The 2003 SARS Outbreaks in Taiwan

Yi-Ming Arthur Chen

Introduction

Severe acute respiratory syndrome (SARS) is caused by SARS-associated coronaviruses (SARS-CoVs) (Drosten et al., 2003; Fouchier et al., 2003; Peiris et al., 2003b; Ksiazek et al., 2003). The first known outbreak of SARS occurred in China's Guangdong province in November, 2002 (Chinese SARS Molecular Epidemiology Consortium, 2004). By August 7 of the following year, SARS had spread to more than 30 countries, affecting 8,096 people and resulting in 774 deaths worldwide (World Health Organization, 2004). In 2003, Taiwan experienced a series of SARS outbreaks and the Municipal Hoping Hospital (referred to hereafter as HP) in Taipei City suffered the first and the most serious outbreak of SARS-CoV nosocomial infections: 137 probable cases and 26 deaths (Division of Surveillance and Investigation, Center for Disease Control, Taiwan, 2003; Lan et al., 2005b). According to the Center for Disease Control (CDC) in Taiwan, 364 of the 664 probable Taiwanese SARS cases reported to the World Health Organization were confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and/or neutralizing antibody tests (Center for Disease Control, 2003a). In this chapter, we will discuss the molecular and clinical epidemiology of SARS infection in Taiwan during 2003.

The First and Second Waves of SARS Infections

In Taiwan, the first SARS case was diagnosed on 14 March 2003 (Center for Disease Control and Prevention, 2003b). This index case involved a Taiwanese businessman who had visited Guangdong province from February 5–21. After he came back to Taiwan, he transmitted the disease to his wife, his son (SARS-CoV-TW1), and the doctor who treated his son (SARS-CoV-TW3). On 15 March 2003, seven employees from a Taiwanese construction company flew from Hong Kong to Beijing. Four of them developed SARS symptoms on March 26, several days after returning to Taiwan (Olsen et al., 2003).

Y. Lu et al. (eds.), *Emerging Infections in Asia.*

The Third Wave of SARS Infection: A Series of Nosocomial Infections

On 26 March 2003, a male resident of the Amoy Gardens housing complex in Hong Kong flew to Taiwan; he stayed overnight in a small hotel in Taipei and took a train from Taipei to Taichung City to visit his younger brother the following day. The visitor returned to his Hong Kong home on March 28 after experiencing fever the preceding evening. His younger brother, who developed symptoms on March 31, became Taiwan's first SARS-related fatality (TC1).

On April 6, a 47-year-old Taiwanese female (TW-HP1) suffering from fever and coughing for several days visited the emergency room at the municipal Hoping hospital. On April 9, this patient was transferred to another private hospital where she was diagnosed to have SARS. Although patient TW-HP1 stayed only in the emergency room of Hoping hospital for 3 days, seven employees including a laundry worker (the index case) developed SARS after she left. In all, 137 probable SARS cases and 26 mortalities resulted from this nosocomial infection.

On April 24, for the reason of quarantine, the Taipei City government shut down Hoping hospital without warning. All the employees of the hospital were asked to return to the hospital and stay with the patients and their visitors during the quarantine. On April 28, the Taiwan government imposed mandatory quarantines on all air travelers from China, Hong Kong, Singapore, Macau, and Toronto, but nosocomial SARS infections continued to be reported in many hospitals island-wide. More than ten hospitals experienced outbreaks of nosocomial SARS-CoV infec-

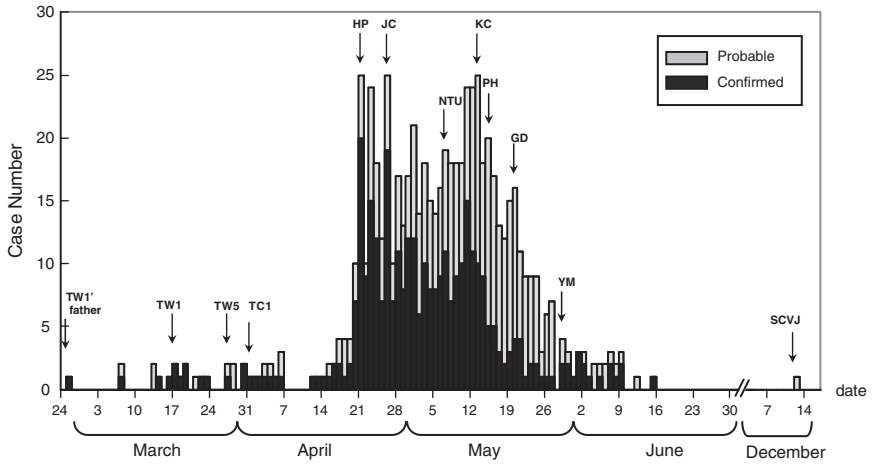

Fig. 1 Epidemiological curves of probable (*gray color*) and confirmed (*darker color*) SARS cases in Taiwan. Confirmed cases were validated by the Taiwan's Center for Disease Control using RT-PCR and serological tests. Arrows mark dates of outbreaks of nosocomial infections in HP, JC, NYU, KC, PH, GD, and YM hospitals and of diagnoses of SARS in several key patients

tions in Taiwan. The following hospitals were marked on the epidemiological curve chronologically (Fig. 1): Taipei Municipal Hoping Hospital (HP), Jenchi Hospital (JC), National Taiwan University Hospital (NTU), Kaohsiung Chang-Gung Hospital (KC), Taipei Municipal Guando Hospital (GD), and Taipei Municipal Yangming Hospital (YM) which had the most severe outbreaks of nosocomial SARS infections.

Development of a New Tool for the Phylogenetic Analysis of SARS-CoV Infections

The SARS-CoV genome size has been measured as 29.7 kb (Marra et al., 2003; Rota et al., 2003). A comparative analysis of SARS-CoV isolates has identified two distinct clades belonging to the early and late epidemics, respectively (Lan et al., 2005a). Conventionally, phylogenetic SARS-CoV analyses require full genome sequences (Lan et al., 2005a). Because of the limited amount of specimens for full-length sequencing, some researchers have used the SARS-CoV spike gene for this purpose, but most results have been less than satisfactory (Guan et al., 2003; Guan et al., 2004). Therefore, we developed a new phylogenetic analytical tool by combining nucleotide sequences from six variable regions, 5.6-kb in total, of a SARS-CoV genome and validated the robustness of the method (Lan et al., 2005b). Since this new method requires only seven RT-PCR reactions to obtain the nucleotide sequences for phylogenetic tree analysis, it is less time-consuming and more efficient than conventional methods. To facilitate future molecular epidemiological studies of SARS outbreaks in other laboratories, we have made the nucleotide sequences alignment file of 80 SARS-CoV reference strains available on our center's website: http://www.ym.edu.tw/aids/Molepi/.

Molecular Epidemiology of SARS-CoV Infections in Taiwan

We applied the new method mentioned above to elucidate the origin and dissemination pathways of SARS CoV infections collected from different hospitals in Taiwan. Phylogenetic analyses demonstrated that the Taiwanese SARS-CoVs were distributed in three clusters: B1, B2, and B3 (Fig. 2). After considering the epidemiological data of the SARS patients, it is clear that Taiwan experienced five infection waves in 2003. The first wave, in early March 2003, was composed of one imported case, two intra-familiar transmission cases (TW1), and one nosocomial infection (TW3). In cluster B1, both TW1 and TW3 SARS-CoVs were clustered with other SARS-CoVs linked to Hotel M in Hong Kong (Center for Disease Control and Prevention, 2003b). The second wave consisted of four Taiwanese (TW5) who contracted the disease as they flew from Hong Kong to Beijing, and then carried it back to Taiwan in mid-March 2003 (Olsen et al., 2003). The third wave, which

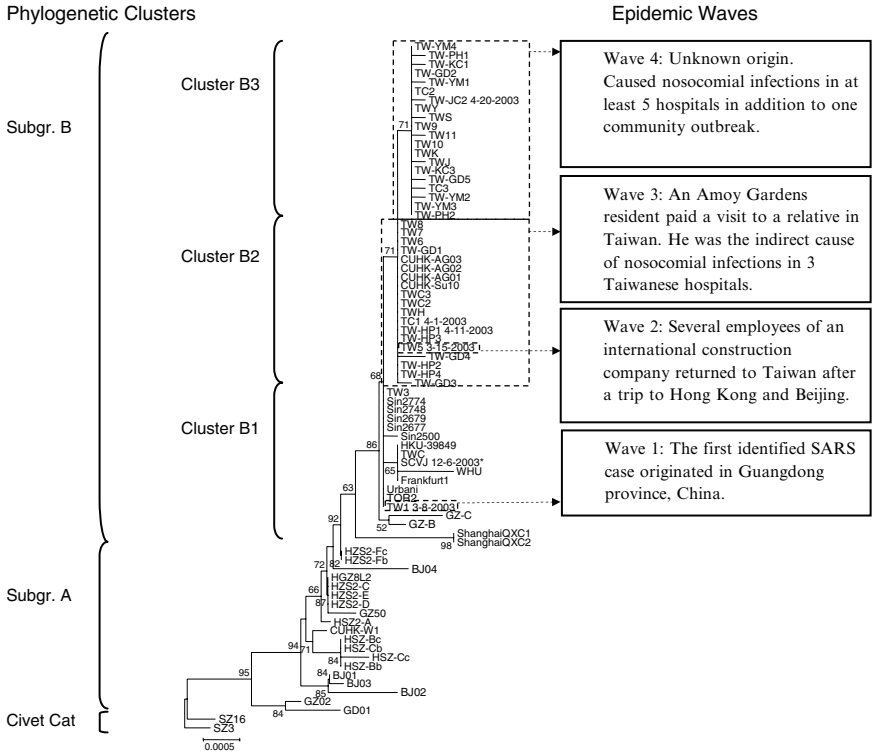

Fig. 2 Phylogenetic tree analysis of 39 Taiwanese SARS-CoVs using a combination of the proposed strategy and neighbor-joining method. A summary of the five infectious waves of SARS infection, corresponding to each phylogenetic cluster, was demonstrated on the right side of the figure. Node numbers indicate bootstrap value (%). Scale bar shows estimated genetic distance using Kimura's two-parameter substitution model. (Adapted from Lan et al., 2005b)

began in late March, consisted of an infection that occurred on a train (TW-HP1), an intra-familiar transmission (TC1), as well as multiple nosocomial infections (all TW-HPs and TW-GD1, TW-GD-3, and TW-GD4). In cluster B2, all the SARS-CoVs mentioned above clustered with the SARS-CoVs from the Amoy Gardens housing complex in Hong Kong (CUHK-AG01, CUHK-AG02, and CUHK-AG03) (Chim et al., 2003). Additionally, we identified a fourth wave of SARS infection (cluster B3), which started in late April and ended in mid-June, that contained SARS-CoVs not only from hospitals JC, KC, PH, GD [TW-GD2 and TW-GD5], and YM, but also from sporadic community outbreaks (TW10 and TW11).

The fifth wave happened in early December 2003 with a laboratory contamination case-SCVJ. It clustered with a SARS-CoV isolate used in the laboratory HKU-39849 and another isolate from Taiwan CDC-TWC (Lan et al., 2005b).

The first and second waves were in different phylogenetic clusters, suggesting they had different origins. Neither the first, nor the second wave led to serious

outbreaks, but the third wave – originating with a visitor to Taiwan from the Amoy Gardens housing complex – led to one transmission on a train (TWC3), one intra-familiar transmission (TC1), and nosocomial infections in at least two hospitals (HP and GD) in the northern region of Taiwan. It is worthy to note that there is only one nucleotide difference between SARS-CoV strains TC1 and TWC3. In addition, TWC3 shared an identical sequence with CUHK-AG01 (Chim et al., 2003), an Amoy Gardens isolate, even though patient TW-HP1 (SARS-CoV strain TC1) never left Taiwan at any time during the epidemic. An epidemiological investigation showed that the Hong Kong visitor and this female patient sat in different cars during their train ride. This is the first documented case with molecular proof of transmission of SARS-CoV infection on a train (Lan et al., 2005b).

If we assume that the CUHK-AG01 represents the first generation virus in the transmission link, then both TC1 and TWC3 were the second generation viruses and TWH was the third generation virus. According to the nucleotide variation analysis, the number of nucleotide change in the SARS-CoV genome per number of intermediate hosts was extremely low (less than 1 nucleotide change per host).

Community-Based Epidemiological Study of SARS in the Wan-Hwa District of Taipei City

In 9 May 2003, one month after the outbreak of a nosocomial infection in the Hoping hospital, there was an outbreak of SARS infection in the Hwa-Chung Residential Complex located in the same district as the Hoping hospital (Fig. 3). Four residents living in the complex had SARS and one of them died. In July, we conducted a sero-epidemiological study to understand the extent and risk factors associated with the infection. The results showed that 2 of 103 (1.9%) residents from Hwa-Chung Residential Complex and none of 76 people who lived in the same neighborhood were seropositive for SARS infection (Fig. 3). In terms of risk factors, one male had contact history (his wife died of SARS), while another female who lived in a different building from that of other cases did not have any contact history.

Clinical Epidemiology of SARS in Taiwan

The transmission of SARS is thought to occur primarily via respiratory droplets or direct contact. Contaminated sewage is believed to be responsible for the first major SARS outbreak in Hong Kong's Amoy Garden housing complex, with over 300 residents affected (Peiris et al., 2003a). Two months after the final outbreak of the SARS nosocomial infection, we recruited 658 employees from Hoping hospital that suffered the first and most severe SARS infections to help us investigate the epidemiological and genetic factors associated with SARS-CoV. SARS-CoV infections were detected using enzyme immunoassays and confirmed by a combination

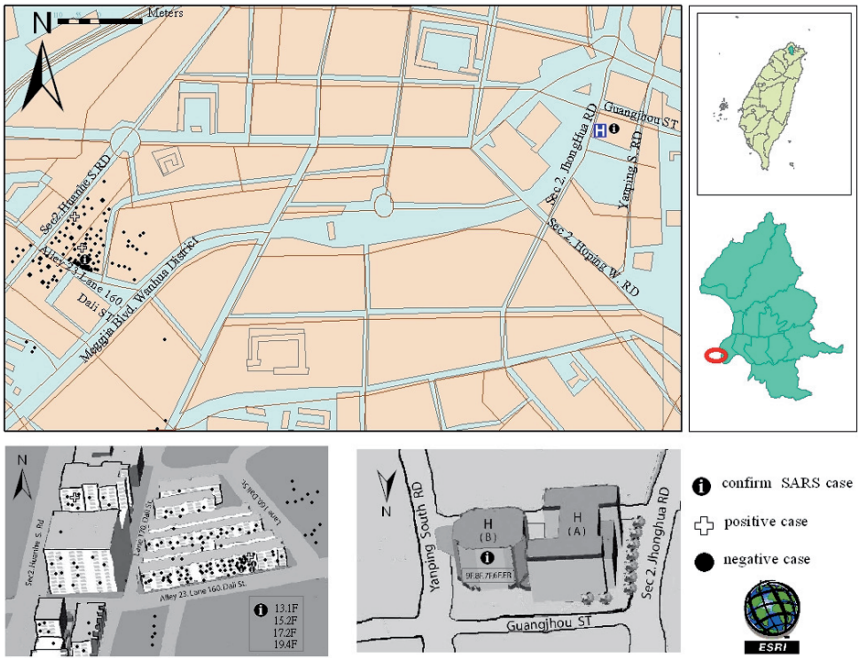

Fig. 3 Geographic locations of Hoping hospital and the Hwa-Chung housing complex in the Wah-Hwa District of Taipei City. Individuals participated in the sero-epidemiological study in the Hwa-Chung housing complex were marked on the map 2006. (Chen YM, unpublished data)

of Western blot assays, neutralizing antibody tests, and commercial SARS tests. Risk factors were analyzed via questionnaire responses and sequence-specific oligonucleotide probes of human leukocyte antigen (HLA) alleles. Our results indicate that 3% (20/658) of the study participants were seropositive, with one female nurse identified as a subclinical case. Identified SARS-CoV infection risk factors include working in the same building as the hospital's emergency room and infection ward, providing direct care to SARS patients, and carrying a Cw*0801 HLA allele (Fig. 3). Three SARS-CoV-infected nursing aides and one infected occupational therapist claimed that they had no direct contact with SARS patients; they may have come into contact with patient specimens or contact with infected bedclothes.

HLA Alleles Associated with SARS-CoV Infection

We found evidence of a link between HLA-Cw*0801 and SARS-CoV infection susceptibility. One of the cases was HLA-Cw*0801-homozygous; we observed that relative risk of infection increased from 3.3 for heterozygous individuals to 6 for homozygous individuals (95% confidence intervals of 0.9–11.6 and 0.2–188.7, respectively). The odds ratio for contracting a SARS-CoV infection

among persons with either a homozygous or heterozygous Cw*0801 genotype was 4.4 (95% confidence interval, 1.5–12.9; $p = 0.007$) (Chen et al., 2006). We also compared our data with data from a normal group provided by a separate Taiwanese research team (Chung et al., 2004) and obtained similar results (OR = 4.1, 95% CI = 1.4–12.0, $p = 0.01$).

The human leukocyte antigen (HLA) complex plays an important role in determining susceptibility to infectious diseases. HLA class I gene products present antigenic peptides to T cells, initiating an immune response and the removal of foreign material (Segal and Hill, 2003). Researchers have demonstrated that specific HLA alleles are associated with susceptibility to and outcomes from such viral infections as HIV-1, HTLV-1, and HCV (Jeffery et al., 2000; Carrington and O'Brien, 2003; Khakoo et al., 2004). During their study of potential SARS patients and high-risk health care workers (HCWs), Lin et al. (2003) observed an association between HLA-B*4601 and SARS-CoV infections. However, their definition of a SARS patient was based on clinical diagnosis rather than serological evidence, and HCWs may not have been a suitable control group. In contrast, 14.6% of our 80-member control group and 5% of the 20 seropositive participants carried the HLA-B*4601 allele (no statistical significance) (Chen et al., 2006). In a Hong Kong study that used bone marrow donors as a control, Ng et al. described HLA-B*0703 and HLA-DRB1*0301 as susceptible and resistant alleles for SARS-CoV infection, respectively. However, they did not collect or analyze HLA-Cw allelic frequencies among their participants (Ng et al., 2004). In our study, the seropositive group had a lower HLA-DRB1*0301 frequency than the seronegative group, but not at a statistically significant level ($p = 0.22$) (Chen et al., 2006).

Previous reports have stated that individuals carrying HLA-Cw*0801 are at significantly higher risk of contracting adult periodontitis (OR = 6.2) (Machulla et al., 2002) and that a link exists between HLA-Cw*04 and persistent hepatitis C viral infection (Thio et al., 2002). A research team in Beijing found that the total numbers of natural killer (NK) and CD158b + NK cells were significantly lower in SARS patients compared to healthy patients (National Research Project for SARS, Beijing Group, 2004). NK cells play a central role in innate antiviral immune response. In vivo, their activity is controlled via inhibitory and activation receptors for major histocompatibility complex class I molecules (Bauer et al., 1999; Ahmad et al., 2001). Therefore, we postulated that HLA-Cw*0801 may affect SARS-CoV susceptibility via its interaction with the killer-cell immunoglobulin-like receptors (KIR) of NK cells.

Subclinical Cases

Very few subclinical cases of SARS-CoV infection have been identified to date (Leung et al., 2004; Woo, et al., 2004; Chen et al., 2006). Of the 242 asymptomatic participants in our study who had close contact with SARS patients, only 1 (0.41%) had a subclinical infection. The anti-SARS-CoV antibody reactivity of the asymptomatic nurse (case no. HP613) was verified by all available serological assays. Her neutralizing antibody (NA) titer was measured at 32 in June of 2003

and it dropped to 2 in December 2003. As an internal medicine ward employee, she had frequent contact with SARS patients. She claimed that she took her own body temperature twice a day for more than 1 month during the nosocomial infection outbreak and that it was slightly above normal (37.4°C) only once. We tried to isolate the SARS-CoV from a nasopharyngeal swab in order to refute the possibility that she was an asymptomatic SARS-CoV carrier, but the results were negative.

The single asymptomatic case was unusual in several respects. In addition to carrying the heterozygous HLA-Cw*0801, she also carried a HLA haplotype (HLA-A*0101/2402, -B*4006/5701, -Cw*0801/0602, -DRB1*0701/0803, and -DQB1*0303/0601) considered rare among the Chinese (Fig. 4). Her HLA allelic frequencies were relatively low compared to the majority of Taiwanese: 1%, 2%, and 2.9% for HLA-A*0101, -B*4006, and -Cw*0602, respectively (http://www.allelefrequencies.net/). On the other hand, all of her HLA class I alleles were heterozygous, which is consistent with the hypothesis of a heterozygote advantage against infectious disease (Carrington and O'Brien, 2003; Doherty and Zinkernagel, 1975).

Public Health Control Measures

In Taiwan, during the SARS epidemic in 2003, different control measures including wearing masks (first only among medical personnel then among all citizens), inclusion of SARS in the infectious disease control law, home quarantine, and taking body temperature (first only among travelers, then among all the citizens) were implemented (Twu et al., 2003; Huang et al., 2005). Some measures were quite innovative, e.g., providing funding for hospitals to build a screening station outside the main building for patients with fever. Some may not have been so effective and needed to be modified, e.g., home quarantine. During the period, more than 150,000 persons were quarantined and 24 of whom were found later to have SARS (Hsieh et al., 2005). Furthermore, instead of using "home quarantine," the Taiwan CDC made a mistake and used "home isolation" in the mass media communication. Fear, stigma, and discrimination were generated among the general public towards SARS patients as well as persons under home quarantine. A mental health coalition composed of different nongovernmental organizations was formed, and they provided counseling through hot lines and radio programs.

Lesson Learned and Future Perspectives

Currently, highly pathogenic avian influenza viruses of the H5N1 subtype are circulating in eastern Asia with unprecedented epizootic and epidemic effects (Li et al., 2004). In 2004, the Council of Agriculture of Taiwan conducted a survey

HLA								
Cw				A	B	Cw	DRB1	DQB1
0801 & 0801	0801 & 1402	0303 & 1203	0102 & 0304	0101 & 2402	4006 & 5701	0801 & 0602	0701 & 0803	0303 & 0601

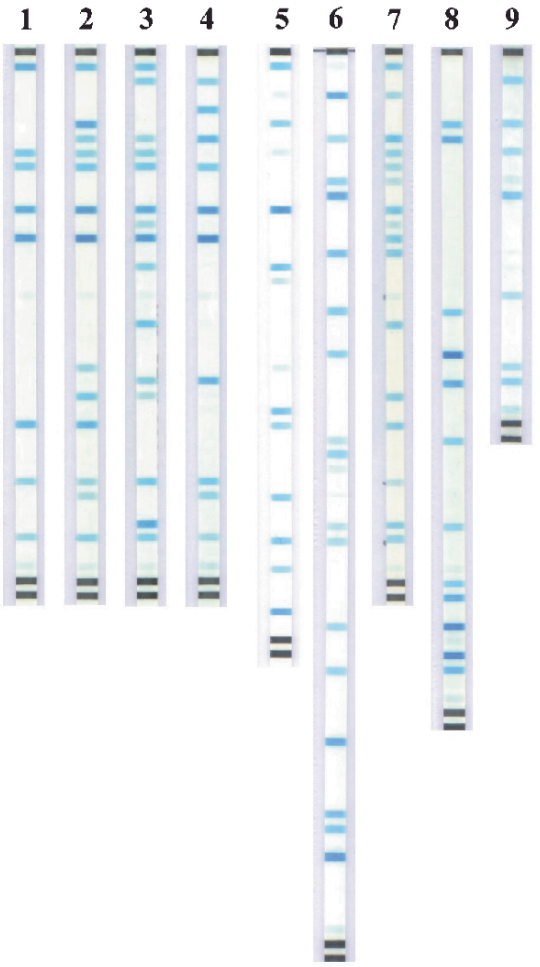

Fig. 4 HLA typing of several anti-SARS-CoV antibody-positive cases. *Lane 1*, case with homozygous HLA-Cw*0801; *lane 2*, case with heterozygous HLA-Cw*0801; *lanes 3 and 4*, two cases with HLA-Cw*0801 null genotype; *lanes 5–9*, the HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1 genotypes of the lone asymptomatic case (HP613). Allele typing was performed via polymerase chain oligonucleotide probing (Dynal Biotech Ltd., Wirral, UK, 2006)

on migratory binds, chickens, ducks, geese, and pigs and found a H5N2 strain in poultry (Bureau of Animal and Plant Health Inspection and Quarantine, 2007). Facing the threats of the pandemic bird flu, Taiwan CDC has built multiple surveillance systems to detect patients infected with avian flu. Twelve virology laboratories belonging to medical centers in different regions have joined the laboratory surveillance system.

The SARS pandemic in 2003 is a metaphor for global public health interconnectivity. It is difficult to draw a conclusion regarding whether better outbreak control would be achieved by placing fewer persons in quarantine or by concentrating on improving the efficiency of detection and isolation procedures. In fact, each area may become more efficient without jeopardizing the other's improvement. It also showed us that international cooperation especially among regional cities is vital to the control of communicable diseases. Balanced aggressive public health measurements should be combined with stringent hospital infection control practices. Although the governments should inform the public as soon and as thoroughly as they can, they must take caution in raising awareness without stigmatizing those infected.

Acknowledgment I thank Dr. Yu-Ching Lan and Mr. Yuan-Ming Lee for their help in preparing the figures of this chapter. This study is partially supported by the following two grants: No. 93004-62-007 from the Department of Health, Taipei City Government and NSC 92-2751-B-010-001-Y from the Taiwan's National Science Council.

References

Ahmad, R., Sindhu, S. T., Tran, P., Toma, E., Morisset, R., Menezes, J., Ahmad A. (2001). Modulation of expression of the MHC class I-binding natural killer cell receptors, and NK activity in relation to viral load in HIV-infected/AIDS patients. *Journal of Medical Virology*, 65, 431–440

Bauer, S., Groh, V., Wu, J., Steinle, A., Phillips, J. H., Lanier, L. L., Spies, T. (1999). Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. *Science*, 285, 727–729

Bureau of Animal and Plant Health Inspection an Quarantine. (2007). Council of Agriculture, Executive Yuan, Republic of China. Animal health inspection: Accomplishment. http://www.baphiq.gov.tw/ct.asp?xItem = 296&CtNode = 1701&mp = 2 (accessed January 29, 2007)

Carrington, M., O'Brien, S. J. (2003). The influence of HLA genotype on AIDS. *Annual Review of Medicine*, 54, 535–551

Center for Disease Control and Prevention (CDC). (2003a). Severe acute respiratory syndrome-Taiwan, 2003. *Morbidity and Mortality Weekly Report*, 52, 461–466

Center for Disease Control and Prevention. (2003b). Update: Outbreak of severe acute respiratory syndrome-Worldwide, 2003. *Morbidity and Mortality Weekly Report*, 52, 241–248

Chen, Y. M., Liang, S. Y., Chu, D. C., Lee, Y. M., Chang, L., Jung, S. Y., Chen, H. Y., Chjan, Y. J., Ho, M. S., Liang, K. Y., Jang, Y. J., Chu, T. C. (2006). Epidemiological and genetic correlates of SARS coronavirus infection in a hospital with the highest nosocomial infection rate in Taiwan in 2003. *Journal of Clinical Microbiology*, 44, 359–362

Chim, S. S., Tsui, S. K., Chan, K. C., Au, T. C., Hung, E. C., Tong, Y. K., Chiu, R. W., Ng, E. K., Chan, P. K., Chu. C.M., Sung, J. J, Tam, J. S., Fung, K. P., Waye, M. M., Lee, C. Y., Yuen, K. Y., Lo, Y. M., CUHK Molecular SARS Research Group. (2003). Genomic characterization of

the severe acute respiratory syndrome coronavirus of Amoy Gardens outbreak in Hong Kong. *Lancet*; 362, 1807–1808

Chinese SARS Molecular Epidemiology Consortium. (2004). Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. *Science*, 303, 1666–1669

Chung, W. H., Hung, S. I., Hong, H. S., Hsih, M. S., Yang, L. C., Ho, H. C., Wu, J. Y., Chen, Y. T. (2004). Medical genetics: A marker for Stevens-Johnson syndrome. *Nature*, 428, 486

Doherty, P. C., Zinkernagel, R. M. (1975). Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. *Nature*, 256, 50–52

Division of Surveillance and Investigation, Center for Disease Control, Taiwan. (2003) SARS probable cases in Taiwan-reclassified on 15 September 2003. In: Su IJ, editor. Memoir of severe acute respiratory syndrome control in Taiwan. Republic of China Center for Disease Control, Taipei

Drosten, C., Gunther, S., Preiser, W., van der Werf, S., Brodt, H. R., Becker, S., Rabenau, H., Panning, M., Kolesnikova, L., Fouchier, R. A., Berger, A., Burguiere, A. M., Cinatl, J., Eickmann, M., Escriou, N., Grywna, K., Kramme, S., Manuguerra, J. C., Muller, S., Rickerts, V., Sturmer, M., Vieth, S., Klenk, H. D., Osterhaus, A. D., Schmitz, H., Doerr, H. W. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *The New England Journal of Medicine*, 348, 1967–1976

Fouchier, R. A., Kuiken T., Schutten, M., van Amerongen, G., van Doornum, G. J., van den Hoogen, B. G., Peiris, M., Lim, W., Stohr, K., Osterhaus, A. D. (2003). Aetiology: Koch's postulates fulfilled for SARS virus. *Nature*, 423, 240

Guan, Y., Peiris, J. S., Zheng, B., Poon, L. L., Chan, K. H., Zeng, F. Y., Chan, C. W., Chan, M. N., Chen, J. D., Chow, K. Y., Hon, C. C., Hui, K. H., Li, J., Li, V. Y., Wang, Y., Leung, S. W., Yuen, K. Y., Leung, F. C. (2004). Molecular epidemiology of the novel coronavirus that causes severe acute respiratory syndrome. *Lancet*, 363, 99–104

Guan, Y., Zheng, B. J., He, Y. Q., Liu, X. L., Zhuang, Z. X, Cheung, C. L., Luo, S. W., Li, P. H., Zhang, L. J., Guan, Y. J., Butt, K. M., Wong, K. L., Chan, K. W., Lim, W., Shortridge, K. F., Yuen, K. Y., Peiris, J. S., Poon, L. L. (2003). Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*, 302, 276–278

Hsieh, Y. H., King, C. C., Chen, C. W. S., Ho, M. S., Lee, J. Y., Liu, F. C., Wu, Y. C., Wu, J. S. (2005). Quarantine for SARS, Taiwan. *Emerging Infectious Diseases*, 11, 278–282

Huang, C. Y., Sun, C. T., Hsieh, J. L., Chen, Y. M., Lin, H. (2005). A novel small-world model: Using social mirror identities for epidemic simulations. *Simulation*, 81, 671–699

Jeffery, K. J., Siddiqui A. A., Bunce, M., Lloyd, A. L., Vine, A. M., Witkover, A. Izumo, D. S., Usuku, K., Welsh, K. I., Osame, M., Bangham, C. R. (2000). The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. *Journal of Immunology*, 165, 7278–7284

Khakoo, S. I., Thio, C. L., Martin, M. P., Brooks, C. R., Gao, X., Astemborski, J., Cheng, J., Goedert, J. J., Vlahov, D., Hilgartner, M., Cox, S., Little, A. M., Alexander, G. J., Cramp, M. E., O'Brien, S. J., Rosenberg, W. M., Thomas, D. L., Carrington, M. (2004). HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science*, 305, 872–874

Ksiazek, T. G., Erdman, D., Goldsmith, C. S., Zaki, S. R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J. A., Lim, W., Rollin, P. E., Dowell, S. F., Ling, A. E., Humphrey, C. D., Shieh, W. J., Guarner, J., Paddock, C. D., Rota, P., Fields, B., DeRisi, J., Yang, J. Y., Cox, N., Hughes, J. M., LeDuc, J. W., Bellini, W.J., Anderson, L. J., SARS Working Group. (2003). A novel coronavirus associated with severe acute respiratory syndrome. *New England Journal of Medicine*, 348, 1953–1966

Lan, Y. C., Liu, H. F., Shih, Y. P., Yang, J. Y., Chen, H. Y., Chen, Y. M. (2005a). Phylogenetic analysis and sequence comparison of structural and non-structural SARS coronavirus protein in Taiwan. *Infection, Genetics, and Evolution*, 5, 261–269

Lan, Y. C., Liu, T. T., Yang, J. Y., Lee, C. M., Chen, Y. J., Chan, Y. J., Lu, J. J., Liu, H. F., Hsuing, C. A., Ho, M. S., Hsiao, K. J., Chen, H. Y., Chen, Y. M. (2005b). Molecular epidemiology of severe acute respiratory syndrome-associated coronavirus infections in Taiwan. *Journal of Infectious Diseases,* 191, 1478–1489

Leung, G. M., Chung, P. H., Tsang, T., Lim, W., Chan, S. K., Chau, P., Donnelly, C. A., Ghani, A. C., Fraser, C., Riley, S., Ferguson, N. M., Anderson, R. M., Law, Y. L., Mok, T., Ng, T., Fu, A., Leung, P. Y., Peiris, J. S., Lam, T. H., Hedley, A. J. (2004). SARS-CoV antibody prevalence in all Hong Kong patient contacts. *Emerging Infectious Diseases*, 10, 1653–1656

Li, K. S., Guan, Y., Wang, J., Smith, G. J., Xu, K. M., Duan, L., Rahardjo, A. P., Puthavathana, P., Buranathai, C., Nguyen, T. D., Estoepangestie, A. T., Chaisingh, A., Auewarakul, P., Long, H. T., Hanh, N. T., Webby, R. J., Poon, L. L., Chen, H., Shortridge, K. F., Yuen, K. Y., Webster, R. G., Peiris, J. S. (2004). Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature*, 430, 209–213

Lin, M., Tseng, H. K., Trejaut, J. A., Lee, H. L., Loo, J. H., Chu, C. C., Chen, P. J., Su, Y. W., Lim, K. H., Tsai, Z. U., Lin, R. Y., Lin, R. S., Huang, C. H. (2003). Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Medical Genetics*, 4, 9

Machulla, H. K., Stein, J., Gautsch, A., Langner, J., Schaller, H. G., Reichert, S. (2002). HLA-A, B, Cw, DRB1, DRB3/4/5, DQB1 in German patients suffering from rapidly progressive periodontitis (RPP) and adult periodontitis (AP). *Journal of Clinical Periodontology*, 29, 573–579

Marra, M. A., Jones, S. J., Astell, C. R., Holt, R. A., Brooks-Wilson, A., Butterfield, Y. S., Khattra, J., Asano, J. K., Barber, S. A., Chan, S. Y., Cloutier, A., Coughlin, S. M., Freeman, D., Girn, N., Griffith, O. L., Leach, S. R., Mayo, M., McDonald, H., Montgomery, S. B., Pandoh, P. K., Petrescu, A. S., Robertson, A. G., Schein, J. E., Siddiqui, A., Smailus, D. E., Stott, J. M., Yang, G. S., Plummer, F., Andonov, A., Artsob, H., Bastien, N., Bernard, K., Booth, T. F., Bowness, D., Czub, M., Drebot, M., Fernando, L., Flick, R., Garbutt, M., Gray, M., Grolla, A., Jones, S., Feldmann, H., Meyers, A., Kabani, A., Li, Y., Normand, S., Stroher, U., Tipples, G. A., Tyler, S., Vogrig, R., Ward, D., Watson, B., Brunham, R. C., Krajden, M., Petric, M., Skowronski, D. M., Upton, C., Roper, R. L. (2003). The genome sequence of the SARS-associated coronavirus. *Science*, 300, 1399–1404

National Research Project for SARS, Beijing Group. (2004). The involvement of natural killer cells in the pathogenesis of severe acute respiratory syndrome. *American Journal of Clinical Pathology*, 121, 507–511

Ng, M. H., Lau, K. M., Li, L., Cheng, S. H., Chan, W. Y., Hui, P. K., Zee, B., Leung, C. B., Sung, J. J. (2004). Association of human-leukocyte-antigen class I (B*0703) and class II (DRB1*0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. *Journal of Infectious Diseases*, 190, 515–518

Olsen, S. J., Chang, H. L., Cheung, T. Y., Tang, A. F., Fisk, T. L., Ooi, S. P., Kuo, H. W., Jiang, D. D., Chen, K. T., Lando, J., Hsu, K. H., Chen, T. J., Dowell, S. F. (2003). Transmission of the severe acute respiratory syndrome on aircraft. *New England Journal of Medicine*, 349, 2416–2422

Peiris, J. S., Chu, C. M., Cheng, V. C., Chan, K. S., Hung, I. F., Poon, L. L., Law, K. I., Tang, B. S., Hon, T. Y., Chan, C. S., Chan, K. H., Ng, J. S., Zheng, B. J., Ng, W. L., Lai, R. W., Guan, Y., Yuen, K. Y. (2003a). Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*, 361, 1767–1772

Peiris, J. S., Lai, S. T., Poon, L. L., Guan, Y., Yam, L. Y., Lim, W., Nicholls, J., Yee, W. K., Yan, W. W., Cheung, M. T., Cheng, V. C., Chan, K. H., Tsang, D. N., Yung, R. W., Ng, T. K., Yuen, K. Y., SARS Study Group. (2003b). Coronavirus as a possible cause of severe cause of severe acute respiratory syndrome. *Lancet*, 361, 1319–1325

Rota, P. A., Oberste, M. S., Monroe, S. S., Nix, W. A., Campagnoli, R., Icenogle, J. P., Penaranda, S., Bankamp, B., Maher, K., Chen, M. H., Tong, S., Tamin, A., Lowe, L., Frace, M., DeRisi, J. L., Chen, Q., Wang, D., Erdman, D. D., Peret T. C., Burns, C., Ksiazek, T. G., Rollin, P. E., Sanchez A., Liffick, S., Holloway, B., Limor, J., McCaustland, K., Olsen-Rasmussen, M., Fouchier, R., Gunther, S., Osterhaus, A. D., Drosten, C., Pallansch, M. A., Anderson, L. J., Bellini, W. J. (2003). Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science*, 300, 1394–1399

Segal, S., Hill, A. V. (2003). Genetic susceptibility to infectious disease. *Trends in Microbiology*, 11, 445–448

Thio, C. L., Gao, X., Goedert, J. J., Vlahov, D., Nelson, K. E., Hilgartner, M. W., O'Brien, S. Karacki, J. P., Astemborski, J., Carrington, M., Thomas, D. L. (2002). HLA-Cw*04 and hepatitis C virus persistence. *Journal of Virology*, 76, 4792–4797

Twu, S. J., Chen, T. J., Chen, C. J., Olsen, S. J., Lee, L. T., Fisk, T., Hsu, K. H., Chang, S. C., Chen, K. T., Chiang, I. H., Wu, Y. C., Wu, J. S., Dowell, S. F. (2003). Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerging Infectious Diseases*, 9, 718–720

Woo, P. C., Lau, S. K., Tsoi, H. W., Chan, K. H., Wong, B. H., Che, X. Y., Tam, V. K., Tam, S. C., Cheng, V. C., Hung, I. F., Wong, S. S., Zheng, B. J., Guan, Y., Yuen. K. Y. (2004). Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. *Lancet*, 363, 841–845

World Health Organization, Geneva. (2004). Summary of probable SARS cases with onset of illness 2002 to 31 July 2003. (Accessed April 21, 2004) http://www.who.int/csr/sars/country/table2004_04_21/en/)