Severe acute respiratory syndrome epidemic in Taiwan, 2003

Po-Ren Hsueh1,2, Pan-Chyr Yang2

Departments of 1Laboratory Medicine and 2Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

Received: March 10, 2005   Revised: March 12, 2005   Accepted: March 12, 2005

In Taiwan, since the first case of severe acute respiratory syndrome (SARS) was identified on February 25, 2003, a total of 3032 cases of suspected or probable SARS were reported prior to July 5, 2003. Among these cases, 664 were classified as probable SARS based on the clinical case definitions and 346 had a positive result for the SARS-associated coronavirus (SARS-CoV). The epidemic in Taiwan could be divided into 2 distinct stages. In stage I (late-February to mid-April) patients had traceable contact with infected patients or travel histories to known affected areas of SARS. By contrast, patients in stage II (mid-April to June) acquired infection via intra-hospital or inter-hospital transmission. The mortality rate directly attributable to SARS during the 2 stages of the outbreak in Taiwan was 11% (37 patients). Phylogenetic analysis of sequences of SARS-CoV strains in Taiwan and other countries showed that Taiwanese strains were closely related to those isolated from patients in Hong Kong and Guangdong. The nonspecific initial symptoms and signs of the illness, the absence of reliable diagnostic tests, as well as the initial lack of strict infection control measures in hospitals and effective national control policies contributed to the island-wide spread of the SARS epidemic in Taiwan. Development of an effective strategy to prepare for future outbreaks will require the implementation of an active coordinated clinical reporting system, international collaboration to identify cases in the early stage, development of laboratory tools for early diagnosis, a robust system of prepared isolation, and adequate quarantine facilities.

Key words: Epidemiology, severe acute respiratory syndrome, Taiwan

Severe acute respiratory syndrome (SARS) is an emerging infecion of the 21st century and poses a global threat to public health [1-3]. This disease originated in November 2002 in Guangdong Province of southern China and subsequently spread to 28 countries, affecting 8098 individuals and causing 774 deaths (9.6%) worldwide [1]. This disease is caused by a novel coronavirus, SARS-associated coronavirus (SARS-CoV), although a human metapneumovirus may also be associated with its pathogenesis [3].

The first case of SARS in Taiwan occurred in a businessman working in Guangdong Province, who developed a febrile illness on February 25, 2003, four days after returning to Taiwan and was admitted on March 8, 2003 [4-7]. In mid-April in Taipei City, a large nosocomial outbreak of SARS occurred in a regional hospital, leading to subsequent countrywide spreads of SARS [8-15]. From February 25 to July 5, 2003, a total of 3032 cases of suspected or probable SARS were reported to the Center for Disease Control of the Department of Health in Taiwan (CDC, Taiwan) [8]. Among these cases, 664 were classified as probable SARS based on the World Health Organization (WHO) and CDC case definitions [8,16,17]. Of the 664 probable cases, 346 (52.1%) were shown to be infected with SARS-CoV by the finding of SARS-CoV RNA in respiratory secretions and/or positive specific immunoglobulin G (IgG) antibody in sera [8].

This article chronicles the course of the SARS epidemic in Taiwan and tries to draw implications from the Taiwan data with regard to preparations against future outbreaks.

Spread of SARS to Taiwan (epidemic stage I)

The epidemiologic curve of the 346 laboratory-confirmed SARS cases [8] is shown in Fig. 1. Cases in the first stage of the epidemic (stage 1, from February 25 to April 15, 2003) occurred in patients who had either returned from an affected area (China or Hong Kong) [71.4%] or had a definite contact history with index cases (family members, friends, and medical staff). During this stage, 10 patients were treated at National Taiwan
University Hospital (NTUH) and 2 clusters involving 9 of these patients were identified [4,7,8]. Transmission among 4 patients of 1 cluster occurred after contact with households with a SARS patient or with health care environments treating SARS patients [4,7]. Five patients from another cluster treated in NTUH had become infected in association with close contact with a SARS patient on an airplane, and a total of 18 passengers on the airplane were consequently documented to have contracted SARS [3,4,7].

**Spread of SARS within Taiwan (epidemic stage II)**

Most of the cases seen in the second stage of the epidemic (from April 15 to June 15, 2003) originated during a large nosocomial outbreak in a regional hospital in Taipei City (stage IIa) and subsequent inter-hospital spreads and intra-hospital transmission in northern Taiwan (stage IIa) and subsequently inter-hospital spread and intra-hospital transmission in both northern and southern Taiwan (stage IIb) [8-15] (Fig. 1). The first large cluster in Taipei City was identified on April 22, and the number of new cases increased dramatically (10-20 cases per day). Nosocomial infections accounted for more than 80% of all probable cases reported [6, 8-15]. The remarkable numbers of new cases reported daily and continual attention of the news media in Taiwan to the threat of this poorly understood disease led to great anxiety, particularly among health care workers. This newly emerging disease adds additional challenges to the health care system in Taiwan already dealing with the pre-existing and difficult-to-control endemic diseases (enterovirus type 71 infection, meningococcal disease and tuberculosis) [3,6,8].

The epidemic began to subside on May 20, 2003 and no new cases were found after June 15 [1,8]. On July 5, 2003, the WHO removed Taiwan from the list of areas with recent local transmission of SARS [1].

**Clinical Features and Outcomes**

Among the 346 SARS cases, 218 (63.2%) occurred in females. The majority (85.3%) of cases occurred in northern Taiwan due to its proximity as a hub of transit for individuals from the origins of the epidemic in Guangdong Province, China, and 66.4% of these cases were 20 to 50 years old [8]. Three cases of SARS occurred in patients aged below 10 years [8]. Twenty-one cases (6.1%) were imported, 38 cases (11.0%) acquired
infection via household contact, 105 (30.3%) were health

care workers, and 142 (41.0%) were inpatients who

acquired SARS during hospital stay. Among the 329

laboratory-confirmed cases of SARS in patients whose

status of underlying diseases was known, 14% had

underlying medical conditions including diabetes

mellitus, cardiovascular disease, chronic obstructive

lung disease, chronic liver disease, and end-stage renal

disease [3,8].

The clinical manifestations of patients with

laboratory-confirmed SARS compiled from several

reports from Taiwan are summarized in Fig. 2 [8,10-

12]. Nearly all SARS patients (>95%) presented initially

with fever (>38°C), more than 60% complained of

non-productive cough, and 10-40% had soft stool

passage or diarrhea early in the disease. Less than 20%

of patients reported upper respiratory tract symptoms

such as rhinorrhea, nasal obstruction, or sore throat.

Accordingly, a 6-item (myalgia, diarrhea, cough prior

to or concomitant with fever, rhinorrhea or sore throat,

lymphopenia, and thrombocytopenia) clinical scoring

system proposed by the NTUH SARS research group

might provide efficient and cost-effective (sensitivity,

92.6% and specificity, 71.2%) mass screening of febrile

patients for SARS during an outbreak [18]. When

encountering a patient with flu-like symptoms such as

fever and/or cough in the absence of otolaryngologic

inflammatory signs (pharyngeal hyperemia and neck

lymphadenopathy), physicians should be alert to the

possibility of SARS [19].

Reported complications of SARS in patients from

taiwan included lung fibrosis, acute myocardial

infarction, rhabdomyolysis, peripheral neuropathy, and

acute renal failure [3,7-14,20]. Among the 346 patients,

73 (21.2%) died and 37 (10.7%) of these deaths were

considered to have resulted directly from SARS [1,8].

Rates of mortality increased with age and occurred in

more than 60% of patients with ages greater than 70

years (Fig. 3) [3,8]. All younger patients (ages <20 years)

had less severe disease and the majority of these

patients recovered without the use of antiviral agents

and corticosteroids [8,21].

Management

During the conditions of the first wave of this poorly

understood, highly contagious and often fatal disease,

the need for design of studies to establish appropriate

treatment regimens had to compete with equally

immediate problems of containment of the spread of
The treatment protocol for SARS patients at most hospitals in Taiwan during the epidemic was established by NTUH in early March 2003 [3,4,10,22]. Ribavirin was given orally for 10 to 14 days for all probable cases. Corticosteroid (intravenous methylprednisolone, 2 mg/kg daily for 5 days followed by oral prednisolone) was used along with ribavirin in initial probable cases but later was used only when patients had fever for more than 8 days, extensive or bilateral chest radiographic involvement or persistent high fever for more than 2 days with clinical, chest radiographic, or laboratory findings suggestive of worsening [22]. Pulse methylprednisolone (500 mg twice daily intravenously for 3 days) was started when deterioration of clinical conditions and lung lesions occurred despite the combination of ribavirin and standard corticosteroid therapy. Intravenous IgG was given at a dosage of 1 g/kg/day for 2 consecutive days when patients failed to respond to ribavirin and corticosteroid treatment or had associated pancytopenia.

Later studies on the involvement of immune-mediated pathologic processes in SARS patients suggested that combinations of antiviral agents (such as ribavirin, liponavir, glycyrrhizin), anticytokine agents/immunomodulators (interferons) and/or convalescent plasma are worth considering as a general therapeutic approach to SARS, although further supporting evidence is required [2,3].

**Etiology, Molecular Epidemiology, Reservoir, and Genetic Correlations**

In Taiwan, the genome of the first SARS-CoV strain (TW1), recovered early in the epidemic, is 29,729 nucleotides in length (accession number, AY291451) [4]. Laboratory tests for detection of SARS-CoV RNA and antibody against SARS became available in Taiwan early in stage II of the epidemic [4,7,8]. Some strategies which improve sensitivity and specificity of laboratory tests for SARS diagnosis in Taiwan have been established [23,24]. A novel, quantitative and real-time nested polymerase chain reaction method can provide earlier detection of SARS-CoV for large-scale screening of SARS [23]. The selected phage clones and B-cell epitope-based peptide antigens, which were demonstrated to be highly specific for sera from SARS patients, may be useful not only in developing diagnostic and prognostic reagents but also in understanding the pathogenesis of SARS [24].
Systemic viral lineage study by sequencing the entire viral genome for 10 SARS-CoV strains isolated from patients during the epidemic revealed that viruses isolated from Taiwan were genotypically closely related to those of patients from Hong Kong and Guangdong Province [25-27]. All patients from stage II of the epidemic in Taiwan belonged to the same lineage [25]. Other molecular data also indicated that the same strain of the SARS-CoV involved in the Amoy Gardens outbreak was involved in an outbreak which occurred later in stage II of the epidemic in Taiwan [27]. The estimated genome mutation rate of SARS-CoV strains in Taiwan was approximately 0.1 per genome [25]. The distribution of the observed pairwise nucleotide site difference (mismatch distribution) analysis indicated that these viral genomes did not reach equilibrium and suggested a recent introduction of SARS-CoV into human populations [25].

The animal reservoir for SARS-CoV in Taiwan is unknown [28]. Some palm civets raised in Taiwan were tested for SARS-CoV RNA and antibody and the results were negative (personal communication). Preliminary results on the human leukocyte antigen (HLA) class I and II allele typing of SARS patients indicated that the severity of SARS infection in the Taiwanese population was associated significantly with HLA-B*4601 allele frequency [29].

**Preparation for New Outbreaks**

Rapid case detection and isolation, coupled with contact tracing and effective quarantine, would undoubtedly be effective as a means of combating the possible recurrence of SARS [3,8,30-32]. By the end of the epidemic, a total of 131,132 persons in Taiwan, including 50,319 close contacts of SARS patients (level A quarantine) and 80,813 travelers from SARS affected countries (level B quarantine), had been placed in quarantine [33]. However, only 112 persons (0.22%) under level A quarantine and 21 (0.03%) under level B quarantine had suspected or probable SARS [33,34]. Overall, only a small percentage of persons quarantined (133 persons, 0.10%) had a subsequent diagnosis of suspected or probable SARS, and an even smaller percentage of persons quarantined (21 persons, 0.016%) had laboratory-confirmed cases of SARS [33]. Due to the huge direct and indirect cost of the quarantine in Taiwan, only persons with fever, and those who returned from areas with local transmission of SARS or close contact with SARS patients were quarantined in the coming winter [8,9]. Other control measures established included designation of dedicated SARS hospitals island-wide, institution of fever-screening clinics for all health care facilities, and SARS fever hotlines [8,9].

On December 17, 2003, a senior researcher working on SARS research in a P4 laboratory in Taipei County was confirmed to have contracted SARS [35]. His work laboratory was suspected as the source of infection, and the case is still undergoing investigation. He had recovered well and pneumonia had resolved satisfactorily 2 weeks later. Follow-up respiratory and stool samples were negative for SARS-CoV. This case appears to have been a laboratory-acquired infection and there has been no evidence of secondary transmission reported to date. This case is the second case of SARS that was likely acquired in a laboratory setting since the initial worldwide epidemic, with the first occurring in Singapore [35]. These cases reinforce the need for strict adherence to recommended laboratory safety practice for SARS-CoV [35]. After this laboratory-acquired infection event, the CDC Taiwan has raised the level for SARS precautionary measures from level zero to the more stringent level B (presence of first confirmed case of primary transmission reported domestically). Fever monitoring and mask wearing in public institutions and schools were initiated. All P3 and P4 laboratories involved in work on SARS-CoV study were closed pending stringent disinfection procedures and all research on SARS-CoV was suspended until the end of March 2004.

The first suspected community-acquired SARS patient unrelated to laboratory exposure after the previous epidemic occurred in the southern Chinese Province of Guangdong (Panyu region), and was reported on December 26, 2003 [36]. No secondary cases among contacts of the index case were identified. The patient was reported to have had no known contact with high-risk groups, such as health care workers or animal handlers. The obscure source of the coronavirus infection for this suspected case of SARS indicates the possible persistence of SARS-CoV in the environment (animals).

The CDC Taiwan is treating the Guangdong case as a confirmed SARS case, and has initiated several prevention measures [8,9]. These measures include screening of all travelers arriving in Taiwan for fever and immediate collecting of relevant samples for SARS-CoV testing from passengers who arrive from China, Hong Kong, and Macau and have signs of fever.
Boat workers at sea and Chinese fishermen hired by Taiwanese companies are advised to undergo self-health management (body temperature measurement twice daily) for 10 days. Stowaways from China who arrive in Taiwan are quarantined for 10 days. All companies were asked to provide proper assistance in self-health management to all personnel bound for China, Hong Kong or Macau until February 25, 2004. The control level of SARS precaution has moved to level A (presence of first confirmed SARS case in other countries) as of January 1, 2004.

Research on laboratory tools for early diagnosis of SARS is ongoing. The 6-item clinical scoring system might be useful in mass surveillance of SARS for febrile patients with exposure risk but not in sporadic cases of SARS [18]. It is hoped that SARS recurrence can be limited to small clusters that could, with present levels of vigilance, be detected rapidly and effectively contained [2,3,32]. Global collaboration in the early recognition and response to any recurrence of SARS will facilitate effective control measures that are less costly and socially disruptive [2,3,37].

**Lessons from the SARS Epidemic in Taiwan**

Taiwan enjoyed a brief honeymoon period during and shortly after the first stage of the SARS epidemic [5, 38]. Health care workers mistakenly deemed this situation to indicate the presence of effective control and optimal clinical management for SARS, which fostered a false sense of safety, and relaxation in vigilance [5,38]. The subsequent nosocomial spread of SARS in more than 10 major hospitals, beginning in northern Taiwan and spreading to southern Taiwan and an isolated island (Penghu) revealed inadequacy in triage and pre-existing infectious control policies in dealing with the epidemic [39-41]. Neglect of proper infection control measures and shortage of personnel, facilities, and effective protective equipment led to disorganization and chaos among some health care staff working at the frontline of the epidemic, particularly during the most chaotic period (early in stage II) [42-44]. The SARS epidemic has exposed many pre-existing problems in the present health care delivery systems and medical practices, which might promote the spread of infections. Improvement in the accuracy and timeliness of reporting and dissemination of relevant information relating to SARS are crucial issues in the effectiveness of programs to limit spread of the disease and in public perceptions of the adequacy of the response.

**References**

15. Wang JT, Wang JL, Fang CT, Chang SC. Early defervescence
SARS in Taiwan