The Surveillance and Epidemiological Analysis of *Streptococcus Pneumoniae* Infection, Category Four Communicable Disease, in Taiwan.

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Abstract

Streptococcus pneumoniae is a common pathogen for pneumonia, septicemia and cerebral meningitis. These diseases are usually seen in children less than 2 years old and senior people older than 65 years old. The infection of this pathogen may cause severe result, even death, while the immune system is compromised. National-wide data and epidemiological analysis for this disease are absent in Taiwan, with only few reports from local hospitals, which resulted in unclear understanding of the national epidemiologic situation and put limitations on the development of immunization policy. This disease was announced as a category four communicable disease in Taiwan on October 15, 2007.

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Local medical institutions should follow the Communicable Disease Prevention Act, which can improve our understanding of the epidemiologic situation in Taiwan.

Based on the analysis result, the male and female ratio of the confirmed cases was 2:1. In terms of age, most cases were less than 4 years old and older than 50 years old, which form a V shape distribution. The mortality rate increased with age. The cases reached the annual peak in March and then decreased gradually, and lowest case number occurred in July. It was suspected that spring and winter were the preferred seasons for this disease. Geographically, most of the confirmed cases were distributed in the counties with large populations. However, the morbidity was higher in the counties with smaller populations, such as Hua-Lien. The bacterial strains from most of the cases were 14, 3, 6B, 6A, 19A, 19F, 23A and 23F. The protection rate of the 23-valent vaccine were 89.1%, 79.1% and 79.6% for 2 to 4 years old, 65 years old and above, and 75 years old and above, respectively; the protection rate of the 7-valent vaccine were 74.5% and 69.3% for less than 2 years old and 2 to 4 years old, respectively. Pneumonia was the most common complication. Other complication included septicemia, cerebral meningitis, bacteremia and peritonitis. The percentage of subclinical diseases increased with age.

The results of this study may provide epidemiologic data for Streptococcus pneumoniae infection in Taiwan, demonstrate the importance of monitoring work, and offer a reference for future immunization policy.

Key words: communicable disease reporting system, geographical information system, Streptococcus pneumoniae infection, immunization policy

Introduction

Streptococcus pneumoniae is a lancet-shaped, Gram positive coccus [1]. Some of the cocci contain capsular polysaccharide, which is recognized as a pathogenic strain. Ninety strains of Streptococcus pneumoniae have been confirmed based on the Danish system capsular polysaccharide antibody quellung reaction [2]. This pathogen is most commonly seen in infants, children and senior people, causing infectious diseases by contact with the respiratory discharge of a patient or through patients' droplets. It may also cause community-wide pneumonia infections in temperate or subtropical countries. Taiwan is located in the subtropical zone, and the population mainly lives in the cities with close contact, which is suitable for the spread and growth of pathogens. This pathogen usually induces clinical signs including bacteremia, cerebral meningitis, peritonitis, septicemia and other respiratory signs (eg. pneumonia, otitis media and nasosinusitis) [3].

According to epidemiologic data from USA, among patients with Streptococcus pneumoniae infection, 50,000 suffer from the complication of bacteremia annually, 500,000 from pneumonia, 3,000 from cerebral meningitis, 7,000,000 from otitis media, and 40,000 eventually die. The diseases and complications listed above mainly occur in patients less than 2 years old and senior people [4]. The results of related research in Taiwan reveal that this disease is also commonly seen in patients less than 5 years old and senior people older than 65 years, which is similar to the situation in USA and other countries [5]. Pneumonia is the most frequently seen clinical sign, followed by septicemia and cerebral meningitis [5].

The first penicilline-resistant Streptococcus pneumoniae was

isolated in 1976, and highly penicilline-resistant stains have been continuously found worldwide [6]. In recent years the drug resistance of this pathogen in Taiwan came out on top of the world [7-11]. This brought out the importance of vaccination research and offered an opportunity for developing relevant immunization policy in Taiwan. There are two approved vaccines for this pathogen in Taiwan. The first one is a 7-valent pneumococcal polysaccharide- -protein conjugate vaccine (PCV-7) for infants less than 2 years old and high-risk population between 2-4 years old, and this vaccine contains stains with capsular antigen 4, 6B, 9V, 14, 18C, 19F and23F. The other one is a 23-valent pneumococcal polysaccharide vaccine (PPV) for senior people older than 65 years old and high-risk population between 2-64 years old, and this vaccine contains strains with capsular antigen 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9B, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F [1].

In Taiwan, research papers on the disease situation and related case studies tended to focus on particular local areas or medical centers, making it difficult to compile complete national-wide epidemiologic data for this disease. Since October 15, 2007, this disease was classified as a category 4 communicable disease. This study, supported by the Geographic Information System (GIS), analyzed the age, gender, preferred season, geographical distribution, morbidity, mortality and subclinical diseases of the patients, and presented the protection rate of the 2 approved vaccines for high risk populations to provide a reference for further immunization policy development.

Material and methods

1. Communicable disease reporting system :

According to Article 3 of the "Regulations Governing the Implementation of the Epidemiological Surveillance and Alert System for Communicable Diseases," a national-wide monitoring and early warning system was established to collect and analyze the reported communicable disease data. All medical facilities and local health authorities should report designated diseases according to this law so that the central government may monitor and analyze the disease situation, provide warning, and implement timely disease control measures to protect the health of society.

2. The reporting definition and time limit for Streptococcus pneumoniae :

The clinical signs and laboratory diagnoses compatible with one or more listed below: septicemia, cerebral meningitis, arthritis, osteomyelitis, pericarditis, hemolytic uremia, peritonitis and patients with Streptococcus pneumoniae isolated from sterilized samples, e.g. blood and cerebral spinal fluid (CSF). The time limit for reporting should be within 1 week.

3. Methods and tools for analysis :

We downloaded the information of confirmed cases, including date of disease onset, gender, age, area of infection, strain type, clinical signs, subclinical diseases, coordinates of infection area and mortality. All collected information was put into a database established by Microsoft Excel and analyzed by SAS 9.1. The morbidity and mortality per 100 thousand people of each age level was calculated on the basis of population in 2007.

4. Application of geographic information system :

GIS is usually applied for monitoring geographic data for public health prevention. We used Arc GIS 9.2 developed by ESRI to transform the living area into coordinates (TWD97) and then overlapped on the map. The distribution of confirmed cases in each county in Taiwan was developed.

5. The protection rate for pathogenic strains of 7-valen and 23-valent vaccines:

Based on the property of he vaccines and related studies [4-7], we calculated the protection rate of 7-valent vaccine for children less than 2 years old and 2 to 4 years old, as well as the protection rate of 23-valent vaccine for people 2 to 4 years old, 65 years old and above, and 75 years old and above, by the formula list below:

Protection rate (%) = patient number with vaccine / total patient number × 100%

6. Clinical signs and subclinical diseases:

We analyzed the most common complications and clinical signs from patients with Streptococcus pneumoniae infection. We also gathered statistics on the distribution in each age level from these patients with subclinical diseases to understand the relationship between immune function and infection. The definition for subclinical diseases was: patients with HIV infection, congenital heart diseases, malignant tumor, immune insufficiency, neurologic diseases, asplenia or splenectomy, chronic pulmonary diseases or other severe diseases.

Results

From October 15, 2007 to September 30, 2008, Taiwan CDC received

reports of 729 confirmed cases (23% from medical centers and 77% from other medical facilities). In these cases, 486 were male while 243 were female, and the ratio of female to male was 2:1. As to the number of each age level, 166 (22.8%) were 75 years old or above, 124 (17.0%) were 65 to 74 years old, and 111 (15.2%) were 50 to 64 years old. We noticed that the morbidity of these confirmed cases was the highest in the age level of less than 4 years old and 65 years old or above, which represented a V shape distribution. As to the mortality for each age level, it gradually raised with age. The level of 75 years old or above had the highest mortality (9%), followed by 35 to 64 years old (8%). As to the age level of less than 5 years old, 1 year old infants had the highest mortality (3%) (Figure 1

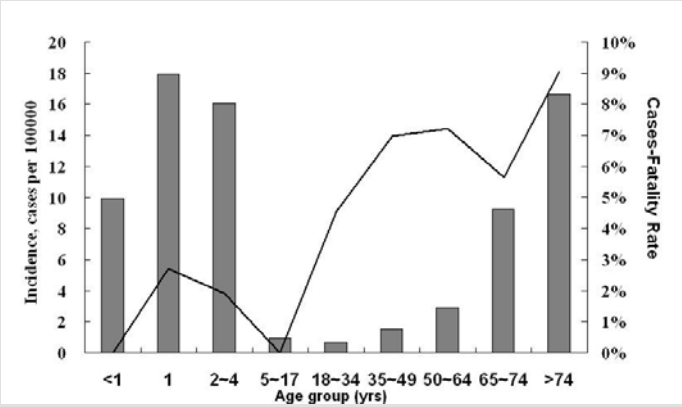

Figure 1. The morbidity and mortality of Streptococcus pneumoniae infection in each age level in Taiwan.

According to the date of disease onset, the number of confirmed cases reached a peak in March and then gradually decreased, with the case number in October 2007 being ignored due to unavailability of data before

October 15. The number of confirmed cases was obviously lower in July than in other months. The average number of confirmed cases was about 80 in November, December, January and February (Figure 2).

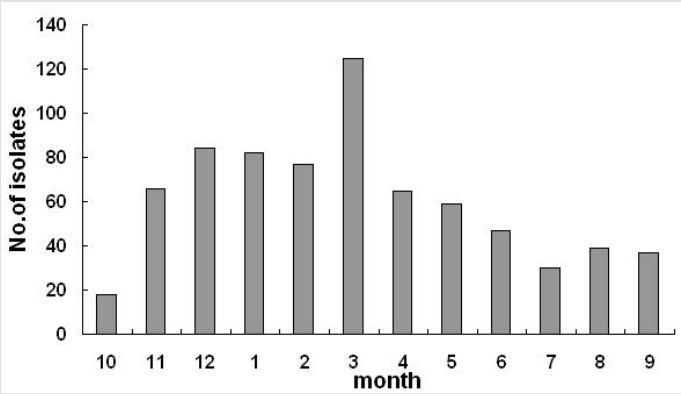

Figure 2. The distribution of confirmed cases of Streptococcus pneumoniae infection in Taiwan (according to the month). Note: the timeframe of this study was from 2007/10/15 - 2008/9/30.

Geographically, Taipei County (110 cases), Taipei City (68 cases) and Taoyuan County (58 cases) were the 3 counties with the highest numbers of confirmed cases. Hualien County (5.53 cases), Chiayi City (5.49 cases) and Yilan County (5.0 cases) were the 3 counties with he highest numbers of confirmed cases per 100 thousand population. No confirmed case was found in the off-shore islands and areas, e.g. Kinmen County, Penhu County and Lienchiang County. The distribution of confirmed cases in Taiwan was listed in Figure 3.

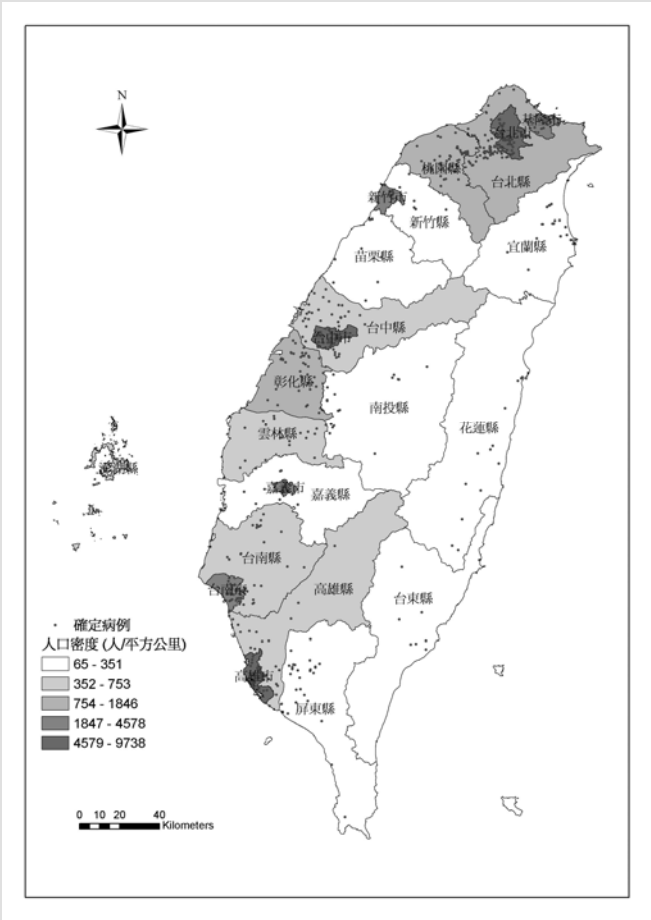

Figure 3. The relationship of geographic distribution of Streptococcus pneumoniae infection and population density.

Six hundred and ninety cases of Streptococcus pneumoniae infection were examined for serotype, and most were serotypes 14, 23F, 3, 6B, 19F, 23A, 19A and 6A, till September 30, 2008 (the 8 main serotypes, listed in Figure 4). As to the 4 preferable age levels of Streptococcus pneumoniae

infection, e.g. less than 2 years old, 2 to 4 years old, 65 years old and above, and 75 years old and above, the former 2 levels respectively contained 15.7% and 4% of the serotypes that were not the main 8 types,,while the main 8 types were 84.3% and 96%, respectively. In the later 2 age levels, more than 70% of the serotypes examined were the main 8 types.

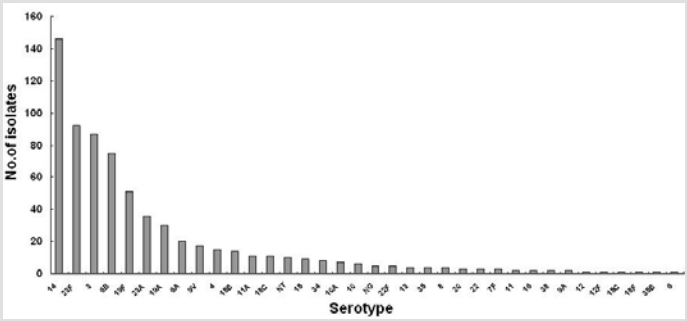

Figure 4. Serotypic analysis for Streptococcus pneumoniae infection in Taiwan.

*** Till 2008/9/30, 690 cases were examined for serotype. NG= no growth; NT= no typable**

**** Serotypes over than 20 strains included: 14, 23F, 3, 6B, 19F, 23A, 19A, 6A**

The protection rate of 23-valent vaccine for 2 to 4 years old, 65 years old and above, and 75 years old and above was 89.1%, 79.1% and 79.6%, respectively. The protection rate of 7-valent vaccine for less than 2 years old and 2 to 4 years old was 74.5% and 69.3%, respectively (Table 1). As to the complications, about 57% of the patients had pneumonia, followed by septicemia, cerebral meningitis, bacteremia and peritonitis. 23.6% of the patients had pneumonia and septicemia simultaneously. In all age levels, 219 patients had subclinical diseases, and 59.8% were those over 65 years old. The age level of 65 to 74 years old had the highest

percentage of patients with subclinical diseases in all age levels (50%), followed by the age level of 75 years old and above (41.6%). 30% of the patients in this study had subclinical diseases.

Table 1. The protection rate of 23-valent and 7-valent vaccines

Age	Number	No. of patients with vaccination		Protection rate (%)	
		7-valent	23-valent	7-valent	23-valent
<2	51	38	-	74.5	-
2-4	101	70	90	69.3	89.1
≧65	278	-	220	-	79.1
≧75	157	-	125	-	79.6

Discussion

Streptococcus pneumoniae usually resides in the nasal mucosa and induces severe infections such as pneumonia, baceremia and septicemia around the world. Direct contact or inhalation of the infectious droplets were the main transmission routes, however, this usually needs long term exposure. This disease is usually seen in patients with a compromised immune system [12]. In studies conducted in USA, children less than 2 years old and senior people over 65 years old are the 2 most vulnerable groups for this disease [4, 20]. According to WHO reports, the morbidity of this disease in developed countries was 8 to 34 cases per 100 thousand people, and the age group of less than 2 years old had the highest morbidity, followed by 65 years old (and above) group (24-85 cases/100 thousand people) [21]. This disease has been classified as a category 4 communicable disease in Taiwan since October 15, 2007. Children less

than 5 years old are the preferred age group of this disease in Taiwan, which is mildly older than that of other studies. The morbidity in senior people over 65 years old is similar to other reports. However, the morbidity of these 2 age groups are still higher than those of 5 to 64 years old (the highest being 3 cases / 100 thousand people in the age group of 50 to 64 years old). As to the result of this study, there is still high risk of this disease in the age group of less than 2 years old, which may be related to the immunization policy, environment and climate. The mortality in Taiwan, although mildly different from the results of other studies (mortality increases with age), is higher in patients with a compromised immune system or subclinical diseases. However, this still needs further monitoring and study. The ratio of male to female was 2:1. In our study, there are higher case numbers in the cold months or months with larger temperature differences. The case number decreases while the temperature rises, which is similar to other studies [5-6, 13-14]. According to the data, we suspect that the risk of Streptococcus pneumoniae infection may increase when the immune system is compromised due to external factors such as temperature change.

In our results, the top 3 counties that had the highest morbidity per 100 thousand people were Hualien, Yilan and Chiayi. This is possibly due to: a) a smaller population in these 3 counties; and b) a higher percentage of the vulnerable age groups of less than 5 years old and 65 years old or above (16.5%, 4.7% and 17%, respectively), which may be caused by the outflows of youth and adult populations. Such population outflows have made the remaining populations in these counties more vulnerable to this disease because most of the people are child and senior people. We used

geographic information system to take into consideration the population density of each county and noted that cities with higher population density had more confirmed Streptococcus pneumoniae infection cases, which conformed to the characteristics of this disease [2]. As for the off-shore island areas, no confirmed case was found. It is suspected that this disease needs constant contact to be transmitted, and it is difficult to be "imported" from other areas. Furthermore, there is less population in the off-shore island areas and thus a lower risk of transmission. In addition, there are fewer medical sources in these areas so people may purchase patent medicine or antibiotics in the pharmacy instead of going to the hospital.

It was difficult to find national reports about the serotypes of the isolated bacteria strains, and serotypes 3, 6B, 9V, 14, 19F, and 23F were mentioned to be the common serotypes in few studies [15-17]. However, such results may not be general situation in Taiwan because these studies were localized. In our study, serotypes 14, 3, 23F, 6B, 6A, 19F, 23A and 19A were the common serotypes in 690 isolated strains, which were similar to other studies. This may be related to the habits of seeking medical service (going to medical centers) or population structure (centralized in the big cities). The common serotypes in the preferred age levels (over 80% in the patients less than 5 years old and over 70% in those who were 65 years old or above) of this disease were also those listed above. Thus, related immunization policies especially for these common strains should be considered, such as developing Streptococcus pneumoniae vaccines directly against the common serotypes listed above.

Drug resistance of Streptococcus pneumoniae has become

increasingly severe in the world, but vaccination may help prevent the drug-resistant strains. 7-valent vaccine and 23-valent vaccine are the 2 vaccines mainly used in Taiwan. 23-valent vaccine is a polysaccharide vaccine which is not suitable for children less than 2 years old [18] and thus, a protein-combined 7-valent vaccine was developed [19]. The most important goal of this study was to evaluate the usefulness in Taiwan, to understand the strains and serotypes for future vaccine development, and to completely analyze the serotypes in Taiwan. In our results, the serotypic coverage percentage of the 7-valent vaccine for children less than 2 years old was 74.5 % (38/51). The coverage rate decreased to 69.3 % (70/101) for children 2 to 4 years old, however, it increased to 89.1 % (90/101) when children received 23-valent vaccines. The serotypic coverage percentage of the 23-valent vaccine for senior people was 79.1 % (220/278) and 79.6 % 125/157) for 65 years (and above) old and 75 years old (and above), respectively.

Pneumonia, septicemia, cerebral meningitis, bacteremia and peritonitis are the 5 most common complications for Streptococcus pneumoniae infection [5-6, 12]. About 20% of the patients in our study had both pneumonia and septicemia, which indicates that this is a very severe and fatal infectious disease. It is a very important issue to understand early diagnosis, treatment and vaccine assistance.

The immune function in patients with subclinical diseases is lower than other patients. According to our analysis, the percentage of containing subclinical diseases in these patients and the risk of Streptococcus pneumoniae infection may increase with age.

Conclusion

It has been a year since Streptococcus pneumoniae infection classified as a communicable disease. Although a long term, continuous investigation is still absent, data have been collected from all areas in Taiwan to help us understand the present situation of this disease in Taiwan and give us a reference for developing related immunization policy. Recently, GIS is commonly used in disease monitoring. Based on the spatial database and geographic modeling analysis, it may provide spatial and geographical information and help further investigation of the relationship between the distribution/transmission of patients/disease resources and geographic characteristics. We will continue the monitoring work and evaluate the disease prevention effects and results associated with other medical data, e.g. national health insurance data.

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