	361	I (20071221)	6B	survived
			ARF		II(20081216)	14	survived
4	87	M	—	68	I (20090415)	14	survived
			COPD		II(20090622)	—	survived
5	2	F	liver transplant	102	I (20090129)	6B	survived
			—		II(20090511)	—	survived
6	12	M	TP	38	I (20090105)	14	survived
			—		II(20090212)	23A	survived
7	73	M	Diabetes mellitus、CVA	390	I (20080402)	6B	survived
			COPD、Diabetes mellitus		II(20090427)	6B	survived

Note：COPD = Chronic Obstructive Pulmonary Disease；ARF = Acute Renal Failure；TP = Thrombocytopenic Purpura； CVA = cerebral vascular accident；— = none

underlying diseases including alcoholism, COPD, cirrhosis, diabetes, stroke, and thrombocytopenia purpura. Two patients were reinfected with the same serotype, 6B and 23 A. All of them survived (Table 3).

Discussion

Epidemiological analysis

Streptococcus pneumoniae locates in nasopharyngeal region and causes severe invasive illness when invading human body. Infection usually occurs through close and long time contact with patients, so infection usually happens when human immunity is weaken [11]. It was classified as a category 4 notifiable disease since October 15, 2007 by Taiwan CDC, which requires all confirmed cases from medical facilities be reported to the system. In the past studies, most cases were collected from medical centers [11]. In this study, 76 % of cases came from other medical facilities, which provides a more complete picture for the epidemiological analysis.

The two highest morbidity age groups of invasive *Streptococcus pneumoniae* infections were children less than 2 years old and the elderly older than 65 years old according to some studies [2,8]. However, in our study, the morbidity of the disease occurred most in children less than 4 years old and elderly 65 years old and above in the country. The infection age of children in Taiwan was higher than other countries might due to the vaccination policy was not completely enforced in children. The new policy has set on July 20, 2009 to vaccinate the high risk group of children younger than 5 years old with PCV-7. With continuous monitoring, the distribution of age specific morbidity shall be clarified. Besides, the fatality gradually rose with age, which was similar to the data from other countries. [8-9]. However, the fatality for the age group of 50 years old and above was higher in the country, which needs further analysis if it was correlated with other diseases. As a whole, the case fatality rate was 9.7 % in Taiwan, which was similar to Australia (9%). The mortality of the disease in the age group of 65 years old and above was the highest. The annual death toll was relative high for children less than 2 years old in other countries [10], but not in this country, which may due to the data was accumulated for many years in other countries, on the contrary, our data only collected for the recent two years. We should continue to monitor to elucidate the result.

The serotypes of bacterial strains was identified by the strain isolation of the participating hospitals and the effort of Taiwan CDC Research and Diagnostic Center. In this study, most serotypes identified were 14, 23F, 3, 6B, 19F, 19A, and 23A; the orders and serotypes were different from the previous research [11]. The data of the previous project was collected from more than 30 regional hospitals. The results of this study revealed that the data was influenced after vaccination policy of PCV-7 and PPV-23 has been implemented in some counties and cities. By analyzing the prevalent serotypes of *Streptococcus pneumoniae* in patients would allow understanding if the marketed vaccines cover the prevalent serotypes or not, and to prevent the disease by vaccination to the elderly at high risk. The vaccine effectiveness can be evaluated by the strain coverage of the prevalent serotypes. During this study, the policy just started to give adults of 75 years and older a dose of PPV-23. After vaccination, comparing the data from January-June 2009 to the same period

in 2008 without vaccination, the only difference was found in the order of number of strains detected; no obvious difference was found in the prevalent serotypes and these were covered in the vaccine. The reason possibly was that the vaccination policy just started; more data was necessary for the evaluation. In the future, detection of drug susceptibility of the isolates would clarify which serotypes are highly drug resistant and if the marketed vaccine would be effective.

Climate and seasonality are the main external factors affecting the number of patients in this disease [12-13]. Besides, duration of daytime, temperature, and rainfall, were also correlated with the incidence of the disease [12]. The onset of the illness mainly occurred from November to next March, and peaks occurred in March and December in 2008. According to the report from Central Weather Bureau, the weather was warm and rainy and the cold front affected the weather for 8 times which caused obvious temperature variations in March 2008 and cold air masses moved south which caused temperature fluctuations in December 2008. Climate change certainly has a huge impact on the susceptibility of human to the disease. In the future, to monitor the seasonality trend of the disease with Geological Information System (GIS) platform would be feasible.

Based on the confirmed cases data, it is evident that the risk of patients with underlying diseases increases with age. In general, the percentage of senior people with underlying diseases was higher than postadolescence and children. We speculate that when patients with underlying diseases and weaker immune system, even if *Streptococcus pneumoniae* at nasopharyngeal region was reducing with age, the invasive disease was still increasing which meant that immunity was the key factor of infection. Although children younger than 4 years old had less chance to have underlying diseases, more *Streptococcus pneumoniae* was colonized in the nasopharyngeal region. Besides, the immune system of children has not well developed and the colonization rate of bacteria in the nasopharyngeal region of children was high. It was possible that bacterial colonization was present in children and reduced their immunity, which caused subsequent infection. Thus, the patient number in children group was high and the result was similar to other studies. In summary, the case fatality of patients with underlying diseases was very high (12.2%), which revealed that the high risk group of patients with underlying diseases should get vaccination to prevent the diseases. We hope that the incidence rate of high risk group of patients could decrease after intensive vaccination, and the mortality could decrease at the same time.

Reinfection

Patients with reinfection have been speculated to have high correlation with HIV infection [5-6]. Others such as cancer, chronic pulmonary disease, even female also have correlation with reinfection [5,14]. The reinfection of children usually correlates with sickle cell trait [15]. However, the real reasons were not known and studies revealed that most reinfection patients have predisposing condition, in other words, most of them have underlying diseases and the percentage was about 60-100% [16-17]. All seven patients in the study had underlying diseases (100%), which was similar to other studies. Even though after vaccination, the patients were still infected again and the percentage was not low [6]. One of the patients

in the study was infected again within one year after receiving PPV-23, which indirectly indicated that either the vaccine did not work effectively, or the immune system of patients with underlying diseases did not respond well as expected [6]. During the study, the percentage of the patients with reinfection was 0.51% (7/1366), which was far less than that in other studies (2.7-5.3%) [5-6, 15, 18]. This may be due to the data collection period was short. In the future, we could retrieve cases by ICD-9 CODE from Bureau of National Health Insurance to understand the reported rate regarding the disease in the notifiable disease database, or try using Capture-Recapture [19] method to predict morbidity and understand the reporting condition.

Examining the bacterial serotypes from these seven reinfection patients, we discovered that the onset of illness occurred most in winter and spring seasons, so climate change was an important factor to the high risk group of people with weaken immunity, which needs more attention. In this study, for the limitation of small sample size, we did not see the high reinfection rate in children less than 2 years old [15], or high mortality of patients with reinfection [20]. More data are needed to understand the distribution of patients with reinfection at each age group.

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Investigation of Tuberculosis Cluster in a Keelung City Hospital

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Abstract

In 2007 between October 3 and October 8, a hospital in Keelung City reported four tuberculosis (TB) cases; three of them were workers of the pathology department. Epidemiologic investigation of the relationship between the patients, place, and time suggested that case 1 might have transmitted the disease to his spouse (case 2), who then transmitted it to two co-workers (cases 3 and 4). Cases 2, 3, and 4 were the same cluster confirmed by restriction fragment length polymorphism (RFLP), suggesting a TB cluster may have occurred in the hospital. Epidemiologic evaluation and preventive measures were carried out by the hospital and the Keelung City Health Bureau, with assistance from the Tuberculosis Advisory Team. The cluster was effectively contained and did not spread further in the hospital. All cases completed their TB treatment on May 9, 2008.

Keyword: Tuberculosis, hospital cluster , restriction fragment length polymorphism(RFLP)

Introduction

Tuberculosis (TB) is an airborne infection transmitted via droplets containing Mycobacterium tuberculosis from the TB patient while talking, coughing, singing or laughing. The bacteria stay afloat in the air after the droplets have dried off, and can cause an infection once they are inhaled and come into contact with alveolar cells in the lung. Only 10-20% of the infected develop visible symptoms; fifty percent of them develop symptoms within the first two years of initial infection. The rest are latent infection. Transmission occurs most frequently between persons with close contact, or living in the same household.

Three primary factors influence infection of Mycobacterium tuberculosis: 1) Environmental factors: the amount of air flow and closed air-conditioning system. Mycobacterium tuberculosis exists in the air as droplets; higher concentration facilitates transmission. It can also be transmitted by air-conditioning system; longer exposure to recirculated air contaminated with TB particles leads to higher chance of infection [2]. 2) Patient factors: patients with TB in the lungs, respiratory track, and throat, with symptoms such as chronic coughing, positive sputum diagnosis, positive chest X-ray diagnosis, immunosuppressive diseases such as AIDS, are more likely to transmit TB due to large amount of TB bacilli excreted [1]. 3) Medical factors: delayed diagnosis and incorrect medication can allow patients to continue spreading TB; induced coughing of hospital patients increase amount of TB droplets in air; improper personal protection facilitates transmission of the disease [3,4]. Two sources provide most of the TB bacterium found in a hospital: already-diagnosed TB patients, and patients that are later diagnosed as TB positive while in the hospital. The latter has a higher chance of causing a hospital TB infection [5]. A hospital in Taipei City had a TB outbreak in 2003, with 60 cases across multiple departments [6]. A hospital in Yilan County also experienced a TB outbreak in the respiratory care unit in 2006.Twenty-two cases were reported, and nine of them were of the same cluster identified by molecular genotyping [7]. Based on these two nosocomial infection incidents, the difficulties of detecting a hospital TB cluster and providing early treatment were easily seen, emphasizing the importance of TB infection control measure in hospitals. This report described the events of an early detection of a hospital TB cluster, and its containment with proper infection control and managements.

Background

Hospital A in Keelung City has 1,097 beds, with inpatient, outpatient, and alternative medication departments, to serve Keelung residents. The hospital building has 13 floors, with centralized air circulation system. The pathology department is on the 7th floor, with 54 staff members, including four Environmental Health Officials. Annual X-ray screening of all staff member takes place between March and May. All screening was normal this year with the exception of four external contractors.

Investigation of the cluster

The index case was a 59 year-old male patient with a history of minor stroke. Patient checked in at Hospital A on June 28, 2007 for coughing. Chest X-rays revealed pneumonia of the lower-right lung; acid- fast stain of the sputum tested negative for TB. Patient's condition improved after antibiotic treatment and was discharged on July 14, 2007. However, sputum culture tested positive for TB two months later. The hospital reported the case as TB on September 21, 2007.

Case two was a 52 year-old female. She worked as a general staff member at Hospital A's pathology department, responsible for specimen collection, blood sample indexing and organization, and cleaning of specimen containers. No disease history or symptoms were noted. She was the spouse of the index case and lived together. Chest x-ray done for contact tracing was negative, but patient requested additional sputum tests. All three sputum sets tested positive for TB. Treatment with anti-TB medication began on September 27, 2007, coupled with home quarantine. The case was reported on October 3.

Case 3 was a 55-year old female. She was also a general staff member at the pathology department, and sit close to case 2. She had a history of acute liver failure. No symptoms were observed at the time of contact tracing. Chest X-ray revealed fibrosis tissues of the upper right lung. However, all three sets of sputum tested positive for TB. Anti-TB treatment began on September 28, 2007, coupled with home quarantine. The case was reported on October 3.

Case 4 was a 39-year old female, co-worker of cases 2 and 3. She had ankylosing spondylitis and rheumatoid arthritis and was on long-term immunosuppressive medication. Second-wave contact tracing chest X-ray was normal but all 3 sets of sputum tested positive for TB. Anti-TB treatment began on October 4, 2007, coupled with home quarantine. The case was reported on October 8.

Local health bureau conducted chest X-ray and tuberculin test on case 3's family (husband, son and two grandchildren) and case 4's family (husband, two sons), and all were negative. Epidemiologic and infectious disease investigation lasted 99 days from the reporting of index case to reporting of case 4. A total of four cases consisting of three hospital pathology workers and one spouse were reported.

Specimen collection and test results

After detection of case 2, 54 staff members of the pathology department (including four Environmental Health Officers) were sent for chest X-ray, and 47 also submitted sputum samples. Two specimens (cases 3 and 4) were TB positive after PCR testing, and their sputum smear and culture were also TB-positive. Mycobacterium tuberculosis was isolated and identified.

Following regulations concerning TB clustering events as outlined in the TB Response Handbook established by the Taiwan Centers for Disease Control, Keelung City Health Bureau collected second sputum samples from cases 2, 3 and 4, and sent to Taipei City Wan Fang Hospital for PCR test, sputum smear and culture. PCR for cases 2 and 3 were positive, and case 4 was not tested. Sputum smear and culture for all 3 cases were positive, with mycobacterium tuberculosis isolated and identified. To determine if a TB cluster occurred, Keelung City Health Bureau sent samples from cases 2, 3 and 4 to CDC's Center for Research

and Diagnostics for restriction fragment length polymorphism (RFLP) test. All 3 cases were from the same cluster, confirming that a clustering event had occurred in the hospital.

Path of transmission

Contact patterns, time and place for all 4 cases were all epidemiologically linked (Figure 1). Record showed case 1 returned to hospital A in September for further testing, and sputum tests showed a high transmission level of 4+ (a quantitative measure of the amount of Mycobacterium tuberculosis in the sputum, 4+ having a high number of bacteria and highly transmissible). Case 2, spouse of case 1, was likely to be infected by case 1, the index case. Cases 2, 3 and 4 were co-workers of the same department and often had lunch together. Cases 2 and 3 also shared office space with the same air circulation system (Figure 2). Case 4 also had pre-existing autoimmune diseases. These factors facilitated the transmission of TB. Results from RFLP showed cases 2, 3 and 4 were of the same cluster, confirming their infections were related. The suggested route of infection for this clustering event is as follows: case 2 contracted TB from case 1 while at home, and infected cases 3 and 4 at work. The CDC TB advisory team determined since cases 2, 3 and 4 were diagnosed early on, they were still in the incubation period and showed no external symptoms and no detectable chest X-ray abnormalities.

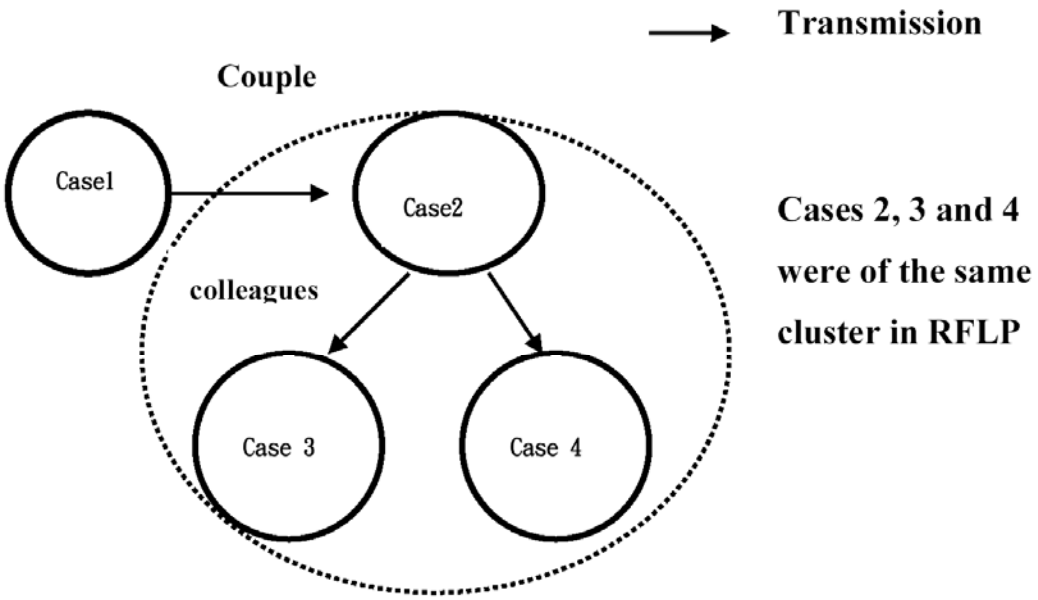

Figure 1. Epidemiological links of tuberculosis cluster cases in a Keelung City hospital, 2007

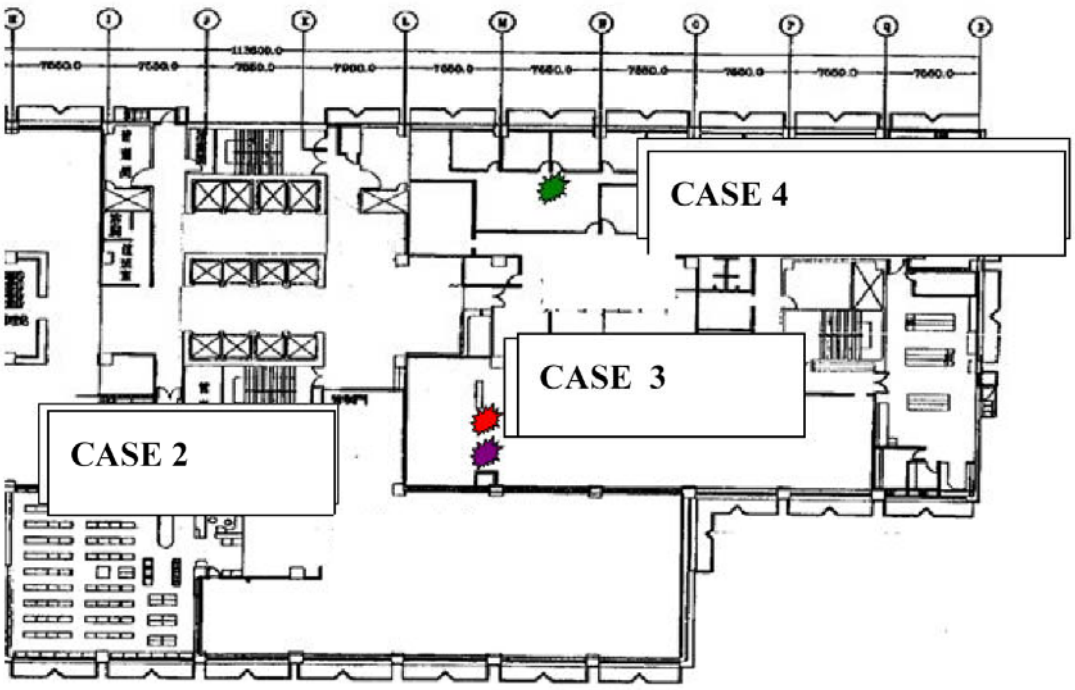

Figure 2. The relative seats location of tuberculosis cluster cases in a Keelung City hospital, 2007

Preventive measures

Hospital A and Keelung City Health Bureau initiated immediate preventive measures after the cluster. The hospital director called an emergency meeting to decide on response actions. The following were also executed at the same time: hospital epidemiologic investigation, sputum tests and chest X-rays for all pathology department staff member, medication and home quarantine for those tested positive, reporting all TB cases to the health bureau and hosting hospital briefing meetings, with chest and infectious diseases experts on hand to answer questions. Infection control personnel assisted in tracking the health of pathology department staff member and those with close contact with the staff member; chest X-rays for 2 years were also monitored. All hospital workers were notified to exercise proper personal hygiene and managers were reminded to monitor workers' health status closely. The infection control team inspected laboratories, mycobacterium laboratory rooms, hospital environment and various staging areas on October 2, 2007, and found all to conform to regulations.

Keelung City Health Bureau, after receiving reports of the TB clustering event from the hospital on October 3, 2007, had conducted emergency epidemiologic investigation, contact tracing of confirmed TB cases, repeat sputum test, and submitted information on all cases to the TB advisory team for review in the October meeting. On October 16, CDC first branch and two members of the TB advisory team visited the hospital to evaluate the situation and provided assistance as needed. For this hospital TB cluster, the last case was reported on October 8, 2007, with all surveillance completed on July 30, 2008. The hospital reported no new TB patients connected to the event. The last case（case 4） completed treatment cycle on May 9, 2008.

Discussion

Early diagnosis of TB cases greatly helps the treatment of patients [9] and decreases the chances of a hospital TB clustering event. The index case of this incident checked into hospital A on June 28, 2007 for coughing. Two months later, the sputum culture tested TB positive. Sputum tests from the same patient taken during the revisit in September tested to be 4+, a highly transmissible state. The hospital did not report the case until September 21, three months after initial visit. The delay in diagnosis unnecessarily increased the possibility of transmitting TB to others [10]. The CDC hospital TB prevention measures include 3 levels: administrative management, environmental control, and personal protection [11]. During this TB clustering event, the hospital called emergency meetings, decided on response measures (home quarantine, X-ray screening of the pathology department staff member, disinfection of the work environment, etc.), which demonstrated competency in handling the incidence. An outbreak often causes panics; the hospital workers, despite being medical professionals, displayed various degrees of panic early in the incident, even leaking the information to the mass media. The hospital hosted information meetings, effectively decreasing the level of panic amongst workers.

Because cases 2, 3 and 4 were diagnosed chronologically close to each other, the health bureau was able to conduct repeat tests, obtain Mycobacterium tuberculosis isolates, and show the 3 cases are epidemiologically related. However, the hospital does not keep Mycobacterium tuberculosis isolates, preventing comparison of the strain from cases 2, 3 and 4 with that of the index case via RFLP. Whether the index case's sputum culture is the same as the others remains unknown. The sample from index case should have been preserved or deliver to Taiwan CDC for testing. Also, cases 2, 3 and 4 displayed no external TB symptoms; chest X-rays and CT scans revealed no abnormalities in the lungs, yet sputum tests from all 3 cases tested strongly TB positive and the same cluster was isolated, suggesting cross contamination may have occurred. However, repeat samples were collected by 2 other health bureaus, using different containers from the first round of tests; repeat tests were also not conducted at hospital A. The same results from different test facilities and newly collected samples ruled out the possibility of cross contaminations during the first round of tests. Research published by Pepper et al. [12] also pointed out some patients with TB positive sputum test may not show any abnormalities on chest X-rays, especially those with autoimmune diseases.

This cluster showed that hospital patients have the potential to become the initial source of TB infection, and hospital workers can be easily infected and transmit disease to others. Recommendations for hospital infection control measures should include implementation of annual chest X-ray screening for all hospital workers.

Conclusion

This incident was a TB cluster event at a Keelung City hospital. RFLP and epidemiologic studies confirmed this hospital TB cluster. One staff member of the pathology department (case 2) contracted the infection from her husband

(case 1), then infected two of her co-workers. One (case 3) was in the same office, and the other (case 4) had autoimmune disease. Notably, only the index case displayed external symptoms; the other 3 cases showed no abnormalities on chest X-ray and CT scan. The hospital and local health bureau's response protocols allowed for early detection of the cases, effectively containing the transmission. Due to TB's long incubation period, those infected may not develop symptoms immediately; therefore those in contact with the pathology department staff member should monitor their health status closely for some period of time.

Acknowledgement

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