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Original Article

Analysis on District Medical Resources and Preparedness Gap on the Health Outcomes of the 2009 H1N1 Influenza Pandemic in Taiwan

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Abstract

To examine and revise the pandemic influenza preparedness and response plan , and to help policy makers decide how to distribute medical resources, we analyzed the relationship between the clinical outcomes of the 2009 H1N1 pandemic, including the proportion of patients with severe complications and deaths, and the distribution of medical resources and the level of pandemic preparedness during the H1N1 epidemic between 2009 and 2010 in Taiwan. Questionnaires were distributed to hospitals and health authorities in all 25 counties and cities in Taiwan, evaluating the healthcare services, laboratory testing results, and distribution of medical resources between March and May, 2009. The preparedness in response to pandemic influenza of the 25 county and city governments was reviewed by the Taiwan Centers for Diseases Control (Taiwan CDC) using a structured evaluation in October, 2008. The numbers of severe influenza-related complications and deaths notified through the Communicable Disease Reporting System between July 1, 2009 and June 30, 2010 were analyzed using regression model. As a result, 264 questionnaires from local health bureaus and 226 questionnaires from hospitals and clinics were returned; the response rates were 71% and 46% respectively. The number of severe influenza-related complications was 939, and 44 patients died. Increasing antiviral stockpile to cover additional 0.01% of our population can statistically decrease 1% of the risk of severe flu-associated complication (p=0.001). Increasing 1% of preparedness also can statistically decrease 1.6% of the risk of

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severe flu-associated complication ($p<0.001$). Although not statistically significant, increasing 1% of preparedness can decrease 2% of the risk of flu mortality. According to this study, medical resources and preparedness were associated with severe influenza-related complications but not associated with death, which might be due to the fact that the 2009 H1N1 pandemic was moderate in severity, and the convenience and proximity of medical care facilities in areas with sufficient medical resources. The relatively low number of deaths (44) probably associated with the vaccination campaign may also result in the insignificant analysis result. The number of flu clinics was highly associated with the antiviral stockpile and the antiviral successfully lowered the risk of severe influenza-related complications. Although there were differences in the distribution of medical resources and the level of preparedness among counties and cities, the distribution of medical resources was planned and controlled by a central command center during the pandemic, and the influence of the minimal geographic difference was insignificant. However, because the difference in the level of preparedness in different counties and cities did affect the risk of severe influenza-related complications and death, maintaining the same level of preparedness is of great importance. We recommended that evaluation of preparedness should be taken into consideration when making policies in response to communicable diseases.

Keywords: pandemic influenza, H1N1, medical resources, antiviral

Introduction

Richard Coker *et al.* from University of London evaluated the overall preparedness toward influenza pandemic in European and Asian countries, and observed that the preparedness was varied because of differences in economic status, health care systems, government structures, medical resources, and control measures, so the ability to mobilize and respond could also be varied accordingly [1-2]. The Taiwan Centers for Diseases Control (Taiwan CDC) also evaluated the preparedness plan of all 25 counties and cities in Taiwan in 2008, and found significant differences, especially in the amount of medical care personnel and the antiviral stockpile. The largest difference could be up to 40% [3]. In addition, Taiwan CDC had participated in the European Union Framework Program 7 – the AsiaFluCap project initiated by Richard Coker to estimate the responsiveness facing a pandemic influenza since 2008. Through qualitative and quantitative studies, field investigation, literature review, questionnaire administration,

modeling analysis, and GIS systems; the health care systems, government structures, storage and distribution of medical resources, and capacity of mobilization of Thailand, Vietnam, Indonesia, Cambodia, Lao, and Taiwan were compared and analyzed [4]. Based on modeling analysis, risk of mortality increased in regions short of resources in all countries. Although lack of resources was not a major problem in Taiwan, the flu-associated death still increased in districts with smaller antiviral stockpile and less ventilator. The magnitude of increased death in Taiwan was less than that in the other 5 Asian countries, which could be a result of the small territory, sufficient resources, effective distribution, and allocation controlled by a central command center [5].

This study was designed based on the Work Package 3 of the AsiaFluCap project to evaluate the resource characterization [4]. In combination with the number of flu clinics in 2010, the storage of medical resources between March and May 2009, evaluated through questionnaires, represented the total resources that can be used in responding to the 2009 H1N1 pandemic. To analyze the relationship between the risks of severe influenza-related complications and influenza-related deaths during the 2009 H1N1 pandemic and the distribution of medical resources and the level of preparedness, structural reviews in 25 counties and cities were conducted by Taiwan CDC in October 2008.

Materials and Methods

Study design

This is a cross-sectional study. Questionnaires aiming to evaluate the reserve of medical resources during March – May 2009 were delivered to 25 counties and cities, including Taipei City, Kaohsiung City, Keelung City, Hsinchu City, Taichung City, Chiayi City, Tainan City, Taipei County, Yilan County, Taoyuan County, Hsinchu County, Miaoli County, Taichung County, Zhanghua County, Nantou County, Yunlin County, Chiayi County, Tainan County, Kouhsiung County, Pingtung County, Taitung County, Hualian County, Penghu County, Kinmen County, and Lianjiang county. The level of preparedness in response to pandemic influenza in 25 counties and cities was reviewed by structural examination in October 2008 [3]. Both results were used to analyze their associations with the numbers of severe influenza-related complications and deaths reported through the Communicable Diseases Reporting System between July 1, 2009 and June 30, 2010.

Questionnaires

Medical resources investigated in the questionnaire, including healthcare infrastructure, facilities, equipment, and manpower, were identified according to systemic literature review and listed by 24 public health professionals or doctors using Delphi; final consensus was reached after discussions and meetings. There were two versions of the questionnaire targeting districts and hospitals respectively.

1. To evaluate medical resources in different districts
   a. Summarize the available medical facilities, drugs, personal protective

equipment in local health bureaus, outpatient clinics, pharmacies, private laboratories in all 25 counties and cities. Hospitals were not included in this survey except for gathering information regarding human resources.

b. Questionnaires were filled out by the director of the local health bureau or his representative, the contents of which were divided into 6 categories: health care providers, human resources, facilities, personal protective equipment and drugs, laboratory capacity, and communication devices.

2. To evaluate medical resources in hospitals

a. District or larger-scale general hospitals in all 25 counties and cities registered with the Bureau of Medical Affairs of the Department of Health were included. The number of hospital beds, facilities, drugs, and personal protective equipment were calculated.

b. The person in charge of the hospital or his representative was designated to fill out the questionnaires. In addition to some basic information about the hospitals, questions were divided into 5 categories: the number of beds, facilities, personal protective equipment and drugs, laboratory capacity, and communication devices.

Questionnaire analysis

We used Excel to establish dataset. For questionnaires that were not answered completely or with missing data, estimation was done based on district characteristics and population size. Since the number of hospital beds and health care professionals were mandatory to register with the national health statistics system, the numbers of hospital beds and health care professionals registered in 2010 were used for this analysis. As for the antiviral stockpile and the number of mechanical ventilator, we used two-step model to estimate the reserve: we first estimated the presence of antiviral stockpile and ventilator, then the capacity.

Evaluation of the preparedness in response to pandemic flu

In October 2008, Taiwan CDC conducted a structural review on the influenza pandemic response plan in all 25 cities and counties. Eight major goals, including response mechanism, epidemic surveillance system, community actions, use of antivirals, management of equipments and supplies for disease control, health care system, risk communication, and continued operation of local governments, and 54 operating objectives were evaluated. The score of each operating objective was gathered to calculate the level of overall preparedness in each county or city [3]. The level of overall preparedness was used as a variable in this study and the coding for each county or city was unified.

Statistic analysis

We used Poisson regression to evaluate the association between the medical resources in 25 counties and cities and the number of severe influenza-related complications and deaths. Variables that may influence the response to influenza pandemic were used to evaluate the capacity of medical resources, including the number of hospital beds, the

number of health care professionals, the antiviral stockpile, the number of ventilators, the number of flu clinics, and the level of preparedness. Relative risks (RR) and 95% confidence interval for each factor were analyzed. The proportions of severe influenza-related complications and death were calculated by dividing the actual number of severe influenza-related complications/ deaths by the population in the county or city. Pearson correlation was used to evaluate the association between the level of preparedness and the proportion of severe influenza-related complications and death.

Results

Number of patients and the results of questionnaires

Between July 1, 2009 and June 30, 2010, 939 patients with severe influenza-related complications and 44 deaths were reported through the Communicable Diseases Reporting System. Questionnaires were delivered to 369 local health bureaus and 495 district general hospitals or large-scale hospitals since June 11, 2009, evaluating the available hospital beds, health-care personnel, ventilators, antiviral stockpile, and other medical resources that can be used in the pandemic during March - May 2009. For local health bureaus and hospitals, the response rates were 71% (264) and 46% (226), respectively.

The proportion of patients with severe influenza-related complications and death

Among the 25 counties and cities in Taiwan, the population size was largest in County/City H (16.4%), followed by County/City A (11.32%) and County/City I (8.54%). The population size of County/City H was about two times of that of County/City I. A total of 939 patients were reported to have severe influenza-related complications between July 1, 2009 and June 30, 2010, while the number of deaths was 44. Considering the proportion of severe influenza-related complications in every 10,000 persons in a county, it was highest in County/City V (266.86%), County/City L (98.04%), and County/City H (54.43%). The mortality rate in every 10,000 persons in a county was highest in County/City W (12.91%), County/City V (8.8%), and County/City C (5.15%). The details are listed in Table 1.

Distribution of medical resources

The number of hospital beds was highest in County/City A (21,216), where the population size was the second highest. The population size was largest in County/City H, with the second highest number of beds (12,457), which was about half of that in County/City A. The number of flu clinics was highest in County/City H (202), while there were only 2 in County/City U. The number of health care personnel was highest in County/City A (27,889), followed by County/City H (14,384), which was about half of that in County/City A. Anti-viral stockpile was largest in County/City A, which could supply 12,122 persons, followed by County/City E, which could supply 3,080 persons. The later was about one forth of the former. The number of mechanical ventilator was highest in County/City A

(2,371), followed by County/City E (1,256), which was about half of that in County/City A.

Considering the available resources divided by the population size of a county or a city, the proportion of hospital beds was highest in County/City G (1.28%), County/City V (1.26%), and County/City E (0.86%). The proportion of flu clinics in every 10,000 persons was highest in County/City Y (5.06), County/City V (1.61), and County / City K and County/City N (both 0.45). The proportion of health care personnel was highest in County/City G (1.21%),County/City A (1.07%), and County/City E (1.04%). The proportion of anti-viral stockpile was highest in County/City Y (0.78%), County/City A (0.46%), and County/City W (0.31%). The number of ventilators in every 1,000 persons was highest in County/City G (1.74), County/City E (1.17), and County/City V (1.15).

Table 1. Population size, number of severe influenza-related complications, and number of deaths in each county / city

County / City	Population size (23,078,139)		Severe influenza-related complications (939)		Deaths (44)	
	Number	Proportion in general population	Number	*Proportion (/10,000 persons)	Number	*Mortality rate (/10,000 persons)
A	2,612,605	11.32%	119	45.55%	4	1.53%
B	1,526,840	6.62%	39	25.54%	3	1.96%
C	388,624	1.68%	13	33.45%	2	5.15%
D	409,365	1.77%	13	31.76%	0	-
E	1,070,792	4.64%	23	21.48%	2	1.87%
F	770,363	3.34%	28	36.35%	1	1.30%
G	274,051	1.19%	8	29.19%	0	-
H	3,857,840	16.72%	210	54.43%	11	2.85%
I	1,970,358	8.54%	56	28.42%	2	1.02%
J	508,157	2.20%	23	45.26%	0	-
K	461,251	2.00%	12	26.02%	0	-
L	560,975	2.43%	55	98.04%	0	-
M	1,559,703	6.76%	42	26.93%	2	1.28%
N	1,311,761	5.68%	41	31.26%	4	3.05%
O	530,941	2.30%	10	18.83%	0	-
P	722,858	3.13%	23	31.82%	1	1.38%
Q	547,525	2.37%	13	23.74%	1	1.83%
R	1,103,909	4.78%	29	26.27%	2	1.81%
S	1,241,902	5.38%	36	28.99%	2	1.61%
T	877,735	3.80%	41	46.71%	1	1.14%
U	95,292	0.41%	5	52.47%	0	-
V	341,001	1.48%	91	266.86%	3	8.80%
W	232,290	1.01%	8	34.44%	3	12.91%
X	92,111	0.40%	1	10.86%	0	-
Y	9,890	0.04%	0	-	0	-

*(number of patients with severe influenza-related complications or number of deaths in a county or city) / (population size) * 10,000

The level of overall preparedness was highest in County/City I (79.6%) and County/City X (39.8%). All of the counties and cities had a level of overall preparedness less than 80%; 8 of them were higher than 70% while 3 of them were lower than 60%. The mean level of preparedness was 66.07%. Eleven counties or cities had a level of overall preparedness higher than average while 14 had a level of overall preparedness less than average (Table 1, continued).

Univariate analysis on the association between medical resources / preparedness and the proportion of severe influenza-related complications / mortality

Univariate analysis revealed significant associations between the proportion of severe influenza-related complications and the number of hospital beds (RR = 1.009, 95% CI: 1.006 - 1.012), the number of ventilators (RR = 1.003, 95% CI :1.001 - 1.006), and the overall preparedness (RR = 0.988, 95% CI :0.980 - 0.997) ($p < 0.001$).

Table 1 (continued)

County / City	Number of hospital beds (135,40)		Number of flu clinics (1,532)		Number of health care personnel (145,091)		*Anti-viral stockpile (29,628)		Number of ventilator (15,037)		Level of overall preparedness
	Number	Proportion (%)	Number	Proportion (‰)	Number	Proportion (%)	Number	Proportion (%)	Number	Proportion (‰)	(%)
A	21,216	0.81	143	0.55	27,889	1.07	12,122	0.46	2,571	0.98	75.0
B	10,627	0.70	81	0.53	11,991	0.79	1,143	0.07	1,050	0.69	65.7
C	2,152	0.55	31	0.8	2,147	0.55	312	0.08	207	0.53	64.8
D	2,193	0.54	29	0.71	2,594	0.63	446	0.11	220	0.54	60.2
E	9,255	0.86	122	1.14	11,153	1.04	3,080	0.29	1,256	1.17	75.9
F	3,923	0.51	42	0.55	5,547	0.72	450	0.06	369	0.48	66.7
G	3,514	1.28	9	0.33	3,316	1.21	639	0.23	477	1.74	63.9
H	12,457	0.32	202	0.52	14,384	0.37	1,464	0.04	1,400	0.36	64.8
I	12,219	0.62	121	0.61	13,266	0.67	994	0.05	985	0.50	79.6
J	2,123	0.42	53	1.04	1,730	0.34	296	0.06	299	0.59	57.4
K	3,728	0.81	67	1.45	2,986	0.65	317	0.07	347	0.75	78.7
L	3,221	0.57	30	0.53	2,224	0.4	221	0.04	348	0.62	69.4
M	7,952	0.51	102	0.65	7,280	0.47	1,005	0.06	815	0.52	64.8
N	7,130	0.54	190	1.45	7,233	0.55	2,017	0.15	868	0.66	72.2
O	3,148	0.59	25	0.47	2,314	0.44	682	0.13	286	0.54	68.5
P	3,381	0.47	60	0.83	3,067	0.42	437	0.06	400	0.55	76.9
Q	3,066	0.56	33	0.6	2,626	0.48	383	0.07	323	0.59	63.0
R	5,573	0.50	51	0.46	5,926	0.54	615	0.06	698	0.63	60.2
S	6,802	0.55	21	0.17	7,664	0.62	801	0.06	774	0.62	71.3
T	5,298	0.60	26	0.3	4,885	0.56	741	0.08	635	0.72	50.9
U	455	0.48	2	0.21	420	0.44	137	0.14	62	0.65	71.3
V	4,294	1.26	55	1.61	2,953	0.87	304	0.09	393	1.15	65.7
W	1,383	0.60	27	1.16	1,250	0.54	731	0.31	199	0.86	63.9
X	251	0.27	5	0.54	204	0.22	203	0.22	55	0.60	39.8
Y	40	0.40	5	5.06	42	0.42	77	0.78	0	-	61.1

*Each patient was supposed to consume 10 tablets of antiviral drug. The anti-viral stockpile referred to the medication reserved in each county or city government. The stockpile managed by the central governmental was not included.

None of these variables was found to be associated with mortality rate. (Table 2)

Analysis on the associations between medical resources

The number of hospital beds was found to be significantly associated with the number of health care personnel (R=0.84) (p<0.001) and the number of ventilators (R=0.85) (p<0.001). The number of flu clinics was significantly associated with the scale of the antiviral stockpile (R=0.74) (p<0.001). The number of health care personnel was significantly associated with the number of ventilators (R=0.74) (p<0.001). (Table 3)

Table 2 Association between medical resources / preparedness and the proportion of severe influenza-related complications / mortality

Resources	Proportion of severe influenza-related complications		Mortality rate	
	RR (95%CI)	p	RR (95%CI)	p
[1]Hospital bed	1.009 (1.006-1.012)	**<0.001***	1.001 (0.986-1.016)	0.874
[2]Flu clinics	1.004 (1.002-1.005)	**<0.001***	1.006 (1.000-1.011)	0.059
[1]Health care personnel	0.999 (0.997-1.002)	<0.852	0.998 (0.985-1.010)	0.717
[1]Antiviral stockpile**	0.998 (0.993-1.003)	0.457	1.004 (0.983-1.025)	0.723
[3]Ventilator	1.003 (1.001-1.006)	**0.004***	1.001 (0.990-1.013)	0.763
Level of overall preparedness	0.988 (0.980-0.997)	**0.009***	0.984 (0.945-1.024)	0.421

[1]The stockpile was sufficient to supply one-ten-thousandth of the population；[2]The stockpile was sufficient to supply one-millionth of the population；[3]The stockpile was sufficient to supply one-hundred-thousandth of the population

* p< 0.001

** The anti-viral stockpile referred to the medication reserved in each county or city government. The stockpile managed by the central governmental was not included.

Table 3 Association between medical resources and level of overall preparedness

	Hospital beds	Flu clinics	Health care personnel	Antiviral stockpile**	Ventilator	Level of overall preparedness
Hospital beds	1.00					
Flu clinics	-0.04 (p=0.838)	1.00				
Health care personnel	**0.84*** (p<0.001)	-0.10 (p=0.641)	1.00			
Antiviral stockpile	0.05 (p=0.820)	**0.74*** (p<0.001)	0.19 (p=0.372)	1.00		
Ventilator	**0.85*** (p<0.001)	-0.34 (p=0.097)	**0.77*** (p<0.001)	-0.04 (p=0.863)	1.00	
Level of overall preparedness	0.30 (p=0.139)	-0.01 (p=0.957)	0.39 (p=0.056)	-0.07 (p=0.742)	0.12 (p=0.555)	1.00

* p< 0.001

**The anti-viral stockpile referred to the medication reserved in each county or city government. The stockpile managed by the central governmental was not included.

Multivariate analysis on the association between antiviral stockpile, hospital beds, preparedness and the proportion of severe influenza-related complications and mortality

According to previous analysis, the antiviral stockpile was significantly associated with the number of flu clinics, the number of hospital beds, the number of health care personnel, and the number of ventilators. Because the number of hospital beds was associated with the number of health care personnel and ventilators, we used the number in combination with the antiviral stockpile to represent the available medical resources in this study. Using multivariate analysis to analyze the relative risk of severe influenza-related complications, increasing the antiviral stockpile to supply additional one-ten-thousandth of the population could significantly decrease the relative risk by 1%($p<0.001$). The relative risk would significantly increase by 1.3% if we increase the number of hospital beds by one in ten thousandth of the population ($p<0.001$). Finally, the relative risk would decrease by 1.6% if the level of overall preparedness could be increased by 1% ($p<0.001$). Considering the relative risk of mortality, although not statistically significant, it would decrease by 2.2 % if the level of overall preparedness could be increased by 1% (Table 4).

Association between population density and proportion of severe influenza-related complications and deaths

The population density of each county or city registered with the Ministry of Interior in 2009 was used for analysis. There was no significant association between the population density and the proportion of severe influenza-related complications or deaths (Figure).

Discussion

In this study, we evaluated the association between the medical resources of all 25 counties and cities in Taiwan between March and May 2009 and the number of patients with severe influenza-related complications and the number of deaths. We found that medical resources concentrated in County/City A and County/City H where more severe influenza-related complications and higher mortality were found. Considering the medical resources divided by the county/city population, the proportion of medical resources was highest in County/City A and County/City V. The proportions of

Table 4 Multivariate analysis on association between antiviral stockpile, hospital beds, level of overall preparedness and the proportion of severe influenza-related complications and mortality

Resources	Proportion of severe influenza-related complications		Mortality rate	
	RR(95%CI)	P	RR(95%CI)	P
[1]Antiviral stockpile**	0.990 (0.984-0.996)	**0.001**	1.007 (0.981-1.034)	0.597
[1]Hospital beds	1.013 (1.010-1.016)	**<0.001***	1.001 (0.983-1.020)	0.895
Overall preparedness	0.984 (0.974-0.993)	**<0.001***	0.978 (0.936-1.021)	0.312

[1]reserve for one in ten thousandth of the population； *p< 0.001；
**The anti-viral stockpile referred to the medication reserved in each county or city government. The stockpile managed by the central governmental was not included.

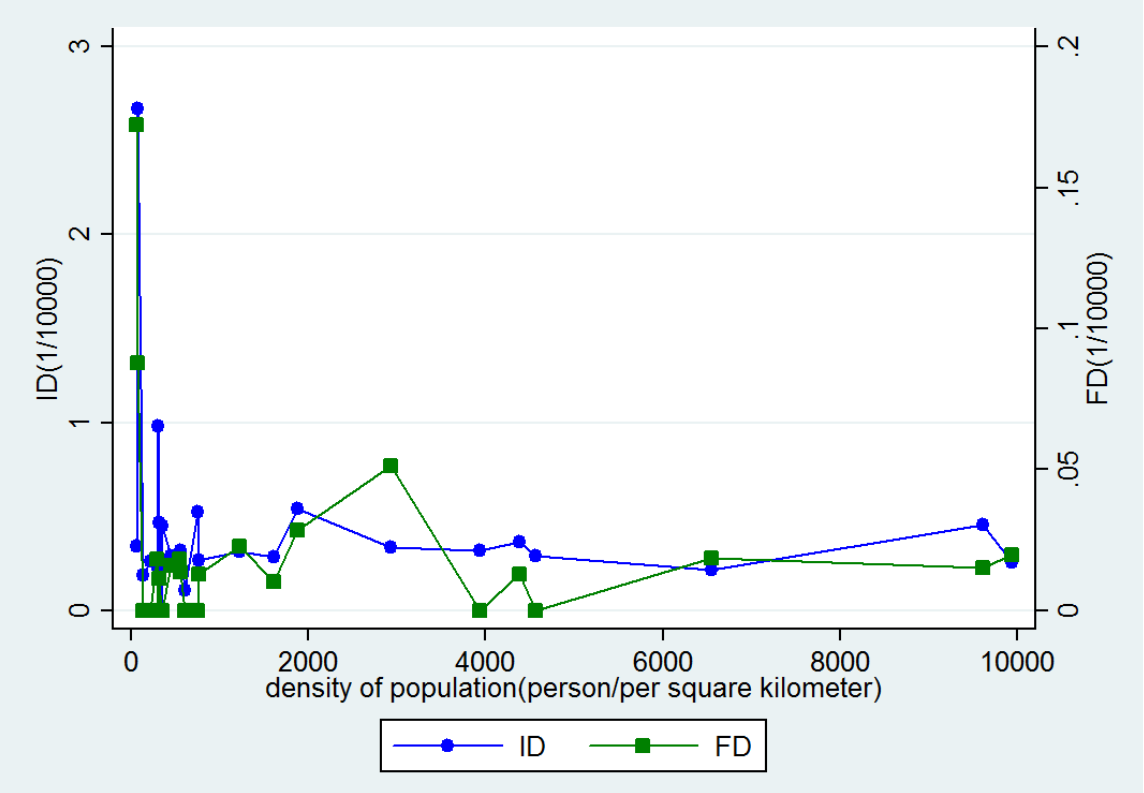

Figure Associations between population density and proportion of severe influenza- related complications and deaths

ID: density of severe influenza-related complications (in every ten thousand population)
FD: density of fatality (in every ten thousand population)

severe influenza-related complications and mortality rate in every ten thousand population were higher in County/City V, County/City L, and County/City W. So the population density was thought to be an important confounding factor. After being corrected by the population density, univariate analysis revealed that the reserve of medical resources, including the number of hospital beds, the number of flu clinics, and the number of ventilators, as well as the level of overall preparedness, was significantly associated with the proportion of severe influenza-related complications, but not with the mortality rate. Our finding was not consistent with the modeling analysis done by Rudge *et al.* in England [5], which might be a result of the fact that the 2009 H1N1 pandemic being moderate in severity and the relative low number of deaths (44) that might lead to a non-statistic significant result. In addition, as the medical resource reserve might change over time, especially the antiviral stockpile, the actual capacity during the pandemic might be different from the capacity at the time we investigated.

Through univariate analysis, the more the hospital beds, the higher the proportion of severe influenza-related complications. This might be a result of the case definition for reporting severe influenza-related complications, which included hospitalization as one of the notification criteria; and the government would subsidize the expense of antivirals for those reported with severe influenza-related complications. The use of

ventilator was thought to be associated with mortality rather than severe influenza-related complications, but our study results were against the assumption, which might be due to a significant association between the number of ventilators and the number of hospital beds (R=0.85). Our analysis also showed that the more the flu clinics, the higher the risk of severe influenza-related complications. The number of flu clinics was significantly associated with the size of antiviral stockpile (R=0.74). As flu clinics provided influenza rapid diagnostic tests, those who visited flu clinics and were found to have a positive influenza test result were immediately prescribed antivirals. Therefore, counties/cities with larger antiviral stockpile were found to have lower proportion of severe influenza-related complications, while counties/cities with more flu clinics were found to have higher proportion of severe influenza-related complications.

In the multivariate analysis, increasing the antiviral stockpile to support additional one in ten thousand of the population could significantly decrease the relative risk of severe influenza-related complications by 1 %. This finding was consistent with previous studies in England, the United States, and Japan [6-8]. We also found that the higher the level of overall preparedness, the relative risk of severe influenza-related complications would be lower. For every 1% increase in the level of preparedness, the relative risk would significantly decrease by 1.6%. According to the analysis, the decline in the number of patients from the 38th week in 2009 [10] could be a result of several factors: the 300 stations that have been subsequently designated for antiviral storage in the country since August 1, 2009, the coverage of antivirals in the National Health Insurance since August 15, 2009 [9], the implementation of policies and measures aimed at improving the accessibility of hospitals, government-funded rapid diagnostic tests and government-funded antivirals, the establishment of flu clinics in the nation, and intensive health education. Considering the number of hospital beds, we found that increasing the number of beds to supply additional one in ten thousand of the population would significantly increase the relative risk of severe influenza-related complications by 1.3%, which might be due to the fact that hospitalization was one of the criteria in the case definition for reporting severe influenza-related complications. When a patient was hospitalized due to severe influenza-related complications and reported to the health authority, our government would cover the cost of antivirals for the patient. As a result, the more the hospital beds, the more number of patients were reported.

Since influenza is a respiratory infection, transmitted by aerosol or close contact, the population density may affect the extent of an outbreak. However, our study results (Figure 1) showed differently. The H1N1 influenza vaccination program was launched one November 1, 2009. By March 2010, the national coverage reached 25% and the coverage rate among health care workers reached 76%, which was the highest in the world [11]. Considering the duration between vaccination and the production of effective antibodies, we used December 1, 2009 to separate the 44 deaths into 2 groups.

Thirty-three of them died before the immunization became while 11 died after. In other words, the control measures implemented by our government, including vaccination and non-pharmaceutical interventions such as health education and class suspension, could have helped lowering the mortality. In addition, the moderate pandemic might also had diluted the effects of population density.

In conclusion, there were some disparity of medical resources among counties and cities, but the disparity did not significantly increase the risk of severe influenza-related complications or deaths. In terms of the level of overall preparedness in a county/city, according to the results of univariate and multivariate analyses, increasing the level of preparedness by 1% could decrease the relative risk of severe influenza-related complications by 1.6% and the mortality rate by 2.2%. Therefore, the response mechanism, epidemic surveillance system, community actions, use of antivirals, management of equipments and supplies for disease control, health care system, risk communication, and continued operation of local governments were of great value in controling the 2009 H1N1 pandemic. The modest effects of medical resources disparity could be due to the small territory size, the good delivery system, and the allocation of anti-viral drugs arranged by the central government. On the other hand, as the level of overall preparedness had greater influence on the extent of the H1N1 epidemic, improvement in the level of preparedness should be continued and included in our future evaluation and plan.

The cross-sectional study has some limitations. For instance, we only analyzed the severe influenza-related complications and death cases, but not those with minor symptoms. The small number of deaths could lead to a statistically insignificant result. The reserve of medical resources in counties/cities varied over time. The antiviral stockpile managed by the central government was not included, and the commander of the Central Epidemic Center had the authority to flexibly relocate all medical resources. Further analysis might be needed to clarify the results and doubtful points.

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Overview of Invasive *Streptococcus Pneumoniae* Infection in Taiwan, 2008 - 2010

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Abstract

This article analyzes the general situation of 2,233 cases of invasive *Streptococcus pneumoniae* infection and 2,141 isolated strains nationally and locally in Taiwan from January of 2008 to December of 2010. The majority of cases are situated in northern Taiwan with 27% of the national numbers, followed by middle Taiwan with 21%. The main epidemic season of *Streptococcus pneumoniae* infection each year starts from December and lasts until March of the following year, whereas the period between June and September has the lowest incident rate. As of March, 2010, the number of infections in Taiwan has shown increase, especially in northern Taiwan, and

among children below 5 years of age. The yearly incident rate in each region is approximately 3 cases in every 100,000 persons, mainly infecting subjects below 5 years of age and above 65 years of age with a total of more than 10 cases per 100,000 persons each year. By analyzing the serotypes of these isolated strains, it is found that the serotype 19A strain cases has mostly increased among children in the northern region and has become the main epidemic serotype of strain in the nation as of 2010; therefore, influencing the protection effectiveness of the currently used 7-Valent Pneumococcal Conjugate Vaccine (PCV7). As of 2010, the coverage rate of PCV7 among children under 5 years of age in northern Taiwan and Taoyuan, Hsinchu, and Miaoli areas has dropped to less than 35%. The change in the serotype of the strain caused the drop in the vaccine coverage rate, has also greatly impacted the infection of invasive *Streptococcus pneumoniae*. Thus, the continuous monitoring of this isolated strain can provide immediate and effective epidemic data for preventive strategy reference.

Keywords: invasive *Streptococcus pneumoniae* infection, the 7-Valent Pneumococcal Conjugate Vaccine (PCV7), serotype 19A

Introduction

Streptococcus pneumoniae is one of the important pathogens that cause human respiratory tract infections and severe invasive disease. In 2005, the World Health Organization estimated 1.6 million people die from *Streptococcus pneumoniae* infection each year, among which 1 million are children below five years of age, and most live in undeveloped countries. In Europe and the Americas, invasive *Streptococcus pneumoniae* infection yearly incident rate is approximately 10 to 100 cases per 100,000 persons [1-2].

Streptococcus pneumoniae is a normal human body flora, yet causes acute invasive infection when the body's immune system becomes weak. The main targets of the infection are among children below 5 years of age, elderly above 65 years of age, and those with dysfunctional immune systems caused either congenitally or by some other disease. Due to the differences in capsular polysaccharide of *Streptococcus pneumoniae*, 92 different pneumococcal capsular polysaccharide serotypes are currently known [1]. Depending on time, ages, and countries, the serotype that causes invasive *Streptococcus pneumoniae* infection and its drug-resistance all differ; for example, serotype 3 mainly infects the elderly, serotypes 1, 18C, and 7F are the main serotypes that causes epidemics in Europe and the Americas, the drug-resistance towards penicillin is higher in Asia than in European and American countries [4-7]. In Germany, domestic studies focused on different regions within the country also show differences in vaccine coverage rates and drug-resistance towards antibiotics. In the past, national and regional studies have also been made in Taiwan, but none have compared the infections of invasive *Streptococcus pneumoniae* in the six main regions of Taiwan [3-7].

In 1983, the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) was approved for sale in the U.S., and can prevent infection from 23 different *Streptococcus pneumoniae* serotypes. In 2000, the 7-Valent Pneumococcal Conjugate Vaccine (PCV7) was released, focusing mainly on children below 5 to prevent from infection from 7 different *Streptococcus pneumoniae* serotypes. Afterwards, due to the changes in the epidemic serotypes caused by the use of vaccines, vaccines that include more serotypes such as 10-valent and 13-valent have been released [8-9]. As of 1998, Taiwan has also continually approved and released several vaccines (PPV23, PCV7, PCV10, and PCV13).

The U.S. Centers for Disease Control and Prevention Active Bacterial Core Surveillance system shows, after the release of pneumococcal polysaccharide vaccine, the incident rate of invasive *Streptococcus pneumoniae* infections among children below one year of age has decreased to approximately 50 cases per 100,000 persons from 150 cases per 100,000 persons. Apart from providing the epidemic situation of invasive *Streptococcus pneumoniae* infections, more importantly, this surveillance system also assesses the effectiveness of the use of vaccines [10]. Taiwan Centers for Disease Control as of October 15, 2007, listed invasive *Streptococcus pneumoniae* infections as a fourth category legal contagious disease and began to officially monitor its epidemic situation in Taiwan. This study collects monitor data from the period between 2008 and 2010, analyzes the epidemic situation of invasive *Streptococcus pneumoniae* infections in Taiwan, and provides important references for prevention strategies of this infection such as the administration of vaccines, in order to lower the impact and harm caused by invasive *Streptococcus pneumoniae* infections to Taiwan's people.

Materials and Methods

A. Origin of invasive *Streptococcus pneumoniae* infection cases

As of October 15, 2007, invasive *Streptococcus pneumoniae* infection was announced as a fourth category legal contagious disease. Any invasive disease caused by *Streptococcus pneumoniae*, such as sepsis or meningitis, and samples taken under normal conditions from sterile regions, such as blood or cerebrospinal fluid where *Streptococcus pneumoniae* are isolated, are in line with notification definition. The subjects analyzed in this study are those reported invasive *Streptococcus pneumoniae* infections, 2,233 cases and the 2,141 strains isolated fit the definition, between January 1, 2008 and December 31, 2010. Their epidemiological data such as ages, gender, and residential city/county were collected and strain characteristics were also analyzed.

B. Identification of *Streptococcus pneumoniae*

Identification of *Streptococcus pneumoniae* uses blood culture medium (BD, USA) which includes 5% sheep blood, and by observation, it can be seen to form a smooth, grey-white, surrounded by an obvious α hemolytic, most of the colonies will form a dented, volcanic-like shape. The suspected colonies were extracted for further Gram staining for microscopic observation,

showing positive strains, single coccus, double coccus, or chain arrangement. In addition, suspected colonies are sent for sub-culture, and 5 μg optochin (BD, USA) paper disks are placed upon the first-marked area; after overnight culture, a suppressive circle larger than 14mm will form. Afterwards, a few drops of 10% sodium deoxycholate (CMP, Taiwan) are directly added to the colonies on the culture, where the colonies will dissolve without floatation.

C. Categorizing *Streptococcus pneumoniae* serotypes

Using the Quellung reaction, the bacterial suspension on an inoculating loop is added to another inoculating loop with a different type of anti-serum (SSI, Copenhagen, Denmark) and mixed on a slide; observation is then made under optical microscope, if the samples are of the same type, the capsule will show obvious swelling, and lead to the determination of its serotype.

Results

A. Geographic trends of invasive *Streptococcus pneumoniae* infection

A total of 2.233 cases of invasive *Streptococcus pneumoniae* infection were documented within the analyzed time period, among which 1,507 cases were male (67%). As for age distribution, 569 cases were under 5 years of age, 78 cases were aged between 6 and 19 years, 287 cases between 20 and 44 years, 503 cases between 45 and 64 years, and 796 cases above 65 years of age. According to the residential areas of the cases, the regions can be categorized as the Northern region (including Taipei City, New Taipei City, Keelung City, Yilan County, Penghu County, Kinmen County, and Lienchiang County), Tao-Chu-Miao region (including Taoyuan County, Hsinchu County, and Miaoli County), Middle region (including Taichung City, Changhua County, and Nantou County), Yun-Chi-Nan region (including Yunlin County, Chiayi County, and Tainan City), Kao-Ping region (including Kaohsiung City and Pingtung County), and Eastern region (including Hualien County and Taitung County) with 602, 310, 470, 355, 395, and 101 cases respectively. The main clinical symptoms portrayed consist of 1,352 pneumonia cases, 1,008 sepsis cases, 98 meningitis cases, and 34 peritonitis cases.

Figure analyzes the epidemic trends of invasive *Streptococcus pneumoniae* infections among the 5 geographical regions (due to the few numbers of cases in the Eastern region, the statistics were not included). The national incident rate reaches the highest each year starting from December and lasts until March of the following year, with an average of 4.6 cases per 100,000 persons; by April and May, the numbers start to decline with an average of 3.4 cases per 100,000 persons; the lowest numbers appear between June and September with an average of 2.0 cases per 100,000 persons; by October and November, the numbers start to increase to an average of 3.0 cases per 100,000 persons. By analyzing the trends in each geographical area, we can see a similar trend between Northern region trends and the national trend from 2008 to 2009, yet the numbers start to increase as of April, 2010 and the incident rates of each month (apart from September) are higher than previous years; in December, the rate reached 4.8 cases per 100,000 persons, higher than the previous

two years. As for Tao-Chu-Miao region, Middle region, Yun-Chia-Nan region, and Kao-Ping region, the trends are also similar to the national trend, however, in some areas, there are larger differences. In Kao-Ping region, the incident rate in November and December of 2008 exceeds the national trend of the same time period by 2.8 and 3.3 cases per 100,000 persons, and in December alone, the incident rate reached as high as 10.2 cases per 100,000 persons, which is also the highest monthly incident rate in this analysis. In Yun-Chia-Nan region, the incident rate of April, 2009 was 7.0 cases per 100,000 persons, 3.2 cases higher than the national incident rate of the same time. However, in the Northern region, the incident rate in January of 2009 was 2.7 cases per 100,000 persons lower than the national incident rate of the same time. All of these statistics show significant differences (P-values < 0.01).

B. Incident rate of invasive *Streptococcus pneumoniae* infections in different age groups

The incident rate of invasive *Streptococcus pneumoniae* infections in different age groups can be seen in Table 1. The yearly incident rate per 100,000 persons from 2008 to 2010 is 3.3, 2.9, and 3.1 cases respectively; the eastern region has the lowest number of reported cases, yet the incident rates per 100,000 persons are 7.1, 5.4, and 4.9 cases respectively, and statistically much higher than the national incident rate and the incident rates of other regions. In the Middle region, Yun-Chia-Nan region, and Kao-Ping region, the yearly incident rate is 3.0-3.8 cases per 100,000 persons; although higher than the 2.1-3.0 cases per 100,000 persons in the Northern region and Tao-Chu-Miao region, there is no statistical difference.

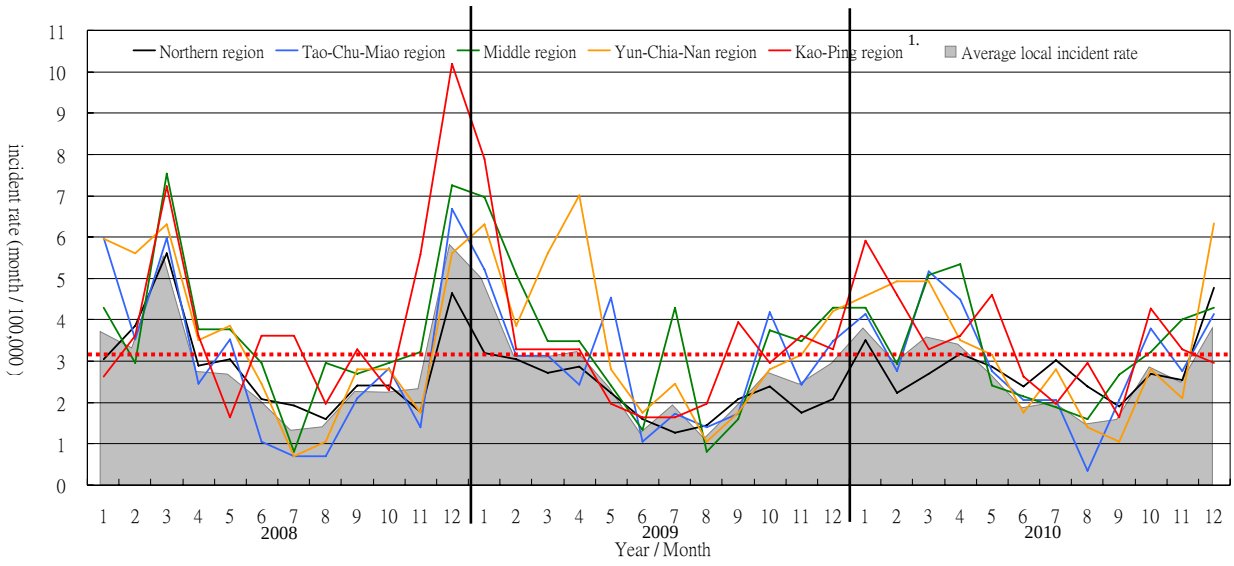

Figure Monthly Incident Rate (/ 100,000) of Invasive *Streptococcus Pneumoniae* Infections, January 2008 – December 2010

*Note: 1.Due to the low numbers of cases in Eastern region, the incident rate shows sudden peaks and drops; thus is not included.

2.The red dotted line indicates the total national number of cases of 2008-2010 divided by the total population.

The incident rate in each of the age groups between 2008 and 2010 are as following: for the elderly above 65 years of age, the national incident rate is 12.8, 9.3, and 9.4 cases per 100,000 persons; 15.9, 13.8, and 19.9 cases per 100,000 persons for children under 5 years of age; the two age groups mentioned are the main infected age groups in Taiwan. Although the incident rates of the two age groups in each of the regions has its highs and lows in the 3 years, the total average of incident rates is higher among children under 5 years of age (16.5 cases per 100,000 persons). The incident rates of children less than 5 years of age in the Northern region and Tao-Chu-Miao region of 2010 are 20.3 and 20.2 cases per 100,000 persons, which is almost double the incident rate in 2009 with 10.8 and 10.6 cases per 100,000 persons. In other regions and age groups, the difference is not as significant. There are fewer cases of children under 5 years of age in the Eastern region in 2009 and 2010 with only 1 and 5 cases, showing a larger fluctuation.

Among the infected age groups, there were more males than females, yet the differences in male and female case numbers among children under 5 years of age was smaller with a ratio of 0.8 to 2.0; apart from the Eastern region, the male to female ratio of elderly above 65 years of age is higher than those of children under 5, ranging from 1.6 to 4.2 (the data is not shown).

C. Distribution of isolated strain serotypes of invasive *Streptococcus pneumonia*

47 different serotypes exist among the 2,141 isolated strains (Table 2), with the serotype 14 as the most prevalent type in each year, yet its incident rate has started to decline over the years. The second most prevalent serotype is 23F; although it rose to take 15.8% of the isolates in 2009, it declined to 11.6% in 2010. Following, the third is serotype 3, which has gradually increased through the years, but with no great changes. Serotype 6B has reduced approximately by 1.5% each year. The changes of serotype 19F are similar to those of serotype 23F, where it rose to 10.6% in 2009 and declined to 8.8% in 2010. Among the prevalent serotypes, the serotype 19A has the greatest changes; its 5.5% in 2008 jumped to 15.7% in 2010.

In examining the isolated serotypes in each of the regions, the Northern region has the most types with 36 different serotypes, followed by Middle region, Kao-Ping region, Yun-Chia-Nan region, Tao-Chu-Miao region, and Eastern region. In Northern region and Tao-Chu-Miao region, the 3 most prevalent serotypes are 14, 19A, and 23F, accounting for 43.9% and 48.2% in the two regions. In Yun-Chia-Nan region, Kao-Ping region, and Eastern region, the 3 most prevalent serotypes are Type 14, 23F, and 3, with percentages of 49.4%, 56.1%, and 37.0%. In Middle region, serotypes 14, 23F, 3, and 19F are the most prevalent, with a total of 55.2%. Apart from Eastern region, the eight most prevalent serotypes (14, 23F, 3, 6B, 19F, 19A, 23A, and 6A) take up a total of more than 80%.

In looking at the serotypes of the isolated strains in each of the age groups, the older the age group, the more types of strains are isolated. Among children under 5 years of age,

the prevalent serotypes are 19A, 14, 23F, 6B, 19F, and 6A, with an 89.8% of isolated strains. In elderly above 65 years of age, the prevalent serotypes are 14, 3, 23F, 6B, 19F, and 23A, accounting for 71.6% of isolated strains. Among these, the distribution of serotypes 3 and 19A show significant differences in the two age groups (P-values < 0.01).

Table 1. Incident Rate (/ 100,000) of Invasive *Streptococcus Pneumoniae* Infections in Different Age Groups

Region	Year	＜5 years old	5~19 years old	20~64 years old	≧65 years old	All ages
Northern	2008	13.5	0.9	1.6	10.9	2.8
	2009	10.8	1.3	1.2	6.7	2.1
	2010	20.3	1.3	1.3	8.2	2.8
Tao-Chu-Miao	2008	17.0	0.7	1.4	11.2	3.0
	2009	10.6	1.6	1.7	9.4	2.8
	2010	20.0	1.6	1.5	7.5	2.9
Middle	2008	21.7	1.0	1.7	13.6	3.7
	2009	20.4	0.9	2.0	9.1	3.2
	2010	23.2	1.3	1.7	9.2	3.2
Yun-Chia-Nan	2008	13.6	0.5	2.1	10.5	3.3
	2009	20.5	0.8	1.7	10.3	3.4
	2010	15.6	1.2	1.6	10.9	3.2
Kao-Ping	2008	12.4	0.9	2.3	17.9	3.8
	2009	10.1	0.8	1.9	12.2	3.0
	2010	18.3	0.6	2.0	10.9	3.3
Eastern	2008	23.5	2.9	4.9	21.0	7.1[1]
	2009	4.1	0.0	5.4	13.9	5.4
	2010	21.5	0.0	3.5	13.8	4.9
Nationwide	2008	15.9	0.9	1.9	12.8	3.3
	2009	13.8	1.1	1.7	9.3	2.9
	2010	19.9	1.2	1.6	9.4	3.1

*Note: 1. the incident rate in the Eastern regions show more significant difference than other regions (P-values < 0.01).

Table 2. Time, Region, and Age Group Distribution of Invasive *Streptococcus Pneumoniae* Strain Serotypes

	Year (%)			Region (%)						Age Group（%）			Total
Serotype	2008	2009	2010	Northern	Tao-Chu-Miao	Middle	Yun-Chia-Nan	Kao-Ping	Eastern	＜5y	5~64y	≧65y	(%)
14	20.2	19.1	15.7	18.5	18.9	15.2	19.2	22.1	13.0	16.6	18.8	19.1	18.4
23F	13.7	15.8	11.6	12.1	12.0	14.8	12.7	17.0	13.0	16.0	11.3	14.9	13.6
3	11.8	14.3	14.0	11.1	10.3	12.6	17.5	17.0	11.0	3.0	15.3	17.8[3]	13.3
6B	11.4	9.9	8.5	11.2	9.6	11.9	8.9	8.1	6.0	14.6	8.4	8.8	10.0
19F	8.1	10.6	8.8	8.0	6.6	12.6	9.5	8.4	9.0	12.2	8.9	7.4	9.1
19A	5.5	6.4	15.7[2]	13.3[2]	17.3[2]	6.2	5.3	3.8	7.0	25.1	5.5	2.9[3]	9.2
23A	4.2	4.0	2.9	3.1	3.7	5.3	4.4	2.2	3.0	2.2	4.5	3.7	3.7
6A	2.6	3.3	4.3	4.3	4.7	2.0	2.7	3.2	4.0	5.4	3.3	2.2	3.4
Other	22.6	16.6	18.3	18.3	16.9	19.4	19.8	18.3	34.0	5.0	24.1	23.3	19.3
Number of strains	769	658	714	578	301	453	338	371	100	501	880	760	2,141
Type[1]	37	37	38	36	27	31	28	30	25	18	42	39	47

*Note:1. Number of all identified serotypes

2. The percentage of serotype 19A between 2009 and 2010 in Northern region or Tao-Chu-Miao region and other regions shows significant differences (P-values < 0.01).

3. Serotypes 3 and 19A show significant differences in the age groups of children under 5 and elderly above 65 (P-values < 0.01).

D. Vaccine coverage rate of invasive *Streptococcus pneumoniae*

Currently, *Streptococcus pneumoniae* vaccines used worldwide include 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23), 7-Valent Pneumococcal Conjugate Vaccine (PCV7), 10-Valent PCV- (PCV10), and 13-Valent PCV (PCV13); different vaccines are administered for different age groups. Table 3 shows the coverage rate for Pneumococcal Conjugate Vaccine on children less than 5 years of age and assesses the protection effectiveness for different vaccines. From 2008 to 2010, the coverage rate of PCV7 vaccine for isolated strains from children under 5 years of age in all regions (apart from nationwide and Eastern region) has started to decline, especially in the Northern region where the 69.8% coverage rate in 2008 dropped to 30.2% in 2010, showing an obvious decline. With fewer infections in the Eastern region, the total coverage rate for isolated strains in children under 5 years of age is 25%. In addition, the coverage rate of isolated strains in 2010 in the North (including Northern region and Tao-Chu-Miao region) and middle-south (including Middle region, Yun-Chia-Nan region, and Kao-Ping region) is 31.6% and 64.5%, showing significant differences. PCV10 has 3 more serotypes than PCV7 (1, 5, and 7F), of which seldom appear in Taiwan; therefore, has similar coverage rates to PCV7. PCV13 has the additional serotypes of 3, 6A, and 19A, which has significantly raised the coverage rate of the isolated strains of the regions to over 90%, with the exception of the Eastern region with only 66.7%. PPV23 is mainly administered to the age group of elderly above 65 years of age, of which the 23 types of serotypes reaches an approximate coverage rate of isolated strains nationwide and regionally 80 -93% (data is not shown).

Table 3. Yearly and Regional Analysis of Pneumococcal Conjugate Vaccine Coverage Rate among Children Under 5 Years-Old

Vaccine Type[1]	Region	2008 (%)[2]	2009 (%)	2010 (%)	Total (%)
PCV7	Northern	69.8	61.8	30.2[3]	51.7
	Tao-Chu-Miao	51.6	52.6	34.3	46.7
	Middle	82.6	69.0	65.2[4]	72.9
	Yun-Chia-Nan	75.0	79.3	57.1	70.2
	Kao-Ping	73.7	73.3	69.2	72.3
	Eastern	33.3	100.0	0.0	25.0
	Nationwide	69.7	67.9	46.4	61.1
PCV13	Northern	90.7	94.1	92.1	92.1
	Tao-Chu-Miao	80.6	100.0	100.0	93.5
	Middle	95.7	95.2	91.3	93.8
	Yun-Chia-Nan	100.0	100.0	95.2	96.4
	Kao-Ping	100.0	93.3	96.2	96.9
	Eastern	66.7	100.0	60.0	66.7
	Nationwide	91.5	96.4	93.4	93.4

*Note: 1. PCV7 (7-Valent Pneumococcal Conjugate Vaccine) includes serotypes 4, 6B, 9V, 14,18C, and 23F. PCV10 (10-Valent Pneumococcal Conjugate Vaccine) includes serotypes of PCV7 plus serotypes 1, 5, and 7F. Since these several serotypes seldom appear in Taiwan, the coverage rate is equal to PCV7 and therefore not shown in the Table. PCV13 (13-Valent Pneumococcal Conjugate Vaccine) includes serotypes of PCV10 plus serotypes 3, 6A, and 19A.

2. The serotypes included in the vaccines covers the isolated strain rates.

3. The coverage rate of PCV7 in 2008 and 2010 in the Northern region shows significant differences (P-values < 0.01).

4. The coverage rate of PCV7 in 2010 in the North (including Northern region and Tao-Chu-Miao region) and middle-south (including Middle region, Yun-Chia-Nan region, and Kao-Ping region) shows significant differences

Discussion

On October 15, 2007, invasive *Streptococcus pneumoniae* infection is listed as a fourth category legal contagious disease and health units are required to report any cases. This study analyzes the incident rate and case numbers of invasive *Streptococcus pneumoniae* infections in Taiwan from 2008 to 2010. It was discovered that the highest number of infections occur between the period of December to March of the following year [6, 9], with a similar trend throughout the country. However, in Kao-Ping region, Yun-Chia-Nan region, and Northern region, higher or lower incident rates have sometimes surfaced; further analysis shows no specific serotype strain epidemic, nor any clusters of infections in the residential areas of infected cases. This trend saw changes in 2010, where the national incident rate in December increased approximately 30% in comparison with the same month of 2009, and by January and February of 2011, the rates continued to increase (the data is not shown). This change already started nationwide and in Northern region in April, 2010; afterwards, the rates of each month were all higher than those of the previous year (with the exception of September), this shows an increase in invasive *Streptococcus pneumoniae* infections nationwide and in the northern region. However, this increase does not exist in all of the regions.

In the past few years, the yearly incident rate of invasive *Streptococcus pneumoniae* infections in Taiwan is approximately 3 cases per 100,000 persons, with a rough total of 9% death rate; thus not a high-infective country. This may be due to the medical environment resources in Taiwan, and the good public health habits of the people. However, the incident rate among children under 5 years of age has risen to 19.9 cases in 2010 from 15.9 cases per 100,000 persons in 2008, especially in the northern region where the numbers rose to 20.3 from 13.5. This is worth noting for preventive units. No obvious increases are seen in other age groups.

In the past few years, serotype 19A has changed the most worldwide [5], and in Taiwan, 2010, it has become the prevalent serotype along with serotype 14 nationwide. This increasing trend can be seen in all regions of the country, with 14 cases in Northern region and 12 cases in Tao-Chu-Miao region in 2009, showing a percentage of 8.8% and 12.5%; by 2010, the cases increased to 45 (21.5%) and 31 (30.4%), showing significant statistical differences (P-values < 0.01). The percentage in children under 5 years of age in these two regions in 2010 reached 49.2% and 60.0% (data is not shown); although higher than the percentage in 2009 with 26.5% and 36.8%, the increase in cases showed no significant statistical difference. Serotype 3 has also slightly increased, yet with different fluctuations in each region, no significant statistical differences were seen. The percentage of serotypes 14 and 23F have gradually decline throughout the past few years, yet the percentage of decline is not obvious; among which serotype 23F shows different changes in percentage in various regions, in Northern region and Tao-Chu-Miao region, the percentage showed obvious decline whereas the percentage shows slight increase in Middle region and Kao-Ping region.

In Taiwan, the 7-Valent Pneumococcal Conjugate Vaccine (PCV7) for *Streptococcus pneumoniae* was approved and released, but since injections were not provided through public expense, the overall administration rate is not high [6]; however, this has not affected the infection situation of invasive *Streptococcus pneumoniae*. Yet, through time cumulative, even though the changes in recent years is not big, the coverage rate for the 7 serotypes in PCV7 in children under 5 years of age has declined to 46.4% from 69.7%, especially in Northern region where the percentage dropped to 30.2% from 69.8%. It can be speculated that these vaccines has caused changes in prevalent serotypes in Taiwan; other countries are also facing the same situation [6, 9, 11-12]. On the other hand, different serotype changes exist in Taiwan's various regions; The coverage rates of PCV7 vaccine among children under 5 years of age in the northern area (Northern region and Tao-Chu-Miao region), middle area (Middle region), and southern area (Yun-Chia-Nan region and Kao-Ping region) are 31.6%, 65.2%, and 63.8%, showing a larger effect of the vaccine in the northern area than in middle and southern area. The newly U.S. released and Taiwan approved PCV13 vaccine has a coverage rate of over 92% in each of the regions in Taiwan due to the fact that it includes serotype 19A. These speculations need further analysis of vaccine administration data to understand the relevance to the use of PCV7.

In view of the changes in invasive *Streptococcus pneumoniae* infections and its status as a worldwide noted and prevented contagious disease, the government has continuously conducted many invasive *Streptococcus pneumoniae* infection preventive measures in the recent years such as public education of public health habits and providing vaccine administration through public expense. However, as of the second time period in 2010 (April to June), the number of national infected cases has slightly increased, although not obviously; yet the number of infected children under 5 years of age in Northern region has significantly increased, among which the ratio of serotype 19A strain increased the most. The serotype 19A strain also has high drug-resistance and multiple drug resistance, causing great impact on preventive measures in Taiwan; however, this is a problem many countries are also facing. After invasive *Streptococcus pneumoniae* infections was listed as a fourth category contagious disease, relevant Taiwan epidemic data has been collected, and due to this continuous and complete monitoring system, immediate reference data can be provided for the government in preventive measures in truly conducting preventive measures against invasive *Streptococcus pneumoniae* infections.

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Biosafety and Biosecurity

Introduction to Biosecurity of Infectious Biomaterials

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Since the attack of anthrax mail occurred in the United States, the biosecurity of infectious biomaterials has been the great concern for laboratory biosafety management in recent years. Laboratory biosecurity describes the protection, control and accountability of infectious biomaterials in laboratories in order to prevent unauthorized access, misuse, diversion, lost, stolen or intended release [1].

In the past, laboratories were loose in using and managing of infectious biomaterials, and the situation of presuming to deal infectious biomaterials between laboratories was also common. Therefore, how to effectively control the storage, use and transactions of infectious biomaterials have become important duties for the laboratory managers and staff. In a broad sense, the laboratory biosecurity covers the valuable biomaterials such as non-pathogenic organisms, vaccine strains, food, genetically modified organisms, cell constituents, genetic materials and the samples of outer space [2]. These biomaterials may have economic and historical value, or probably detrimental to the public, thus the holders, users, managers or institutional biosafety committees should take related administrative control measures within the laboratories, determine the attribution of responsibility, and implement protective surveillance, to keep the organization’s profit and public safety.

Presently, Taiwan’s management on laboratory biosecurity is primarily based on Article 9 of "Regulations governing the infectious biomaterials and specimens collection from communicable disease patients” [3]. There are three requirements for the organizations that conserve infectious biomaterials above RG2: (1) specific designated person to manage; (b) with access control; and (c) provide detailed list of infectious biomaterials. Moreover, Taiwan CDC compiled “The guideline of laboratory biosecurity management" [4] in 2010, that provided references for organizations in developing management regulations fit in the individual size and characteristics, boosting the matters in documental norms, such as the storage area classification of infectious biomaterials, security management for staff and visitors, the response plans for contingency, personnel training and responsibilities, information security, and transporting safety.

Besides, the biosecurity magnitude of valuable biomaterials differs from each other. To operate laboratory biosecurity has to identify the valuable biomaterials that organizations need to protect through biological risk assessment in advance. For example, the bacterial strains with value of

comparison or research, and the pathogens or toxins which may cause serious harm to public health require different magnitude in security management or monitor measures. Once the above-mentioned pathogens or toxins are itentionally released, serious social, economic and public health hazard will occur. These pathogens or biological toxins, such as *Bacillus anthracis*, *Yersinia pestis*, monkeypox virus, Botulinum neurotoxin, are called biological select agents, In addition to strict security control measures, for the staffs who are possibly expose to biological select agents, their reliability should be fully assessed in advance. Furthermore, to avoid staff taking desperate behaviors due to personal or family reasons and resulting in social panic and anxiety, laboratory directors should concern about the staffs' lives, financial affairs, physical and psychological conditions. For controlling biological toxins, the United States has stipulated each laboratory PI in allowed maximum amount for holding with specific biological toxins.

In summary, biosecurity of infectious biomaterials can help us to reduce the misuse of its pathogenic properties that poses the public in harm, as well as to protect owner's intellectual property rights or patent. Therefore, management policies for infectious biomaterials will gradually implement the biosecurity measures. How to share the resource in research and development and achieve the balance in biosecurity management, nevertheless, depends on the competent authorities' policy scheme and the organizations' efforts and cooperation together.

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The Current Management on Exportation and Importation of Biomaterials in Taiwan

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As scientific research progressed and convenient transportation developed, the international communication and cooperation has become more frequent. Hence, the exportation and importation of infectious biomaterials containing pathogenic microbes is often needed for biotechnological research

development. The infectious biomaterials are group 2 (RG2). Since the infectious biomaterials are possible to endanger citizen's health, contaminate the environment, and even affect the socio-economic stability, the government has the responsibility to take necessary control and regulation on the exportation and importation of these materials.

The Centers for Disease Control, Taiwan (Taiwan CDC) conducts the exportation and importation business of infectious biomaterials based on the Paragraph 2, Article 9 of “Communicable Disease Control Act” [1] and the Articles 16 and 17 of "Regulations governing the infectious biomaterials and specimens collection from communicable disease patients” [2]. Currently, the exportation and importation of infectious biomaterials cannot be granted to any individual but only to organizations which hold, preserve, or use infectious biomaterials. The organizations should apply to Taiwan CDC in official documents and submit: (I) the application for exportation (or importation) of infectious biomaterials; (II) the documents of the risk group level of the exporting (or importing) infectious biomaterials, and the required biosafety level (BSL) for laboratory operation; and (III) the approval from the Institutional Biosafety Committee when exporting (or importing) the infectious biomaterials above RG2 (including RG2) [3]. Additionally, the organizations are required to login to Taiwan CDC’s website “Infectious biomaterials inspection and clearance system” [4] to register before application, provide the relative information, and print out the aforementioned documents. For trade convenience, the system links to the single window joined with customs, port and trade, and also facilitate the visa comparing and information checking for the customs.

The common issues of previous applications include: (I) incomplete submission (for example, without indicating the name and the source of the pathogens) or information error; (II) lack of the permits from the Institutional Biosafety Committee when applying for exporting (or importing) the infectious biomaterials above RG2 (including RG2), or misuse of the Institutional Review Board (IRB) consent instead; (III) no approbation of the organization’s biosafety committee by Taiwan CDC (According to Item 1, Paragraph 1, Article 69 of the Communicable Disease Control Act, Taiwan CDC can impose a fine at NT$ 10,000 dollars - NT$ 150,000 dollars, and set the deadline to make up the approbation); (IV) regarding the exportation (or importation) of zoonotic pathogens, it is necessary to apply to both Taiwan CDC and Bureau of Animal and Plant Health Inspection and Quarantine, Council of Agriculture, Executive Yuan.

With regard to the management of exporting (or importing) the infectious biomaterials, besides honest declaration to the relevant competent authorities according to the law, the packaging and labeling should also comply with the relevant international regulatory requirements to ensure the safety of the transportation process, including the “Guidance on regulations for the transport of infectious substances 2011-2012” of WHO, and the “Dangerous Goods Regulations” of International Air Transport Association (IATA).

Since the Customs has limited biomaterial professionals, clearance will grant only after the relevant authorities assisting in identification. Therefore, the current authorized agencies which are responsible for the exportation and importation of "non-infectious biomaterials" are under the command as follows: (I) Forestry Bureau, Council of Agriculture, Executive Yuan is in charge of exporting and importing wild live animals and protected wild animal products; (II) The exportation and importation of animal microorganisms, serum, animal cell cultures and related products are administered by the Bureau of Animal and Plant Health Inspection and Quarantine, Council of Agriculture, Executive Yuan; (III) The exportation and importation of human organs, tissues, cells involved transplantation (such as umbilical cord blood and cornea), and the containing substances (such as antibodies, nucleic acids, and proteins) are managed by the Bureau of Medical Affairs, Department of Health, Executive Yuan; (IV) The exportation and importation of human organs, tissues, cells for research purpose (like human cell strains), and materials from microbial sources (like plasmids, nucleic acids, and proteins), or derived substances are Taiwan CDC's jurisdiction; (V) The Food and Drug Administration, Department of Health, Executive Yuan directs the exportation and importation of the materials mentioned in paragraph (III) and (IV) that used as the raw material of products, medicines, and medical equipment, or used in manufacturing process [5].

The above-mentioned administration is stated by law. In recent years, Taiwan CDC found that many organizations also have demands for exporting and importing "non-infectious biomaterials" (such as cell strains, nucleic acids, and antibodies). Currently, Taiwan CDC merely provides assistance for exporting and importing of "non-infectious biomaterials" based on the spirit of serving the public. The legitimacy will be a key point of amending the law in the future.

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