疫情報導 Taiwan EB
Taiwan Epidemiology Bulletin
Biweekly October 19 , 2010 / Vol.26 / No.21

Taiwan Pathogenic Microorganism Genome Database and Its Applications

Yuan-Pin Huang, Ching-Yuan Yao, Yu-Ju Chen, Po-Cheng Chuang, Li-Ching Hsu, Ho-Sheng Wu

Research and Diagnostic Center, Centers for Disease Control, Taiwan

Abstract

Taiwan CDC established the "Taiwan Pathogenic Microorganism Genome Database" (website address: http://tpmgd.cdc.gov.tw/tpmgd_public) to integrate the virus gene sequences and epidemiological information, which is the unique pathogenic microorganism genome database with integrity and diversity in nation. Through pathogen data analysis and monitoring gene sequence variation, the database provides valuable molecular and epidemiological information for disease control purposes, as well as developing pathogen test technologies and a powerful tool for assessing the effectiveness of the vaccine. This database contains over 11,000 records including essential sequences and epidemiological information of enterovirus, influenza virus, and adenovirus. Taiwan CDC updates domestic information in the database frequently and also imports virus sequences released from National Center for Biotechnology Information (NCBI) and World Health Organization (WHO). The database has successfully provided epidemic prediction model for Taiwan local influenza virus, antigenicity and drug resistance surveillance for 2009 H1N1 influenza, rapid comparison of Enterovirus 71 subtypes, and provided warning for enterovirus outbreaks in the early 2008. Inquiry and sharing of information in the database is open to public access and free of charge. We expect by sharing the pathogenic microorganism genome database could improve the output for related health technologies and collaboration and communication with international society in pathogens information.

Keywords:sequence, database, enterovirus, influenza virus, adenovirus

Introduction

Taiwan CDC project titled "Establishment and Application of Pathogen Genome Sequence Database in Taiwan" is under the project of "Genomic Medicine and

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].

Biotechnology Development – Application of Health Care Services". This project is aimed to apply genomic sequence analysis to prevent, diagnose, and treat endemic diseases, and combine basic research, clinical evaluation and technology transfer to improve the production efficiency and establish international competitiveness in medical technology industry. Due to the lack of a database combined with pathogen genome sequence and epidemiological information, Taiwan CDC systematically established nationwide pathogen genome database for clarifying source of infection, disease control, vaccine development, reagent and rapid diagnostic kit design, to improve CDC's capacity in disease control as well as development of biotech industries.

On the principles of openness and sharing of government resources and for more efficient utilization of pathogen genome database, Taiwan CDC collaborated with "Advances Bioinformatics Core" team at National Yang Ming University to construct "Taiwan Pathogenic Microorganism Genome Database-open version (TPMGD-open version)" on December 2008. The records, with a total of over ten thousands, included enterovirus, influenza virus, and adenovirus and linked with epidemiological information (gender, age, residence area, onset date; no personal identification data). The database is open for public access.

Aforementioned pathogen data were collected and analyzed by Taiwan CDC over the years, and now updated every 6 months. The downloaded sequences from National Center for Biotechnology Information (NCBI) and World Health Organization (WHO) were also renewed. Therefore, this innovative database combined with pathogen genome sequences and epidemiological information, complete and up to date, greatly reduces the time for data gathering and information search.

In addition to basic data storage, to efficiently integrate pathogen information for disease control and prevention measures, Taiwan CDC integrated multi biotech software and third party packages (including batch download, multiple sequence alignment, primer design, enterovirus 71 subtyping, recommended influenza strain subtypes), and displayed on web pages to increase efficiency, convenience and functions. Since the construction of this website, Taiwan CDC utilized that to monitor the mutations in pathogen genome, establish the virus evolution model, realize the enterovirus subtype, and evaluate the efficacy of flu vaccine; the system had successfully assisted in several disease control measures, and could be used to develop pathogen rapid diagnosis, promote biotech industry and

international collaboration. The website page were viewed over 14,000 counts, and downloaded more than 4,500 records, and many hospitals and research institutes had established links with this system, which showed this database was the primary source of pathogen information for industry and academic society. We expect sharing of pathogenic microorganism genome database could improve the output for related health technologies and pathogen information and increase the visibility of disease control capability internationally.

Materials and Methods

A. Genome database development

Taiwan CDC established the "TPMGD-open version" (website address: http://tpmgd.cdc.gov.tw/tpmgd_public) with operation system of Redhat Enterprise Linux 5, and used Apache 2 webpage server with database system of MySQL 5.0.77, and PHP Version 5.1.6 for genome database development. Taiwan CDC referenced to related websites and evaluated frequently used sequence analytical tools and free software, and integrated analytical tools into this database. The sequence analysis function in the genome database included the following features: 1. enterovirus 71 (EV71) subtyping and recommended influenza vaccine strains information [1], 2. sequence matching (Basic Local Alignment Search Tool, BLAST) [2], 3. primer design (Primer3) [3], and 4. multiple sequence alignment and dendrogram construction [4, 5].

B. Information obtainment of genome database

Pathogen isolates comprising enterovirus, influenza virus and adenovirus are collected by Taiwan CDC's thirteen virus contract laboratories, while virus isolation and sequencing are confirmed by CDC laboratory. Virus isolate identification and sequencing processes are as previously described [6 - 8]. All sequence data are placed in order by using the BioEdit software [9], integrating with epidemiological information, then uploaded to the website. The sequencing gene fragments are HA gene of influenza virus (~ 1,000 bp), VP1 gene of enterovirus (~ 500-700 bp), and hexon gene of adenovirus (~ 800 bp). The sequence would be screened out if inadequate sequence-length, poor quality or incomplete epidemiological data. The epidemiological data will be stored into the genome database following compiling detail information of serial numbers, case number, age, gender, cities and onset date.

C. Enhancement the advocacy of genome database use

In order to improve the utilization of genome database, the documents and press releases were sent to the relevant academic institutions regarding to the establishment of this website, the registered users were informed about database updates via E-mail, furthermore, the brief introduction and link connection were placed on both Taiwan CDC's web page and the website of National Research Program for Genomic Medicine.

Results

A. The functions and applications of genome database

As the genomic medicine research blooming, international large-scale pathogen genome database and analytic platforms are

also actively developing. To build the web services for Taiwan's domestic pathogen genome database is not only following the trend, but can also strengthen the information integration of different orientation. In response to disease control, besides the storage of pathogens' data, we also include many commonly used analytical tools, and continuously update content information and develop new features to satisfy various requirements. In the function of "sequence data comparison", user can upload the sequence then choose to compare with the sequence of pathogen gene / amino acid either from Taiwan CDC or NCBI. The website offers different comparison algorithms, such as Blastp, Blastn, Blastx, Tblastn, Tblastx, etc (Figure 1-A). Result outputs and the fasta format sequence can also be downloaded by single or batch (Figure 1-B). This is the most basic and important function on the website. Through rapid matching comparison, the similarity between query sequence and the sequence data in Taiwan or other countries can be obtained; the group and type of pathogen can be determined preliminarily, or if the detected pathogen is a new unknown. For example, when pandemic influenza A (H1N1) circulated in 2009, Taiwan's first isolate from severe case was confirmed as pandemic influenza virus by sequence analysis.

Proceeding with "multiple sequence alignment and dendrogram construction" on web, one can further learn the phylogenetic

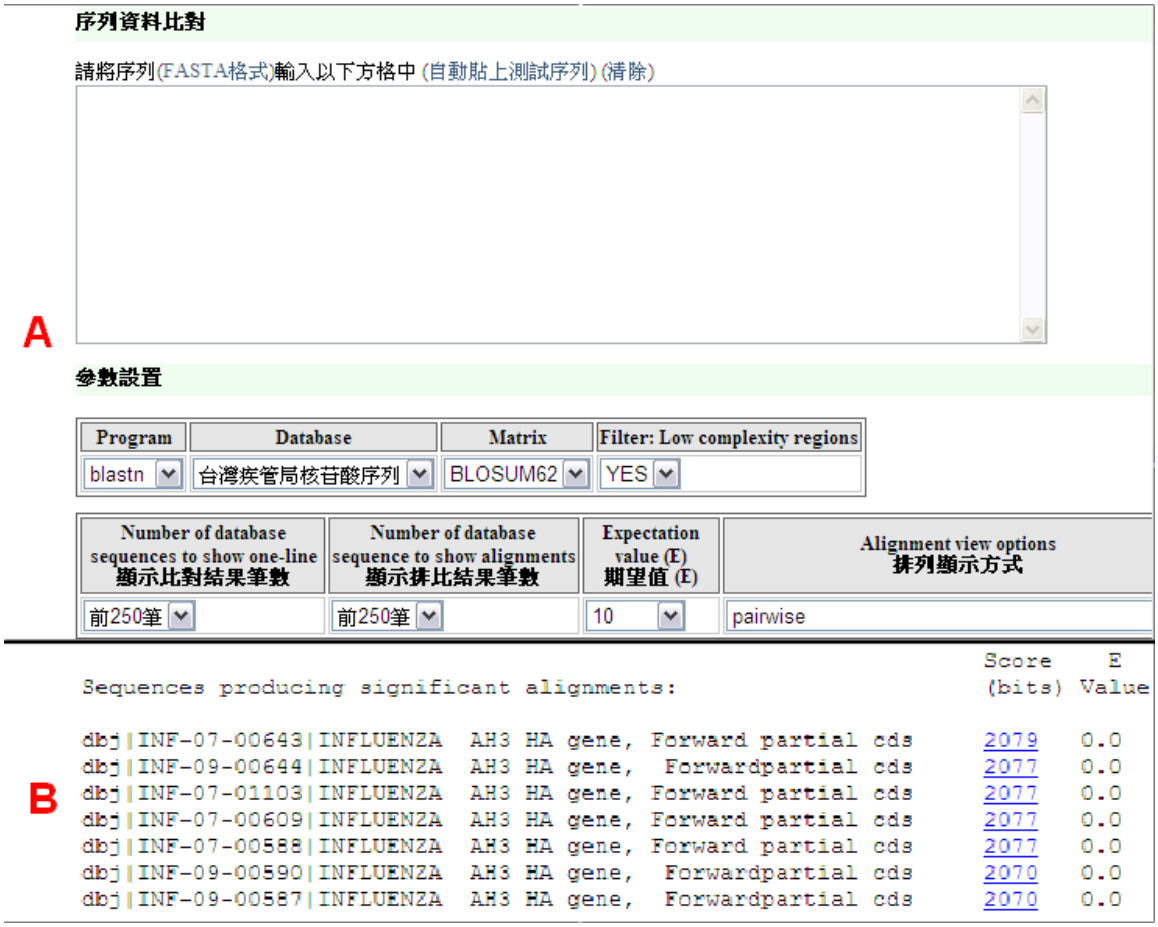

Figure 1. A Systematic interface of sequences comparison data and related parameters

B Comparison results are available to browse and download

relationship among multiple pathogen sequences and ascertain the evolutional status between each virus strain. We consolidate the related functions to form a single interface that users, after uploading sequence (in fasta format), may use ClustalW2 program (third party package) [4,5] for multiple sequence alignment with available relevant parameters as TYPE, ALIGNMENT, BOOTSTRAP., etc. Also, for more convenience, user can use Jalview program (third party package) to edit the results of multiple sequence alignment directly (Figure 2-A). On phylogenetic tree drawing (Fig. 2-B), there are different parameters for customization options. Alignment results after operation may send by E-mail to save time.

User may get the appropriate primer sequence through "primer design" from this website for performing PCR or RT-PCR to amplify nucleic acid sequences, hence to detect pathogens or follow-up sequencing analysis. This software adopts Primer3 package [3] and offers various modification options of related parameters, such as product size ranges, number to return, left primer input, right primer input, etc. (Figure 3). User only needs to upload sequence and set parameters, then figure out suitable primers and download the results for reference.

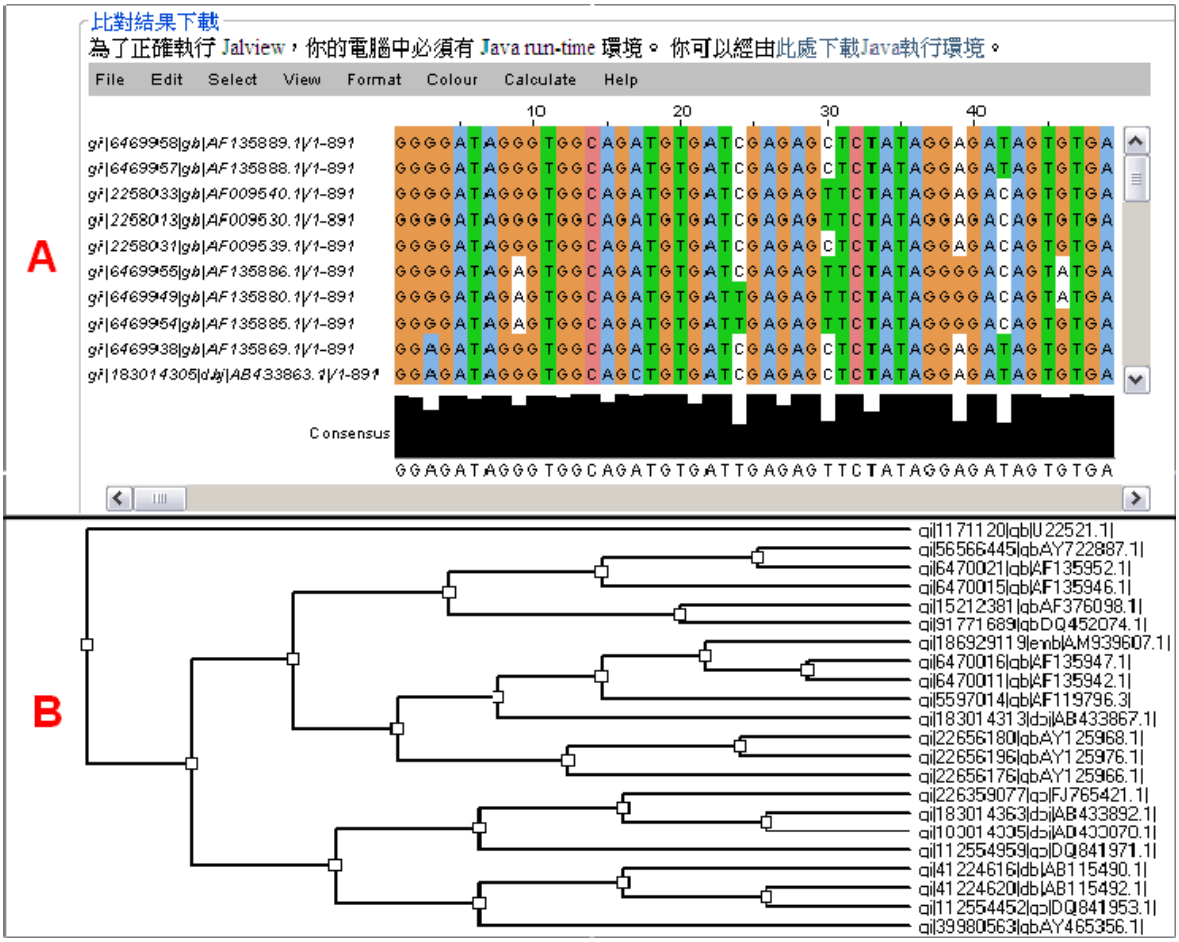

Figure 2. A System provides online editing results of multiple alignment

B Multiple alignment sequences can generate phylogenetic tree by the system

Figure 3. Primer design and adjustment of relevant parameters

On the other hand, in view of integrating molecular biology and epidemiological information is an important foundation for pathogen research and disease control, this website originates the single corresponding mode to compiled sequence data and epidemiological information into the same database. After sequence comparison, user can access the epidemiological information and inquire the interested serial number for in-depth research. This website provides users the drop-down menu, by year or month, and category to inquire epidemiological data by current system (including serial number, patient number, age, gender, cities, onset date, etc.), and detailed sequence information statements (including varied columns of serial number, type, virus, locus, and onset date). As of April 2010, the pathogen information stored in genome database contains a total of 4,864 sequence data for influenza virus, 5,695 for enterovirus, and 674 for adenovirus during 2005 to 2009. Data cover subtypes with high reference value for either analysis of gene evolution or epidemiology.

B. The effectiveness of genome database in disease control

This genome database contains plentiful information and analytical function and has been extensively applied to the research of domestic enterovirus, influenza virus and adenovirus. As enterovirus affects citizens enormously, of which EV 71 causes the most

harm, subtyping analysis are very important in enterovirus identification not only to comprehend origin and transmission mode of virus but can also prevent and take measures for specific strains. Using the website's gene subtyping function, after uploading a single VP1 gene sequence of enterovirus, and BLAST comparing with EV71 genetic subtype database, one can acquire the closest or most likely genetic subtype from marked subtype, such as A, B4, C5, etc., in compared results. User can download the compared results, and draw phylogenetic tree (Figure 4) as well, or upload compressed multiple sequences to make batch subtype matching with numerous EV 71 strains. The comparison results output by text file are user-friendly for reference and greatly improve the efficiency of phylogenetic analysis. In recent years, the genetic database is notable in application of enterovirus prevention. During 2006 to 2007, subtypes B5 and C5 of EV 71 emerged in Taiwan were confirmed through sequence comparison [8]. Possible prevalence warning of enterovirus was made based on sequence comparison in early 2008, moreover, the primary pathogen in severe enterovirus cases was confirmed to be EV 71 subtype B5 which was not connected with China's subtype C4 pandemic and reduced public panic and worry. According to phylogenetic tree, subtype C4 is confirmed as circulation strain this year, 2010, and similar to strains in China, so that citizens going to China for travel or business need to be more vigilant to avoid infection.

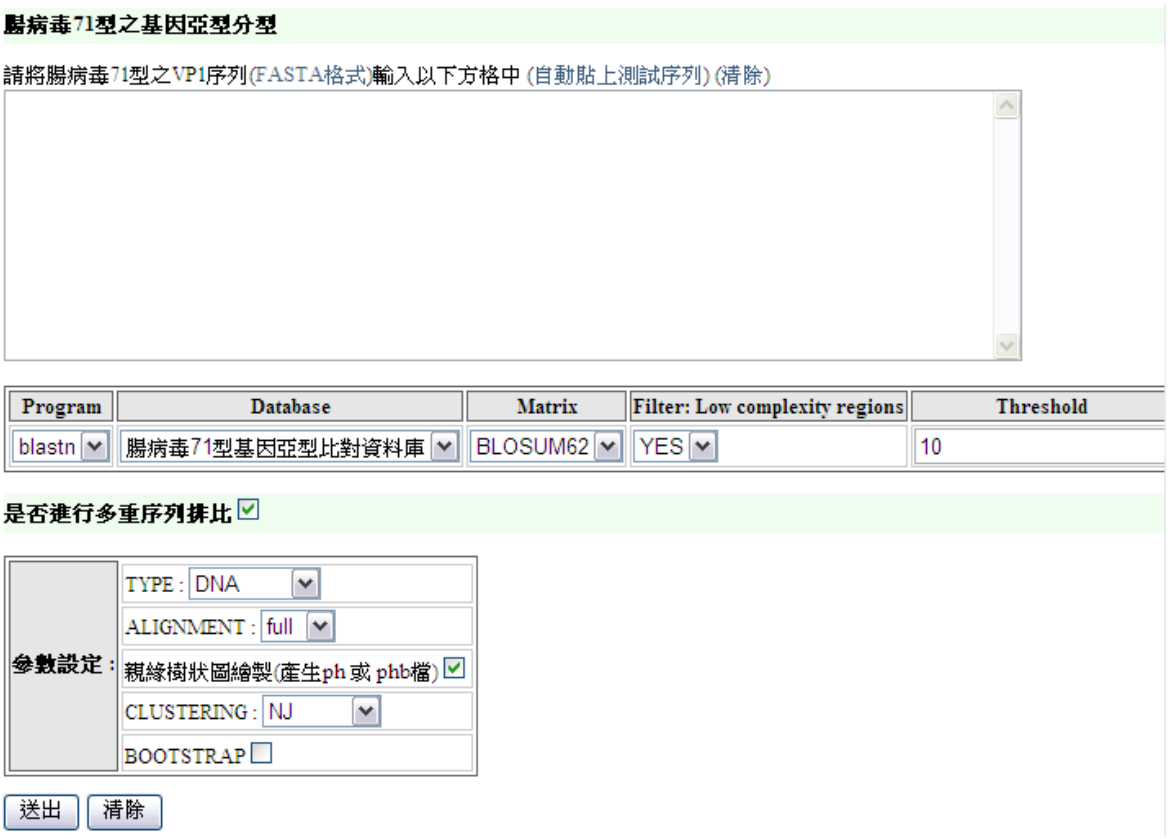

Figure 4. Subtyping interface for EV 71

Besides enterovirus, the influenza virus also has caused several waves of major epidemic worldwide over the years. The subtype identification of virus strain and the analysis of proposed influenza vaccine strains are highly important in terms of influenza control. The function of "recommended influenza vaccine strains information" resembles to the above-mentioned EV 71 subtyping that allows user to BLAST with WHO's recommended influenza vaccine strains database or draw the phylogenetic tree by uploading a single HA gene sequence of influenza virus or batches comparison for compressed multiple influenza virus sequences. One then knows the most similar or most likely vaccine strain to the compared sequences from the marked influenza vaccine strains in results, such as AH1, PH1, B-Yam, etc. In order to achieve the accuracy of sequence comparison, we also regularly update the sequence data of WHO's recommendatory vaccine strain (the proposed vaccine strains for Northern Hemisphere announced in February and in September for Southern Hemisphere). Besides to analyze the subtypes of the virus strains and to confirm the origin of virus, these results can be used for preliminary determination of antigenic differences between epidemic strains and recommended vaccine strains, in addition to assess if the protectiveness of vaccine is enough through laboratory antibody data. The analysis results are also reported regularly in National Influenza Center's meetings with considerable reference value for forecasting epidemic trend, research and selection of vaccine strains, or policy-making for disease control.

C. The promotion of genome database

Since the building funds and resources of the genome database are derived from the population, the research results should not be obtainable confined to specific individuals, organizations, or through particular ways. Therefore, the database is accessible to the general public through register, and the information acquirement process is constantly abridged. Currently, user only needs to register by filling out the basic information for free downloading and use of the web resources, sharing government's research with everyone is our goal. To publicize and promote the genome database, Taiwan CDC has issued a press release in March 2009, sent documents to research institutions and biomedical colleges in May, to inform the establishment of this website. So far there have been many medical and research organizations set up web links. Meanwhile, the brief introduction and connecting routes are on motif zone of Taiwan CDC's homepage and the website of National Research Program for Genomic Medicine. Furthermore, the registrants are notified periodically about genome database update message by E-mail, and we take the initiative in introducing and promoting this website in Taiwan CDC's conference of "Establishment of Taiwan's pathogen genome database" project and at the preparatory meeting of National Science Council's science and technology program. As of April 2010, exceeding 245 users have registered and more than 1,560 times to login on this website.

Discussion

To identify and test infectious disease pathogens by molecular biology methods,

either nucleic acid or protein, are not only more efficient, but also reduce the error of strain typing and untypeable virus strain by traditional methodology. Epidemiological information of the infected case are essential for case managing, pathogen sources finding, epidemic forecasting, and related health policy making. All of these rely on molecular epidemiology database establishment, collection, and integration, and which could be used for infectious diseases control, and also the basis of biotech industry research and development, and international collaboration. Through the collaboration of nationwide clinics and hospitals, CDC branch offices and headquarter laboratories, bio-material reserve center, and information technology professions, the genome database contains sequences and epidemiology information of influenza virus, enterovirus, and adenovirus. The pathogens are collected and isolated by CDC virus contract laboratories, sequenced and confirmed by CDC laboratory, and exclusion of inadequate sequence length, low quality and incomplete patient information. After alignment and integration of epidemiological information, the sequence data are uploaded to keep this genome database in both good utility and sample representativeness.

However, in the construction process of genome database, what we faced were effectiveness of website promotion, usefulness of analytical tools, updating frequency of sequence information, volume of sequence data, and information safety. Under the circumstances of insufficient promotion and inadequate analytical tool, more genome database efficiency and precise epidemic forecasting and research are challenges. Therefore, to solve those problems in different dimensions should be important considerations. Also, the information safety and privacy issues should be addressed. On the other hand, due to leakage of personal privacy and other security incidents, information security protection issues deserve more attention. When we designed the genome database, in addition to the account and password protection, system weakness detection, firewall setup, computer virus, and hack programs detection were critical for user information protection and privacy assurance.

Based on the principles of government information sharing, Taiwan CDC genome database is open to the public in improving the biological information technology exchange and promotion. In addition, since Taiwan CDC opened pathogen sequence data application from 2006, and till now, over 20 scholars have accessed 25,000 gene sequence records and epidemiology information, and published papers, such as evolution of influenza virus [6], findings of imported Taiwan enterovirus 71 [8], and secular trend of genome types of respiratory adenovirus [10].

Genome database included HA gene of influenza virus, VP1 gene of enterovirus, and hexon gene of adenovirus. Selection the location of these genes is based on antigen detection or common areas for genotyping. Other important genes such as NA gene related with drug resistance of influenza virus, VP4 gene and recombination associated non-structural protein gene for enterovirus typing, are target goals for future expansion.

Larger and more comprehensive gene databases in the international community, e.g.,

GenBank, EMBL-EBI, DDBJ, ViPR and NMPDR, which covered wide range of species and more analyzable gene numbers (including enzymes or structural proteins), and integrated a variety of analytical tools for biological information (such as gene annotation, protein structure and search for motif, epitope, as well as sequence polymorphism analysis, etc.), were no doubt more innovative and practical in analyzing known and unknown pathogens in the gene function and development or exploring of new drugs or test kits. However, considering the emerging public health issues and regional communicable diseases, relying on international information collected from foreign countries was not reasonable. Therefore, Taiwan CDC established the pathogen genome database followed the NCBI model. It contains frequent epidemic viruses such as influenza virus, enterovirus, and adenovirus, provides essential references for epidemiological linkage and data sharing, and is highly valuable to public health research and infectious disease control. Refer to the development model and advantages of large scale gene databases in international society could improve the infectious diseases control efficiency in the short run; and in the long run, it could improve the health of population and international collaboration. We welcome feedbacks from users to improve system integration and development of useful software, and also expect to derive more valuable information for infectious disease control and biotechnology development. Therefore, the system is not merely a database, but also applicable in realty levels. In the future, we expect to collaborate with academic society for analytical software development and expand sequence volume and variety of pathogens to achieve the best efficiency of the database.

Acknowledgements

Partial sequence information of this website derived from “Taiwan Pathogenic Microorganisms Genome Database” offered by Taiwan CDC (supported by National Research Program for Genomic Medicine 99-0324-01-F-12). We would like to thank the advanced bioinformatics core facilities conduct by National Yang-Ming University and National Science Council, Jhih-Wei Jian (research assistant from alternative military service), and Hao-Chang Hsu (research assistant) for system development; and virus contract laboratories in National Taiwan University Hospital, Tri-Service General Hospital, Taipei Veterans General Hospital, Chang Gung Memorial Hospital (Linkou Branch), Taichung Veterans General Hospital, China Medical University Hospital, Chung Shan Medical University Hospital, Changhua Christian Hospital, National Cheng Kung University Hospital, Kaohsiung Medical University Hospital, Kaohsiung Veterans General Hospital, Chang Gung Memorial Hospital (Kaohsiung Branch), and Buddhist Tzu Chi General Hospital for collection and providing of specimens.

References

1. WHO. Recommendations for influenza vaccines. Available at: http://www.who.in/csr/disease/influenza/vaccinerecommendations/en/index.html
2. NCBI. BLAST NEWS. Available at: http:

//www.ncbi.nlm.nih.gov/blast/Blast.cgi?CMD=Web&PAGE_TYPE=BlastNews#1
3. Primer3. Available at: http://primer3.sourceforge.net/.
4. EBI. Tools. Sequence Analysis. ClustalW2. Available at: http://www.ebi.ac.uk/Tools/clustalw2/index.html
5. Thompson JD, Higgins DG, Gibson TJ. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice**.** Nucleic Acids Res 1994;22(22):4673-80.
6. Jian JW, Lai CT, Kuo CY, et al. Genetic analysis and evaluation of the reassortment of influenza B viruses isolated in Taiwan during the 2004-2005 and 2006-2007 epidemics. Virus Res 2008;131(2):243-9.
7. Tseng FC, Huang HC, Chi CY, et al. Epidemiological survey of enterovirus infections occurring in Taiwan between 2000 and 2005: analysis of sentinel physician surveillance data. J Med Virol 2007;79(12):1850-60.
8. Huang YP, Lin TL, Kuo CY, et al. The circulation of subgenogroups B5 and C5 of enterovirus 71 in Taiwan from 2006 to 2007. Virus Res 2008;137(2):206-12.
9. Hall TA. BioEdit: a user-friendly biological sequence alignment editor and analysis program for Windows 95/98/NT. Nucl Acids Symp Ser 1999;41:95-8.
10. Lin YC, Lin KH, Ke GM, et al. Secular trend of genome types of respiratory adenovirus type 3 during 1983-2005: a study from Taiwan. Arch Virol 2010;155(2):287-92.

Analysis and Evaluation of the National Notifiable Diseases in Taiwan, 2008

Sau-Yu Liao, Che-Chieh Yen, Hui-Hsun Hung

Fifth Division,
Centers for Disease Control, Taiwan

Abstract

To evaluate the trend of notifiable diseases in 2008, this study analyzed the surveillance data of notifiable communicable diseases in Taiwan, starting from January 1 to December 31, 2008 (disease onset in year 2008). The results of this study indicated that the Category Four notifiable diseases had the highest case number (13,254 cases). The major diagnosis of the imported cases was dengue fever (226 cases), and most of these cases were from Southeast Asian countries, such as Indonesia and Vietnam. “Invasive pneumococcal disease” had the highest confirmed cases (805 cases), and “severe complicated influenza” had the highest fatality rate (13.6%). The ratio of male to female in notifiable diseases in 2008 was 1.8:1. Not only children younger than 5 year-old and the elderly older than 65 year-old, but also people aged between 25 and 64 had a considerable proportion of being infected by acute notifiable diseases. Regarding chronic notifiable diseases, tuberculosis was still the most common disease in 2008, but there was an upward trend in syphilis and gonorrhea.

Keywords: Notifiable Diseases, acute notifiable disease, trend, disease surveillance

Introduction

Despite of the technologic development in the twenty first century, the communicable diseases are still the potential risks for people, which threaten people's health and increase social cost. For instance, in Taiwan, the dengue outbreak in 2002, SARS outbreak in 2003, and in recent years, human avian influenza cases still happened in the world.

According to the announcement from Department of Health, Executive Yuan, on October 24, 2008, the sixty notifiable diseases were classified into five categories [1]. Acute and chronic notifiable diseases differ based on the incubation period. Among all of these diseases, gonorrhea, syphilis, leprosy, HIV infection (including maternal vertical transmission), AIDS, and tuberculosis belong to chronic notifiable diseases, and the others are acute notifiable diseases. All diseases should be reported. This study investigated the reported and confirmed cases of acute notifiable diseases and the laboratory findings, as well as confirmed cases of chronic notifiable diseases. It also compared the statistics of domestic and imported cases, imported countries, and fatal case number in each disease in the past three years, in order to evaluate the trend of infectious disease in 2008 and offer the reference materials for disease control policies.

Materials and Methods

We analyzed the reported cases in 2008 (onset year) from WEB system, Taiwan CDC (TCDC), including basic data, the reporting number, reported diagnosis, confirmed diagnosis, imported cases, as well as case interpretation, and acquired the information in 2005-2007 from "Statistics of Communicable Diseases and Surveillance Report" issued by TCDC. We used pivot table of Microsoft Excel software for statistical analysis. We also used mid-year population in 2007 published by Ministry of the Interior to calculate the incidence rate and mortality rate (per one hundred thousand population) of each acute notifiable infectious disease. The death number was determined as those who died from infectious diseases, and the evidence was based on death certificate. Patients with positive laboratory findings were identified as confirmed cases after case investigation. The formula of fatality rate is as follows:

$$\text{Fatality Rate}(\%) = \frac{\text{Deaths}}{\text{Confirmed Case}} \times 100\%$$

Results

Acute Notifiable Infectious Diseases

A. Reported case number, confirmed cases, mortality, and positive rate in each category of notifiable infectious diseases

There were 27,112 reported cases, a total of 16,991 confirmed cases, and 41 mortality cases of acute notifiable infectious diseases in 2008. Among all of these cases, no case was reported in Category One and Five. A total of 3,208 reported cases and 1,474 confirmed cases were Category Two; 3,689 reported cases and 2,065 confirmed cases were Category Three; and 20,215 reported cases and 13,452 confirmed cases were Category Four. The death number in Category Two, Three, and Four were 1, 16, and 24, respectively.

In addition, for reported case which needs specimen collection for testing according to the regulation [2], the laboratory findings were classified as positive, negative, exclude,

uncertain, pending, and others. The “others” include: past infection with antibody or positive result and uncertain diagnosis, etc.

B. The distribution of notifiable infectious diseases

In 2008, the numbers of confirmed cases in acute notifiable infectious diseases in descending order were 815 in invasive pneumococcal disease, 714 in dengue fever, 482 in scrub typhus, 373 in enterovirus infection with severe complication, and 236 in acute hepatitis A etc. The fatality rates were 13.6% in severe complicated influenza, 3.8% in enterovirus infection with severe complication, and 2.5% in invasive pneumococcal disease. Invasive pneumococcal disease had the highest mortality rate (0.087/100,000 population) (Table 1).

Table 1.Confirmed cases, incidence, deaths, mortality, and fatality of acute notifiable diseases – Taiwan, 2008

Disease	Confirmed cases	Incidence Rate◎	Deaths ※	Mortality Rate #	Fatality Rates (%)
Invasive Pneumococcal Disease	805	3.5	20	0.0873	2.5
Dengue Fever	714	3.1			
Scrub Typhus	482	2.1			
Enteroviruses Infection with Severe Complications	373	1.6	14	0.0611	3.8
Acute Viral Hepatitis type A	236	1.0			
Acute Viral Hepatitis type B	229	1.0			
Amoebiasis	221	1.0	1	0.0044	0.5
Acute Viral Hepatitis type C	124	0.5			
Q Fever	90	0.4			
Shigellosis	90	0.4			
Acute Flaccid Paralysis, AFP	74	0.3			
Legionellosis	68	0.3	1	0.0044	1.5
Melioidosis	45	0.2			
Leptospirosis	44	0.2			
Pertussis	41	0.2			
Rubella	33	0.1			
Typhoid Fever	32	0.1			
Endemic Typhus Fever	30	0.1			
Cat-Scratch Disease	28	0.1			
Severe Complicated Influenza Case	22	0.1	3	0.0131	13.6
Acute Viral Hepatitis, Untyped	20	0.1			
Meningococcal Meningitis	19	0.1			
Malaria	18	0.1			
Japanese Encephalitis	17	0.1	1	0.0044	5.9
Creutzfeldt-Jakob Disease	16	0.1	1	0.0044	6.3
Acute Viral Hepatitis type E	14	0.1			
Invasive Haemophilus Influenzae type b Disease	12	0.1			
Botulism	11	0.0			
Paratyphoid Fever	11	0.0			
Measles	10	0.0			
Chikungunya Fever	9	0.0			
Dengue Hemorrhagic Fever/Dengue Shock Syndrome	5	0.0			
Acute Viral Hepatitis type D	4	0.0			
Toxoplasmosis	2	0.0			
Lyme Disease	2	0.0			
Hantavirus Syndrome	1	0.0			
Cholera	1	0.0			
Congenital Rubella Syndrome	1	0.0			
total	3,954	17.3	41	0.1789	1.0

◎Per 100,000 population, confirmed case divided by number of mid-year population in 2007.
※Number of confirmed case died due to notifiable disease.
Per 100,000 population, deaths divided by number of mid-year population in 2007.
☆Number of mid-year population in 2007 is 22,917,444.

C. Statistics of imported confirmed cases

The number of imported confirmed cases in 2008 was 493, and which was 12.5% of the total confirmed cases (Table 2), including dengue fever (226 cases), amebiasis (82 cases), bacillary dysentery (44 cases), acute hepatitis A (35 cases), and typhoid fever (19 cases), etc. These imported cases came from 28 countries, including Indonesia (151 cases), Vietnam (85 cases), China (44 cases), Thailand (40 cases), and Philippines (40 cases), etc. The majority of imported cases were from Asia, especially Southeast Asia area.

D. The comparison in case number of acute notifiable infectious diseases between 2008 and the average from 2005 to 2007

The comparison of the case number in acute notifiable infectious disease between 2008 and the average number from 2005 to 2007 is shown in Figure [3-5]. The figure illustrated that the most marked increase in

Table 2. Imported confirmed cases of acute notifiable diseases, by imported countries – Taiwan, 2008

Diseases	Indonesia	Vietnam	China	Thailand	Philippines	Kampuchea	Malaysia	India	Japan	Myanmar	Singapore	Other countries∗	Total
Dengue Fever	48	73		30	25	10	8	3		14	7	8	226
Amoebiasis	62	2	4		10							4	82
Shigellosis	12	4	7	2		8	1	3			2	5	44
Acute Viral Hepatitis type A	2	2	12	1	3	3	3	4	1			4	35
Typhoid Fever	17							1		1		0	19
Malaria	2			2		1	1	2				10※	18
Other Diseases ◎	8	4	21	5	2	2	7	5	1	0	1	13	69
Total	151	85	44	40	40	24	20	18	2	15	10	44	493

∗Other countries: Korea, Brunei, Pakistan, Bangladesh, Malawi, Mozambique, Chad, Papua New Guinea, Egypt, Guinea Equatorial, Sao Tome and Principe, the United States, Honduras, Denmark, Tonga, Australia, Unknown (patient had been to more than two countries).

◎Other diseases: Acute hepatitis B, Chikungunya Fever, Rubella, Paratyphoid fever, Measles, melioidosis, Acute hepatitis E, Legionellosis, Epidemic Typhus, Acute hepatitis C, Lyme disease, Scrub typhus, Q fever, Pertussis, Dengue hemorrhagic fever/Dengue shock syndrome, Congenital Rubella Syndrome

※2 cases in Malawi, 3 cases in Mozambique, 4 cases in Papua New Guinea, 1 case in Guinea Equatorial, all the countries are in Africa.

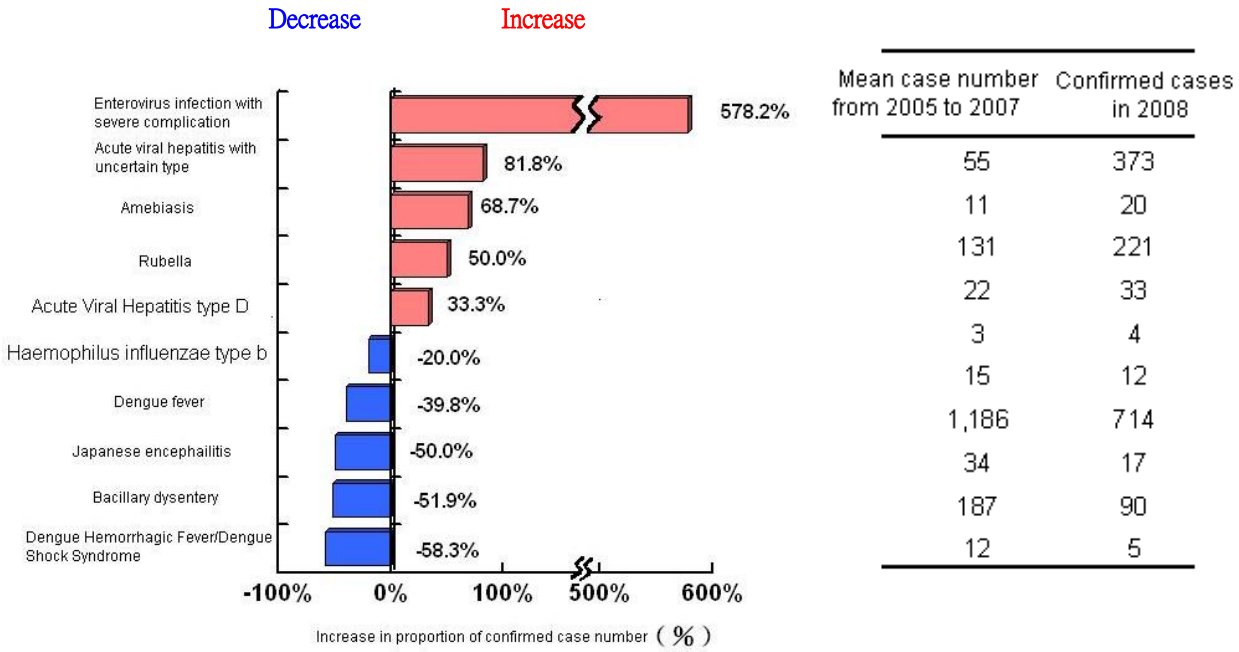

Figure. The comparison of the case number in acute notifiable infectious disease between 2008 and the mean case number from 2005 to 2007 in Taiwan

proportion of confirmed case number were "enterovirus infection with severe complication" (578.2%), "acute viral hepatitis with uncertain type" (81.8%), "amebiasis" (68.7%), "rubella" (50.0%), and "acute hepatitis D" (33.3%). Diseases with the most significant decrease in proportion of case number were "dengue hemorrhagic fever/dengue shock syndrome" (-58.3%), "bacillary dysentery" (-51.9%), "Japanese encephailitis" (-50.0%), "dengue fever" (-39.8%), and "Invasive Haemophilus influenzae Type b infection" (-20.0%).

E. Statistics of gender, age of onset, month of onset in acute notifiable infectious diseases

The gender and age of onset (Table 3) and onset month (Table 4) in acute notifiable

Table 3. Confirmed indigenous cases of acute notifiable diseases, by sex and age group-Taiwan, 2008 (excluding varicella, tetanus and mumps)

	sex		Age group (yrs)					
Disease	Female	Male	0~14	15~24	25~39	40~64	≧65	Total
Invasive Pneumococcal Disease	257	548	205	10	57	216	317	805
Enteroviruses Infection with Severe Complications	144	229	373					373
Acute Flaccid Paralysis, AFP	24	50	74					74
Pertussis	19	21	33	3	2	2		40
Meningococcal Meningitis	13	6	10	1		3	5	19
Invasive Haemophilus Influenzae type b Disease	6	6	11			1		12
Measles	3	1	2	1	1			4
Rubella	9	16		21	3	1		25
Dengue Fever	225	263	39	45	104	231	69	488
Scrub Typhus	165	316	31	80	94	204	72	481
Acute Viral Hepatitis type B	89	126	3	25	105	72	10	215
Acute Viral Hepatitis type A	85	116	9	41	74	54	23	201
Amoebiasis	19	120	2	7	29	86	15	139
Acute Viral Hepatitis type C	36	86	1	10	40	53	18	122
Q Fever	13	76		5	22	52	10	89
Legionellosis	14	51	1		4	25	35	65
Shigellosis	21	25	18	5	12	6	5	46
Leptospirosis	6	38		3	12	23	6	44
Melioidosis	5	35			4	22	14	40
Cat-Scratch Disease	11	17	11	6	6	5		28
Endemic Typhus Fever	11	16		2	6	18	1	27
Severe Complicated Influenza Case	11	11	5	2	4	5	6	22
Acute Viral Hepatitis, Untyped	11	9	3	1	8	7	1	20
Japanese Encephalitis	5	12	1	2	5	9		17
Creutzfeldt-Jakob Disease	7	9				10	6	16
Typhoid Fever	5	8	1	2	7	2	1	13
Botulism	8	3			4	6	1	11
Acute Viral Hepatitis type E	5	5		1	6	1	2	10
Dengue Hemorrhagic Fever/Dengue Shock Syndrome	2	2		1	1	1	1	4
Acute Viral Hepatitis type D		4			1	3		4
Paratyphoid Fever	2	1	1		1	1		3
Toxoplasmosis	1	1		1	1			2
Hantavirus Syndrome		1			1			1
Cholera	1						1	1
Total	1,233 (35.6%)	2,228 (64.4%)	834	275	614	1,119	619	3,461

Table 4. Confirmed indigenous cases of acute notifiable diseases, by month-Taiwan, 2008（excluding varicella, tetanus and mumps）

Disease\Month	1	2	3	4	5	6	7	8	9	10	11	12	Total
Invasive Pneumococcal Disease	82	77	125	65	59	47	30	37	50	52	52	129	805
Dengue Fever	21		3			5	40	91	48	131	131	18	488
Scrub Typhus	47	14	11	15	24	61	100	47	37	39	48	38	481
Enteroviruses Infection with Severe Complications	13	6	14	40	100	137	31	13	6	4	2	7	373
Acute Viral Hepatitis type B	17	11	17	19	20	24	14	14	22	24	15	18	215
Acute Viral Hepatitis type A	24	23	42	21	14	8	11	8	17	13	9	11	201
Amoebiasis	12	24	44	9	4	11	7	1	5	10	7	5	139
Acute Viral Hepatitis type C	7	7	15	13	9	14	12	9	5	16	9	6	122
Q Fever	7	5	18	15	10	13	7	3	3	3	3	2	89
Acute Flaccid Paralysis, AFP	6	6	7	8	9	10	5	5	5	6	3	4	74
Legionellosis	2	6	2	8	4	6	7	4	5	8	5	8	65
Shigellosis	1	4	5	17	3		1	2	9		2	2	46
Leptospirosis	3	1	2	2	3	5	2	8	10	4	3	1	44
Melioidosis	1	2	2	3		2	10	7	2	3	5	3	40
Pertussis		1	4	1	3	8	11	6	4	1	1		40
Cat-Scratch Disease					1	3	8	4	6		6		28
Endemic Typhus Fever	1	1	1	1	5	2	8	1	2	3	1	1	27
Rubella	1	1	5	11	1	4		2					25
Severe Complicated Influenza Case	6	3	4							2		7	22
Acute Viral Hepatitis, Untyped		1	2	5			3	1	2	2	3	1	20
Meningococcal Meningitis	3	3	4			2		5	1		1		19
Japanese Encephalitis					1	9	6				1		17
Creutzfeldt-Jakob Disease	1	3	2	4	3	1	1		1				16
Typhoid Fever			1	2	5	1			3		1		13
Invasive Haemophilus Influenzae type b Disease	1		1	1	2			1	1	1		4	12
Botulism		4	1	6									11
Acute Viral Hepatitis type E		2		1	1		3	1	1	1			10
Measles						1		1				2	4
Dengue Hemorrhagic Fever/Dengue Shock Syndrome							1			2		1	4
Acute Viral Hepatitis type D		1				1	1		1				4
Paratyphoid Fever					2	1							3
Toxoplasmosis						1					1		2
Hantavirus Syndrome			1										1
Cholera					1								1
Total	256	206	333	267	284	377	319	271	246	325	309	268	3461

infectious diseases in 2008 demonstrated that both men and women easily suffered from “invasive pneumococcal diseases”, “scrub typhus” and “dengue fever”. According to different age of onset, “enterovirus infection with severe complication” was common in children younger than 14 year-old. “Invasive pneumococcal disease”, which had the highest case number, was common in the elderly older than 65 year-old and children younger than 14

year-old. Considering the total number of acute notifiable infectious disease, people aged between 25 and 39 (614 cases) and aged between 40 and 64 (1,119 cases), with 17.7% and 32.3% of the confirmed cases in total, respectively, should not be ignored.

According to month of onset, the average case number of each month was approximately 289, but the case number reached a peak (377 cases) in June. “Invasive pneumococcal disease” occurred all over the whole year, but happened more frequently between December and next March. “Dengue fever” was common starting from June to next January. “Enterovirus infection with severe complication” reached a peak during April and July, while “severe complicated influenza” took place usually from December to next March.

Discussion

A. The analysis of notifiable infectious diseases and laboratory results

The statistics of acute notifiable infectious diseases indicated that Category Four had the highest number of both reported cases (20,215 cases) and confirmed cases (13,452 cases). Even if the diseases which do not need specimens collection were excluded, such as varicella (11,875 cases), mumps (1,144 cases), tetanus (18 cases), Category Four still had the highest number of confirmed cases. It is noticeable that there was a higher proportion of uncertain diagnosis in Category Three. The main reason was that specimens could not be collected and sent for laboratory examination, which may result from death or missing cases, as well as patients or family refused a second specimen sampling when the first laboratory finding was uncertain and patients felt better, or the clinical doctors thought second sampling was not needed. For some special specimens, like CSF in “Japanese encephalitis”, it should be collected during admission. Failure of specimen sampling was mostly caused by patients or family’s refusal, or discharged. Acute hepatitis C was another disease easily classified as uncertainty. The diagnosis of acute hepatitis C was confirmed by system only if “negative anti-HCV antibody before and converted to positive anti-HCV antibody”. If reported cases only had single positive anti-HCV antibody, the diagnosis would be uncertain by the system. However, some cases were interpreted as negative or uncertain due to laboratory findings, even clinical manifestation correlated to the disease. In addition to improve the timing and technique of specimen collection, we need to evaluate the methods and items of laboratory examinations, as well as the laboratory technique, in order to increase our capacity of diagnosis for other unknown infectious diseases, and assist the clinical diagnosis.

B. The epidemiology of acute notifiable infectious diseases

“Severe complicated influenza” happens in all ages of people and cannot be ignored. Although TCDC has the immunization policy, annual vaccination for influenza is necessary for prevention. Continue monitoring and surveillance of influenza cases is suggested for further evaluation. “Invasive pneumococcal disease” had the highest number of confirmed cases in the whole year (805 cases, the incidence rate was about 3.5/100,000), and it usually occurred in ages younger than 14 or older than 65. This disease

had been enrolled in Category Four in October 2007, and the immunization of pneumococcal vaccine had been implemented recently. Therefore, we have to closely observe the vaccine effectiveness on the case numbers. “Dengue fever” had the second highest confirmed case number in this country. After the efforts of the heath authorities, the case number was lower than that in 2007. However, Taiwan is situated in subtropical area and Southeast Asia is the endemic area. The frequent international travels bringing in the risk of dengue outbreak in endemic seasons. The local health authorities must enforce control measures such as elimination of breeding sites and monitoring. Moreover, “scrub typhus” and “enterovirus infection with severe complication” should be closely followed up. The case numbers of scrub typhus remained a steady trend in recent years. The case number of enterovirus infection with severe complication in 2008 was higher than the average number in the past three years, and which indicated that the control measures of enterovirus infection should be carried out more hardly, in particular, the development of vaccine.

C. Analysis of imported cases

In 2008, the most common imported acute infectious disease was “dengue fever”, and followed by “amebiasis” and “bacillary dysentery”. Amebiasis and bacillary dysentery are acute gastrointestinal infectious diseases, and both are transmitted via fecal-oral route. Therefore, apart from prevention of mosquito bites, we need to emphasize the importance of food sanitation and personal hygiene to the public. Southeast Asia is the main source of imported cases, especially Indonesia, Vietnam, and China, and nearly half of the imported cases were from these countries. Providing health education to the tourism staff, foreign labors, foreign spouses, and visitors will be one of the major tasks in the future.

D. Analysis of gender, age, and endemic seasons

In indigenous acute notifiable infectious diseases, the number of confirmed cases in “invasive pneumococcal disease”, “scrub typhus”, and “amebiasis” was much higher in men; the total number of confirmed cases in men was twice as many as that in women. The age distribution of acute notifiable infectious diseases demonstrated two vulnerable groups, who aged younger than 14 and older than 65. Adults aged between 25 and 64 had many confirmed cases too; there was an upward trend of acute hepatitis in this group, so the surveillance targets shall be focused on not only children and the elderly but also the adult group in the future. In month of onset, “invasive pneumococcal disease” usually happens between fall and winter, while “dengue fever” occurred in the beginning of the year and the second half of the year. Looking at the total case number in each month, there were approximately 200-300 confirmed cases every month. There was the highest case number in June, and the reason could be that June was the endemic season for many acute notifiable infectious diseases. In the planning of future surveillance system, we will closely monitor each disease in the endemic season, especially at the peak seasons for different diseases. We will make the coping strategies to prevent disease outbreak and cluster.

E. Chronic notifiable infectious diseases

In 2008, tuberculosis was still the most common chronic notifiable diseases, but the case number was decreasing. The change of case numbers in HIV infection and AIDS might involve some issues, such as drugs or homosexual problems. It should be noted that there was an upward trend in case numbers of syphilis and gonorrhea, and it meant that we still need work hard to control and monitor of the diseases.

The analysis of this study was based on the information from the surveillance system, and the targets were reported cases. For the patients who had not been reported, we need to use “reporting rate” in each disease for further evaluation. We can combine other medical information, such as databank of national health insurance and analyze further in the future. Some diseases with pending laboratory results, or uncertain diagnosis might lead to little inaccuracy in case number. For chronic notifiable infectious diseases, since the date of onset was not easy to define, we used “date of diagnosis” for statistics. The different timings for collecting data probably made an error of case number, but it did not change the distribution of case number. We wish our study can provide the trend of notifiable infectious diseases in 2008, and offer the reference materials for making future policies on disease control.

References

1. Taiwan DOH. Categories of Communicable Diseases of The Categories of Communicable Diseases and Preventive Measures for Category Ⅳ and V Communicable Diseases 2008. Available at: http://dohlaw.doh.gov.tw/Chi/EngContent.asp?msgid=197
2. Taiwan CDC. Guidelines for Communicable disease Surveillence 2008. Available at: http://www.cdc.gov.tw/public/data/031014264371.pdf
3. Taiwan CDC. Statistics of Communicable Diseases and Surveillance Report, Republic of China, 2007. Available at: http://www.cdc.gov.tw/public/data/922617103071.pdf
4. Taiwan CDC. Statistics of Communicable Diseases and Surveillance Report, Republic of China, 2006. Available at: http://www.cdc.gov.tw/public/data/89117122671.pdf
5. Taiwan CDC. Statistics of Communicable Diseases and Surveillance Report, Republic of China, 2005. Available at: http://www.cdc.gov.tw/public/data/89311283571.pdf