Taiwan Epidemiology Bulletin
Biweekly November 16 , 2010 / Vol.26 / No.23

Preliminary Report - Effectiveness of Taiwan Multiple Drug Resistance Tuberculosis Consortium (TMTC)

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Abstract

In contrary to the conventional model of DOT for MDR-TB patient care, Taiwan CDC launched a hospital-initiated, patient-centered treatment program (Taiwan MDR-TB consortium, TMTC) since May 2007. A total of 370 MDR-TB cases that were diagnosed before 30th Aug, 2008 were enrolled and 225(60.8%) MDR-TB patients receiving TMTC care for at least 6 months within 6 months of diagnosis were classified as TMTC group. All others were classified as control group. The crude conversion rates of smear and culture were better in TMTC group than control group. After stratification by patient classifications, the culture conversion rate for TMTC group at 18 months was 87.6 %, which was 1.64 (95% confidence interval = 1.38-1.95, p<0.001) fold better than control group. The model of government-organized, hospital-initiated and patient-centered treatment, revealed better process indicators in this preliminary report. Further analysis for treatment outcome in long term follow-up in order to evaluate the policy of disease prevention is warranted.

Keywords: MDR-TB, DOTS, treatment outcome evaluation, strategy

Introduction

The threat of multidrug-resistant tuberculosis (MDR-TB) to the global public health is an important issue. According to the fourth Global Drug Resistance Surveillance Project, 0-22.3% of patients had primary multiple drug resistance and 0-62.5% had

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

secondary multiple drug resistance [1]. In 2007, Taiwan Centers for Diseases Control (Taiwan CDC) analyzed all TB patients. Among them, 1% of new, never-treated cases and 6.2% of all previously treated patients had MDR-TB. The total number of MDR-TB patients under case management was around 400 to 430 [2].

World Health Organization (WHO) initiated a working group in 1999 to advocate DOTS (direct observed treatment, short course) – Plus. To implement the comprehensive management strategy in communities, to provide concessionally-priced second-line anti-TB drugs, and to monitor and control the quality of those drugs, the DOTS-Plus was incorporated into the projects of the Stop TB Partnership established in 2000, and a subgroup called the Green Light Committee was set up to be in charge [3]. In Latvia, 204 patients with MDR-TB reported in 2000 underwent individualized treatment [4]. One hundred thirty-five patients (66%) cured, 14 patients (7%) died, 26 patients (13%) were lost from follow up, and 29 patients (14%) failed treatment. In Peru, DOTS-Plus operated by the Non-Government Organizations of the United States in 2008 also observed similar treatment results [5]. For more than 400 patients with MDR-TB, the cure rate was 66.3%. For the 29 extensively drug-resistant tuberculosis (XDR-TB) patients, a cure rate of 60.4% was also impressive. The cure rate was not significantly different between these two groups. Therefore, to non-HIV TB patients, treatment outcomes of MDR-TB could be improved and XDR-TB could be cured even in countries with limited resources, if DOTS-Plus could be implemented, effective drugs could be given, and an adequate control program could be launched.

A study was performed to analyze the outcome of MDR-TB in Taiwan. A total of 299 patients with newly diagnosed pulmonary MDR-TB in a referral center between 1992 and 1996 were enrolled. After 6 years, 153 patients (51.2%) were cured, 31 patients (10.4%) failed treatment, 28 patients (9.4%) died, and 87 patients (29.1%) defaulted [6]. Documentations about treatment outcomes and prognosis in patients with MDR-TB in Taiwan were scarce thereafter.

In May 2007, Taiwan CDC launched a new diagnostic and treatment program for MDR-TB according to the guidelines established by WHO [3]. Taiwan CDC offered the financial resources and established the Taiwan Multiple Drug Resistance Tuberculosis Consortiums (TMTC). Through five professional therapeutic teams, TMTC not only provided general medical care to patients, but also operated DOTS-Plus projects. In contrary to the conventional

model of hospital-treated and government-DOT, a hospital-initiated, patient-centered treatment program was used. Designated observers were employed by therapeutic teams to deliver the correct drugs to patients and watch them ingest the medicine before leaving, therefore connecting the gaps between physician care and public health control and facilitating communication and rapport. We hope that the patient-centered treatment program could improve both the compliance and treatment outcome for patients and effectively control MDR-TB in Taiwan [7].

The objective of this study is to evaluate the effects of the new project which integrated the conventional treatment program with the medical and public health resources, see if it could improve the process indicators and treatment outcomes of MDR-TB patients in Taiwan.

Materials and Methods

A. Study population and data collection

MDR-TB patients with positive culture results after January 2007 were eligible to participate in DOTS-Plus project. Diagnosis, treatment course, and outcomes in those participating in DOTS-Plus were mandatory to be recorded in the DOTS-Plus database. We enrolled all MDR-TB patients diagnosed before Aug 30, 2008. Because the number of patients who did not attend DOTS-PLUS was too small to analyze, we re-defined the study population as following. The first 6 month of treatment is intensive phase of the treatment for MDR-TB[3]. Therefore, MDR-TB patients receiving TMTC care for at least 6 months within 6 months of diagnosis of MDR-TB were categorized as TMTC group, assuming that they have received more comprehensive DOTS-plus treatment. All the other patients were categorized as control group. The outcome of the enrolled patients was followed-up until Nov 30, 2009.

B. Classifications of MDR-TB patients

Previous anti-TB treatment had great influence on the prognosis of MDR-TB cases, so registering patients based on their history of anti-TB treatment was important. According to the Guidelines for the Programmatic Management of Drug-resistant Tuberculosis released by WHO, these patients could be classified into six groups [3]. Group assignment was determined by history of previous treatment at the time of collection of the sputum sample that was later used to confirm MDR-TB.

1. New. Patients who have never received anti-TB treatment, or who have received treatment for less than one month. For those TB patients who had been treated with first-line drugs according to drug sensitivity test (DST), they would be placed in this category because of resistance even if they have received more than one month of treatment.
2. Relapse. Patients previously treated for tuberculosis and declared cured, or treatment completed, and then diagnosed as MDR-TB.
3. Treatment after default. Patients who return to treatment with confirmed MDR-TB after interruption of treatment for two months or more.
4. Treatment after failure of the first treatment. Patients who returned after the first treatment has failed, which was

defined by positive sputum culture ≧ 4 months or positive sputum smear ≧ 5 months after commencing treatment.

5. Treatment after failure of re-treatment. Patients whose first treatment was defaulted or failed returned for re-treatment, but the re-treatment has failed.
6. Others. Patients whose previous treatment history does not fit the above definitions.

C. Process indicators

To monitor the progress of treatment, monthly sputum smear / culture are recommended in patients with MDR-TB [3]. In this study, we analyzed the results of sputum examinations at month 2,6,12, and 18. Sputum conversion at month 2 and 6 were indicators for initial phase while sputum conversion at month 12 was indicator for middle phase. Because the recommended duration of treatment was guided by smear and culture conversion, the minimal recommendation was that treatment should last for at least 18 months after sputum conversion [3]. We therefore took sputum conversion at month 18 as an indicator, representing the end of treatment. We defined sputum conversion at month 2,6,12, or 18 as two consecutive negative smears and cultures taken 30 days apart. In addition, patients should have at least one positive pre-treatment smear or culture and have no positive smear or culture after sputum conversion [3].

D. Treatment outcomes

Based on physicians' clinical judgments, the treatment outcomes were classified into cured, treatment completed, died, failed, and defaulted as defined by WHO [3]. A patient would be considered cured only when he had completed treatment without evidence of clinical deterioration, had at least five consecutive sputum cultures collected at least 30 days apart in the final 12 months of treatment, and the last 3 cultures must be negative. For patients who had completed the treatment course but could not meet the definition of cure, they were classified as "treatment completed". Treatment would be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if all of the final three cultures are positive. A patient whose treatment was interrupted for two or more consecutive months for any reason would be considered defaulted.

For patients with definitive treatment outcomes, we also compared the duration of treatment between TMTC group and control group.

E. Statistical analysis

Statistical analyses were performed using SAS 9.1. We compared variables including gender, age, alcohol consumption, underlying diseases, classifications of patients, date of initiating second-line drugs, date of the end of treatment, treatment outcomes, and results of sputum smears and sputum cultures between TMTC group and control group. Chi-square test was used to compare categorical variables. Cochran-Mantel- Haenszel method was used to control variables with significant difference between two groups. For continuous variables such as duration of treatment, t-test was used to compare the means.

Results

Among the 370 patients enrolled in this study, 225 (60.8%) met the criteria and were classified as TMTC group and the remaining 145 were classified as control group. For 145 patients classified as control group, 138 of them were classified as control group due to receiving TMTC care after 6 months of diagnosis of MDR-TB. Only 7 patients were those who received TMTC care within 6 months of diagnosis of MDR-TB, but died during the initial 6- month care of TMTC, and therefore be classified as control group. As listed in Table 1, patient characteristics, including gender, age, alcohol consumption, and underlying diseases, were not significantly different between the two groups. Considering the age distribution, although the proportion of patients between 40-49 years of age was more in the control group (29.7%), there was no significant difference in proportion of patients above 40 years between TMTC group (71.1%) and control group (77.9%). Considering the underlying diseases,

Table 1. Characteristics of study population

	TMTC group (n=225)		Control group (n=145)		Chi-square
	NO.	%	NO.	%	p-value
Gender					
Female	52	23.1	32	22.1	
Male	173	76.9	113	77.9	0.815
Age (yr)					
0-14	3	1.3	2	1.4	
15-19	9	4	0	0	
20-29	18	8	12	8.3	
30-39	35	15.6	18	12.4	
40-49	47	20.9	43	29.7	
50-59	52	23.1	35	24.1	
≧60	61	27.1	35	24.1	0.145
Alcohol consumption					
Yes	31	13.8	22	15.2	0.709
Underlying diseases					
Diabetes	71	31.6	50	34.5	0.558
Hypertension	41	18.2	20	13.8	0.262
Hepatitis B					
No	200	88.9	133	91.7	
Yes	15	6.7	6	4.1	
Unknown	10	4.4	6	4.1	0.580
Hepatitis C					
No	199	88.4	130	89.7	
Yes	17	7.6	9	6.2	
Unknown	9	4	6	4.1	0.884
Patient classification					
New	88	39.1	30	20.7	
Relapse	70	31.1	42	29.0	
treatment after default	11	4.9	12	8.3	
treatment after failure of the first treatment	45	20.0	17	11.7	
treatment after failure of re-treatment	11	4.9	43	29.7	
others	0	0.0	1	0.7	<0.001

the proportion of patients with hypertension, hepatitis B, and hepatitis C were more in TMTC group, but the difference was not significant. Compared the classifications of patients in TMTC and control group, the proportion of patients classified as new (39.1% in TMTC group versus 20.7% in control group), relapse (31.1% versus 29.0%), and treatment after failure of the first treatment (20.0% versus 11.7%) were higher in TMTC group, while the proportion of patients classified as treatment after default (4.9% versus 8.3%) and treatment after failure of re-treatment (4.9% versus 29.7%) were higher in the control group. Only one patient in the control group (0.7%) was classified as others because the previous treatment history was unknown. The distribution in classification of patients was significantly different (p<0.001) (Table 1).

Sputum conversion rates at month 2, 6, 12, and 18 were shown in Figure, and all of them were higher in TMTC group. At month 18, the sputum conversion rate was significantly higher in TMTC group than in control group (87.6% versus 44.1%, p<0.001).

Comparing all variables which might influence the treatment outcomes, classification of patients was significantly different between TMTC group and control group. After stratification by patient classifications using Cochran-Mantel-Haenszel (CMH) method, the homogeneity of each stratum of patient classification was good (p>0.05) (Table 2). The probability of culture conversion at month 18 was 64% increment compared to control group, indicating that the association between treatment and response remained strong after adjusting for patient classifications. Similar results were found in culture conversion rates at month 6 and 12. The homogeneity test for each stratum of patient classification for smear conversion rate at month 2 was poor (p=0.011). The cause of this heterogeneity was due to that the huge improvement of smear conversion in patients classified as "treatment after failure of re-treatment" between the two groups compared to all the other patient

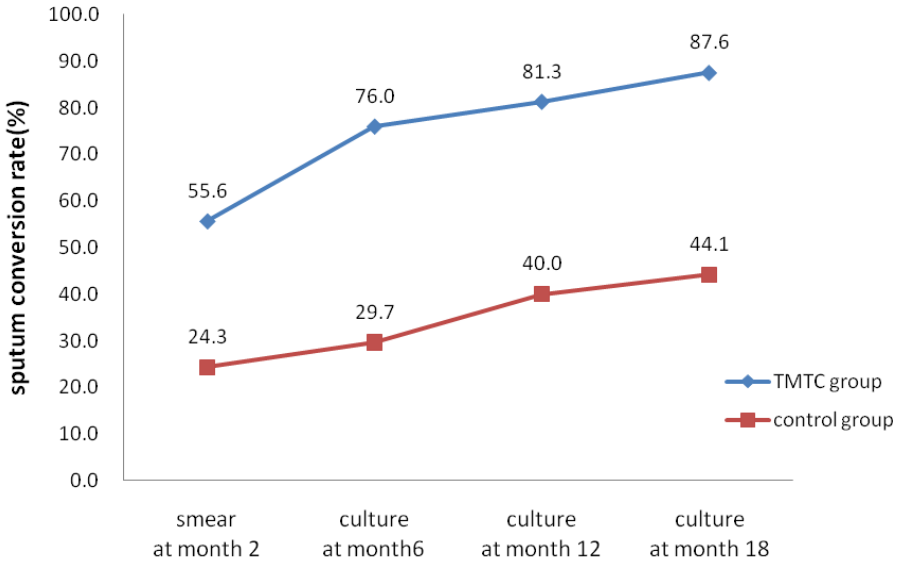

Figure. Comparison of the sputum conversion rates between TMTC and control group

classifications (OR = 19.55(2.54-150.61)). Overall, the performance of culture conversion, no matter at month 6, 12, or 18, was better in patients classified as "relapse" and "treatment after failure of re-treatment".

Treatment outcomes by November 30, 2009 were shown in Table 3. Thirteen patients in TMTC group died, and the death was

Table 2 .Comparison of sputum conversion rates between TMTC group and control group at month 2, 6, 12, and 18 adjusted by patient classifications using Cochran-Mantel-Haenszel method

	homogenous p-value	OR* (95% CI)
Smear conversion at month 2	0.011	1.79(1.34-2.38)
new		1.10(0.74-1.63)
relapse		2.58(1.46-4.57)
treatment after default		1.09(0.43-2.77)
treatment after failure of the first treatment		2.08(0.84-5.15)
treatment after failure of re-treatment		19.55(2.54-150.61)
Culture conversion at month 6	0.125	1.97(1.55-2.49)
new		1.30(0.99-1.69)
relapse		3.36(1.93-5.84)
treatment after default		1.64(0.62-4.30)
treatment after failure of the first treatment		1.76(0.89-3.49)
treatment after failure of re-treatment		6.52(1.83-23.18)
Culture conversion at month 12	0.134	1.64(1.35-1.99)
new		1.19(0.96-1.46)
relapse		2.57(1.66-3.99)
treatment after default		1.31(0.55-3.09)
treatment after failure of the first treatment		1.51(0.88-2.59)
treatment after failure of re-treatment		2.44(0.99-6.01)
Culture conversion at month 18	0.368	1.64(1.38-1.95)
new		1.25(1.02-1.52)
relapse		2.19(1.50-3.19)
treatment after default		1.27(0.62-2.62)
treatment after failure of the first treatment		1.55(0.97-2.48)
treatment after failure of re-treatment		3.04(1.46-6.33)

*Compared with sputum conversion rates in control group (OR as 1.00).
** Only 1 patient was classified as "others" in control group, so he was not included in this table.

Table 3. Treatment outcomes in TMTC group and control group

	NO.(%)		Average duration of treatment days (SD)		t-test
Outcomes	TMTC group	Control group	TMTC group	Control group	p-value
Cured	78(34.7)	41(28.3)	680.9(318.6)	972.0(485.3)	0.001
Treatment completed	34(15.1)	14(9.7)	662.2(201.9)	1001.4(664.7)	0.082
Death associated with tuberculosis*	1(0.4)	7(4.8)	1140.0(N/A)	854.7(866.0)	N/A
Death not associated with TB	12(5.3)	24(16.6)	412.0(178.6)	624.5(530.6)	0.086
Failed	7(3.1)	13(9.0)	1051.1(593.3)	1845.5(1227.3)	0.127
Defaulted	3(1.3)	3(2.1)	384.7(319.3)	492.0(172.8)	0.636
Not available**	90(40.0)	43(29.7)	616.7(507.5)	1075.5(705.0)	<0.001

* Because of the limited number of patients died in TMTC group, SD could not be calculated and t-test could not be performed.
**For those treatment outcomes not available, the duration of treatment was the average days from the date that second-line drugs was initiated to November 30, 2009.

associated with tuberculosis in one patient (7.7%). In contrast, 31 patients in control group died, and the death was associated with tuberculosis in 7 patients (22.6%). In TMTC group, the duration of treatment (the average days from the date that second-line drugs were initiated to the date that treatment outcome was available) in cured patient and in those classified as treatment completed were 680.9 days (about 22.7 months) and 662.2 days (about 22 months) respectively. In control group, the duration of treatment in cured patient and in those classified as treatment completed were was 972.0 days (about 32.4 months) and 1001.4 days (about 33.4 months). Overall, control group tended to have longer duration of treatment, but the difference was significant only in cured patients (p=0.001).

Discussion

In May 2007, Taiwan CDC launched a new hospital-initiated, patient-centered MDR-TB treatment program. By integrating the medical resources and DOTS-Plus project, the objectives of this program were to improve the cure rate, decrease defaults, and control the community spread [7]. New patients who had never received anti-TB treatment were more easily to be cured. But the cure rate in previously treated patients was 50% less than that in new patients [8]. Outcomes in patients who had received second-line anti-TB drugs were even worse. The risk of death or treatment failure was 5 times higher in new patients [4]. In this study, after adjusting by patient classifications, it is found that the sputum culture conversion rates at month 6, 12, and 18 were significantly better in TMTC groups than in control group. The better conversion rates noted in patients classified as “relapse” and “treatment after failure of re-treatment” compared to the other classifications in the preliminary stratified analysis shed the light on the effectiveness of early intervention, patient centered DOT-plus project, especially on difficult MDR-TB cases.

Besides patient classifications, the other variables analyzed, such as gender, age, alcohol consumption, and underlying diseases, did not reveal significant difference between these two groups. Although there were other possible factors that might be associated with sputum conversion rates, including social-economic status of patients, the availability of medical resources, and etc., we could not analyze them unless more information could be filled in database. The presence of drug resistance was associated with poor prognosis [9]. But we did not analyze this factor because only 7 out of the 370 patients had XDRTB and all the extensive drug-resistance emerged after initiation of treatment.

Because the duration of treatment for MDR-TB was longer than TB without drug resistance, treatment outcomes in 40% of patients in TMTC group were not available by the end of this study period. Limited by the number of samples, we only focused on the analysis of patients who died during treatment. The mortality rate was 5.7% in TMTC group, while that in control group was 21.4%. By our definition, patients

would be categorized into TMTC group only if they received TMTC care within 6 months of diagnosis of MDR-TB and for at least 6 months. We found only 7 patients were categorized into control group because they died within 6 months of diagnosis, despite they were actually under TMTC care. The other 24 patients in the control group who died during treatment, including 5 deaths associated with TB, could be contributed to the delayed initiation of DOTS-Plus care. Overall, the mortality rate was significantly lower in TMTC group (p=0.036).

For those with definitive treatment outcomes, the duration of treatment was longer in control group. Because the program was implemented since May 2007, some patients failed to complete treatment before that date would be re-evaluated by therapeutic teams and retreated under supervision, leading to a longer duration of treatment. On the other hand, the shorter duration of treatment in TMTC group revealed the potential benefits of a patient-centered treatment program.

In a previous study analyzing the treatment outcomes of 1027 patients with MDRTB or XDRTB in Latvia between 2000 and 2004, the cure rate was 67.9%. For the 48 patients with XDRTB, the cure rate in 5 years was 38%. After excluding XDRTB patients, the average duration of treatment in cured patients and in patients with complete treatment were 599 days and 618 days respectively [10]. Compared to the data from Latvia, the duration of treatment in our study was similar both in cured patients and in patients with complete treatment; all were consistent with WHO guidelines, which recommended a course of 18 to 24 months. For those categorized as treatment failure, the duration of treatment was longer in Taiwan than in Latvia (1051 days versus 348 days), which could be resulted from a more strict criteria we used to define treatment failure. Because ineffective treatment leads to waste of medical resources, we should be more cautious on this problem. More studies could be done to elucidate the prognostic factors in MDRTB patients. Therapeutic teams should also urge patients to control other chronic illnesses, quit smoking, and stop drinking and discuss with patients about adjustments of anti-TB drugs and surgical excision of the lesion if necessary [11].

In the future, by keeping track the treatment outcomes of these cases and by chart review, to collect sufficient samples of control group, we could conduct a comprehensive study to evaluate the effectiveness of DOTS-Plus project.

References

1. WHO. Anti-tuberculosis drug resistance in the world :fourth global report. The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 2002–2007. 2008:37-9. Available at: http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
2. Taiwan CDC. Taiwan Tuberculosis Control Report 2009. Available at http://www.cdc.gov.tw/ct.asp?xItem=27032&ctNode=1947&mp=1

3. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis : Emergency update 2008. Available at http://whqlibdoc.who.int /publications/2008/9789241547581_eng .pdf
4. Leimane V, Riekstina V, Holtz TH, el at. Clinical outcome of individualised treatment of multi-drug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318-26.
5. Mitnick CD, Shin SS, Seung KJ, el at. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008;359:563-74.
6. Chiang CY, Enarson DA, Yu MC, et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. Eur Respir J 2006;28:980-5.
7. Huang SH, Lin CH, Chan PC, et al. Introduction of Medical Care System for Multi-drug Resistant Tuberculosis in Taiwan. Taiwan Epidemiol Bull 2009;25:86-95.
8. Johnston JC, Shahidi NC, Sadatsafavi M, et al. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 2009;4:6914.
9. Shah NS, Pratt R, Armstrong L, et al. Extensively drug-resistant tuberculosis in the United States, 1993-2007. JAMA 2008;300:2153-60.
10. Leimane V, Dravniece G, Riekstina V, el at. Treatment outcome of multidrug/ extensively drug-resistant tuberculosis in Latvia, 2000-2004. Eur Respir J 2010. Feb 25.
11. Kim DH, Kim HJ, Park SK, el at. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med 2008;178:1075-82.

Response Measures of the Communicable Disease Control Medical Network to H1N1 Novel Influenza

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Abstract

In late April 2009, outbreaks of H1N1 novel influenza occurred in the United States and Mexico, and spread around the world in six weeks. The World Health Organization (WHO) announced the start of a global pandemic of H1N1 novel influenza on June 11, 2009. Taiwan announced H1N1 novel influenza as a category 1 communicable disease on April 28. On May 20, the first imported case appeared in Taiwan. In response to the imported cases, four designated communicable disease response hospitals were recruited to isolate and treat cases. In response to changes in the H1N1 pandemic, the main focus of disease control has shifted from containment to mitigation. The management of increasing numbers of patients, treatment of severe influenza cases and preservation of the medical system will be the focus of work.

In this article, we describe and review

measures implemented by the Communicable Disease Control Medical Network in response to H1N1 novel influenza cases between May and mid June, 2009. We also suggest measures that should be implemented by the medical system in response to the second wave of pandemic and main focus of disease control work in the future.

Keywords: H1N1 novel influenza, Communicable Disease Control Medical Network, response hospitals

Introduction

The outbreak of H1N1 novel influenza in April 2009 has subjected our society to the threat of a pandemic for a second time after the outbreaks of SARS in 2003. The experience gained and the Communicable Disease Control Medical Network (CDCMN) established during the SARS outbreaks have helped us go through the first wave of H1N1 outbreaks. Recent H1N1 outbreaks can also help us improve each response measure. Although the CDCMN has accomplished tasks in treatment of the cases and disease control, the second wave of outbreak will be an even bigger challenge.

According to the Pandemic influenza preparedness and response guidance of WHO, which announced level 6 pandemic alarm on June 11, national governments should focus resources on medical care of cases, continue monitoring and adjusting set policies during the pandemic, and gradually administer control measures on mitigation. Proper treatment of cases should be emphasized to alleviate the impact on individual health and society, instead of trying to stop disease transmission. The health system should be prepared to handle a large number of cases and more severe cases [1]. Hence, our disease prevention focus was shifted from containment to mitigation in June. In the future, the main targets of disease control are to disperse patients, decrease and treat severe cases, and ensure continuous operation of the medical system. Through proper infection control and integration of the CDCMN, emergency medical network, and contracted medical resources of Bureau of National Health Insurance, cases are treated timely and continuous operation of the medical system is ensured.

Response Measures of the Communicable Disease Control Medical Network

In April 2009 outbreaks of H1N1 novel influenza and mortalities occurred in Mexico and the southwest area of the United States. In response to the outbreaks and to protect our medical system and the health of the general public, the CDC on April 26 asked the Communicable Disease Response Hospitals to stand by, reviewed preparation for the outbreaks in hospitals, and strengthened preparation of software, hardware, and personnel. If required, the hospitals can be evacuated in order to treat patients of communicable diseases following government directions. According to case definition of H1N1 novel influenza by the WHO, H1N1 novel influenza has been announced as a category 1 communicable disease. In response to the rise in global pandemic level, H1N1 Novel Influenza Central Epidemic Command Center was

established on April 28 and response hospitals followed it's directions to control the epidemic. In addition, the region commanders of CDCMN immediately convened meetings to discuss local responses for the epidemic.

A. Prepare and sustain response hospitals

According to the "Influenza Pandemic Strategic Plan", preservation of the medical system is an important goal. In the beginning of a pandemic, response hospitals are responsible for treating highly transmissible/ severe cases. Hence, 25 response hospitals were informed in the first place to enter the preparative/response mode. Preparedness of the 25 hospitals also was followed. Items to be checked include self-assessment of negative pressure wards, plans of man power mobilization, education/training/drill , preparedness of wards, disease control supplies, transportation routes, etc. The hospitals are also required to cooperate with local disease command centers of the local governments in drills, and report periodically in the meetings of the Central Command Center.

B. Adjustment of the principles to treat H1N1 cases based on the evolution of the epidemic

In the beginning of the pandemic, disease control strategy was mainly focused on "containment abroad; border control". Passengers were checked at airports, and cases under investigation were isolated and treated in hospitals. Other cases under investigation were mainly isolated at home, unless admission was required. Considering the capacity of the medical system, the Command Center on May 27 authorized region commanders of each medical network to adjust criteria of admission based on disease severity, progression and availability of negative pressure wards. Cases under investigation are mainly admitted to the hospitals. If negative pressure wards are not available, regular wards may be used as long as patients are treated separately from other patients. If both negative pressure and regular wards are not available, mild cases may be isolated at home after having been assessed by doctors.

C. Maintenance facility and functionality of negative pressure isolation wards

Patients of category 1 and 5 communicable diseases are primarily treated in the response hospitals. Negative pressure isolation wards are important protective facility for medical personnel to avoid nosocomial infections. Hence, the CDC has commissioned the Institute of Occupational Safety and Health (IOSH) to guide the annual checking up of negative pressure isolation wards. Personnel in the hospitals are also trained for self-monitoring. In response to the pandemic, all hospitals were required to finish checking up standard negative pressure isolation wards and comply with the "Plan of negative pressure isolation wards checking up of the CDCMN" this year. The IOSH, branches of the CDC, local health bureaus, and Commission of Infection Control finished checking 25 response hospitals in a month. Hospitals were asked to correct the flaws found within a set period of time, and follow-ups were conducted to monitor improvement.

D. Activation of response hospitals to treat cases

In response to the first imported case of

H1N1 novel influenza on May 20 and following cases under investigation, patients of category 1 and 5 communicable diseases are mainly treated in the response hospitals, according to Article 8 of the Practices of the Communicable Disease Control Medical Network. After discussion of commanders of region medical networks and the CDC branches, and a consensus was acquired from commander of the Central Epidemic Command Center, TaoYuan General Hospital Shin-Wu Branch (May 21), Taipei County Hospital Sanchong Branch (May 22), Taipei City Hospital Ho-Ping Branch (may 30), and Keelung Hospital (June 13) were activated to treat confirmed H1N1 novel influenza cases.

E. Monitoring negative pressure wards in response hospitals

In the beginning of the pandemic, the number of available negative pressure wards was still sufficient; to prevent disease spreading, cases under investigation were mainly isolated and treated in hospitals. Hence, to fully monitor negative pressure wards in response hospitals, response hospitals were temporarily required to change the schedule for reporting availability of negative pressure wards from twice a month (on the 1st and 15th) to daily report.

F. Adjusting policy with the suggestion from WHO

The WHO on June 11 announced that the global H1N1 novel influenza pandemic had been raised to level 6 (global pandemic), although it's a mild pandemic. Current epidemiology of H1N1 novel influenza shows that rates of severe complication and mortality are close to the seasonal flu; WHO has emphasized that governments should focus on treating patients and provide useful information about self-protection to the general public to reduce panic, instead of ineffective measures such as border closing, stopping the virus at the airports, or travel restriction. Hence, since June 19, 2009, H1N1 novel influenza was removed from category 1 communicable diseases and was instead controlled by regulations regarding influenza with severe complications in the category 4 communicable diseases. isolation in addition to medical treatment is not required.

Outcomes of the CDCMN response measures

A. Education, training and drill

Since the outbreaks of H1N1 novel influenza in April 2009, response hospitals of the 6 medical networks have started to prepare actively by training and educating personnel and strengthening facility. Fifty seven trainings and 59 drills (Table) have been held in the 6 areas. The focus of the trainings and

Table. Trainings and drills by each medical network in response to pandemic of H1N1 novel influenza, 28 April -7 May 2009

Areas	Training	Drill
Taipei（6 response hospitals）	12	9
Northern Taiwan（4 response hospitals）	4	8
Central Taiwan（4 response hospitals）	12	5
Southern Taiwan（5 response hospitals）	13	4
Kaohsiung-Pingdong（4 response hospitals）	15	16
Eastern Taiwan（2 response hospitals）	1	17
Total	57	59

drill included reporting of and sample gathering from suspected H1N1 novel influenza cases, introduction and prevention of transmissible diseases, using of personal protective equipment, transportation routes, treatment of confirmed cases, and patient referral.

B. Inspection of negative pressure isolation wards

Inspection of negative pressure isolation wards was done between May 8 and 26, 2009. Two to three beds were checked each floor (the first and last one and one in the middle or ones that have special locations). A total of 31 wards and 78 beds were checked. Among them, 3 beds in 2 hospitals had abnormal negative pressure, and 2 beds in 2 hospitals had insufficient ventilation. They have been improved on May 18, 31 and June 15, respectively.

C.Admission to the negative pressure isolation wards in response hospitals

A total of 660 isolation beds are available in the 25 response hospitals, including 495 beds in negative pressure isolation wards and 165 beds in regular isolation wards. Occupancy of negative pressure isolation wards between May 1 and June 19 was between 50.5% and 36.2%, with an average of 40.6%. Occupancy rate had increased since June 10, which might be related to an outbreak of H1N1 novel influenza in a graduate travel group to Thailand.

Response and preparation to outbreaks in the fall and winter

The fall and winter are flu seasons. Since the H1N1 novel influenza has caused a global pandemic since its emergence in April 2009, based on case numbers during flu seasons in Australia, a large number of patients will overload emergency medical system [2]. If patient flow is not managed properly, emergency rooms in hospitals will not be able to respond to the demand of the whole medical care. Some patients will have severe complications, and transfer or intensive care will be needed. Hence, the strategies to respond to the flu in the fall and winter should be “triaging patients in a timely fashion” and “caring of severe cases” [3, 4].

To organize medical resources for the outbreaks in the fall and winter 2009, Ching-chuan Yeh, commander of the H1N1 Novel Influenza Central Epidemic Command Center, supervised preparedness of the CDCMN command centers of the 6 areas in person in order to expedite preparedness for the outbreaks. Response principles of the medical system include:

A. A large number of patients are expected in the second wave of outbreaks of H1N1 novel influenza. The focuses would be caring patients to avoid severe complication, triaging patients in the emergency rooms, and caring cases having severe complications.

B. Commanders of the CDCMN are authorized to organize the CDCMN, Emergency Medical Networks, and contracted medical resources of Bureau of National Health Insurance to treat patients. The Emergency Medical Network, integrating the 119 emergency transportation, can fully control distribution and usage of intensive care units to effectively transfer and treat severe cases.

C. Division of responsibility and authority of the command system:
   1. Command centers of region medical networks were mainly responsible for clinical care and availability of wards.
   2.Response centers of the local governments supervise civil affairs, social affairs and the fire departments to support resource distribution and basic affairs such as public health, disease control, health education, and emergency transportation.

D. Re-education and training for first line doctors
   1. Bureau of National Health Insurance together with local health bureaus and medical associations hold clinical medical education and trainings for local primary care doctors and assist transmission of public health information.
   2. Local health bureaus hold education and trainings for fire fighters to avoid panics. Regular ambulances and surgical masks for patients are sufficient for transporting flu patients. Negative pressure isolation ambulances are not required.
   3. Hospitals over certain scale should hold education and training for personnel by themselves.

E. Although patients of H1N1 novel influenza are not required to be treated in negative pressure isolation wards, if drug-resistant viral strains do appear, isolation wards in response hospitals will be utilized to isolate and treat patients.

F. Antiviral drugs for influenza have been included in the National Health Insurance on Aug. 15, 2009. Mild cases could have proper treatment at local hospitals without the need to go to medical centers or emergency rooms.

G. Clinical teams: the clinical teams are formed by the Bureau of National Health Insurance, Bureau of Medical Affairs, Bureau of Pharmaceutical Affairs, CDC and medical associations to discuss clinical care and use of antiviral drugs. The teams are subdivided into “medical teams” and “treatment teams”:
   1. Medical teams: medical teams are supervised by the Bureau of Medical Affairs and are responsible for coordinating the emergency medical networks and CDCMN, and planning patient admission and transfer.
   2. Treatment teams: treatment teams are supervised by the Bureau of National Health Insurance and are responsible for clinical medications, expenses and examinations, drafting clinical guidelines, and trainings for medical personnel.

Conclusion

The CDCMN is a collaboration of the medical and public health systems, and uses local partnerships to organize and utilize disease control and medical resources. During the H1N1 novel influenza outbreak, the commander of the H1N1 Novel Influenza Central Epidemic Command Center has rapidly utilized the original structure of the Communicable Disease Medical Network to implement all the disease control and medical measures. Response hospitals have also followed orders to treat confirmed cases of

H1N1 novel influenza. However, if the pandemic is more severe, the large numbers of patients, public panic and the treatment of severe cases will have a severe impact on the medical system. Hence, strengthening the surge capacity of hospitals, integrating emergency medical networks and the national insurance system, centralization and management of resources, and collaboration of the medical and public health systems are required to protect health of the general public.

Acknowledgement

Sincere thanks to the directors and staff of the response hospitals, commanders/vice commanders of the 6 region networks, and branches of the CDC for their participation and collaboration so that the CDCMN has been able to treat patients in time without any rejection of hospital admission.

References

1. WHO. Pandemic influenza preparedness and response guidance document. Available at:http://www.who.int/csr/disease/swineflu/frequently_asked_questions/levels_pandmic_alert/en/index.html
2. Department of Health and Ageing. Available at: http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/news-030
3. CDC. 10 Steps You can take: Actions for Novel H1N1 Influenza planning and response for medical offices and outpatient facilities. Available at: http://www.cdc.gov/h1n1flu/10steps.htm
4. Departamento de Epidemiología.-Ministerio de Salud de Chile. Ministerio de Salud Infuenza A(H1N1). Available at: http://www. andemia.cl/pagnew/prensa/ REPORTE_30_06_09.pdf