Severe Acute Respiratory Syndrome—Retrospect and Lessons of 2004 Outbreak in China

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Objective To summarize lessons learned from an outbreak of severe acute respiratory syndrome (SARS) in China during the spring of 2004. **Methods** Data of SARS cases were officially reported by Beijing Municipal Center for Disease Control and Prevention (BCDC) and Anhui Provincial Center for Disease Control and Prevention (APCDC) and results of epidemiological investigations were collected and analyzed. **Results** Three generations of 11 cases of SARS were identified during the outbreak. Initial two cases were most likely to be infected in Diarrhea Virus Laboratory of National Institute of Virology, China Centers for Disease Control and Prevention and main mode of transmission was direct contact with SARS patients. Delay in detecting initial case resulted in spread of the illness at hospitals and communities with two generations of secondary cases. **Conclusions** SARS outbreak in 2004 has yielded following lessons for public health globally. (1) Lab bio-safety programs should be made and should be strictly abided by. Studies in highly pathogenic viruses such as SARS coronavirus should be utmost cautious. (2) Management systems of occupational exposure to virus and disease surveillance need to be strengthened to take all risk factors into account so as to detect potential patients with infectious disease as early as possible.

Key words: Severe acute respiratory syndrome (SARS); Outbreak; Bio-safety; Laboratory; China

INTRODUCTION

On April 22, 2004, the Ministry of Health (MOH) of China informed World Health Organization (WHO) of one suspected case of severe acute respiratory syndrome (SARS)[1] occurred in Beijing, China, indicating SARS came back to China again after its outbreak in 2003. Authorities in China immediately implemented measures to isolate the patients and trace the contacts to minimize further transmission in community and institutional settings, and carried out an investigation on cause of the outbreak. This paper describes epidemiological characteristics of the outbreak, and especially explores its lessons for international public health.

METHODS

There are about 13.8 million population in Beijing city, with 14 districts and four counties. Beijing experienced a serious outbreak of SARS during March to June in 2003 with 2521 probable cases diagnosed clinically, causing 193 deaths. Specimens for detecting SARS coronavirus (SARS-CoV) were stored at 13 institutions in Beijing, and lab experiments using live SARS-CoV to study its pathogenicity and to develop effective vaccine were conducted at some of these institutions, such as National Institute of Virology (NIV) of Chinese Center for Disease Control and Prevention (CCDC) and Institute for Experimental Animals under the Chinese Academy of Medical Sciences (CAMS).

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0895-3988/2006
CN 11-2816/Q

Based on experiences and lessons learned from SARS outbreak in 2003, the Ministry of Health (MOH) and Beijing Municipal Health Bureau developed a practical manual for emergent public health events, especially for SARS outbreak. Although, there were only four new SARS cases occurred in Gunagzhou, Guangdong Province in early 2004 at the end of SARS outbreak in China during March to June of 2003, daily notification of SARS case all over the country continued until April 1, 2004.

Data Source

All information of the patients was collected from a dataset of MOH. Notification and investigation on all SARS cases were conducted through collaboration of BCDC, APCDC and all district CDCs in Beijing according to the guidelines for surveillance and investigation on SARS cases issued by MOH and supplemented by Anhui Provincial Health Bureau. General information of SARS patients, including their dates of onset, activities before and after onset, histories of contact with others and mode of contact, was collected by trained investigators.

Case Notification

When a SARS-like case was admitted to Ditan Hospital, a panel of experts was invited to review his or her clinical information and result of lab tests to classify his or her illness as suspected, probable and confirmed cases or cases under observation. Case classification was updated on the basis of their clinical courses and results of lab tests. A patient (or his or her family member) was interviewed by a trained investigator and completed a standardized questionnaire regarding his or her demographic and clinical data, close contacts within two weeks before and after onset in an attempt to identify source of infection, and then the patient was placed in quarantine or under close medical observation.

Laboratory Test

Blood specimen was collected from each patient for detection of serum anti-SARS-CoV IgM and IgG by two kinds of enzyme-linked immunosorbent assey (ELISA) kits developed locally, one prepared by the North Center of National Institute for Genomics (NCNIG) in partnership with the Academy of Military Medical Sciences (AMMS), and the other by Peking University Health Science Center (PUHSC). If a specimen was tested positive both by two different kinds of diagnostic kits (ELISA and indirect fluorescent assay, IFA) at two collaborative network labs, including those in BCDC, AMMS, PUHSC, Peking Union Medical College Hospital, NCNIG, then its positivity was confirmed. All specimens were sent to the Public Health Laboratory Services Branch, Center for Health Protection, Department of Health of Hong Kong Special Administrative Region, a WHO Network Laboratory for SARS, for validation with Real Art TM HPA-Coronavirus LC RT-PCR Reagents made in Germany approved by WHO.

Case Definition

A suspected case was defined according to the following criteria: (1) history of either contact with SARS patient or travel to an area affected by SARS within 14 days before his or her onset; (2) symptoms and signs of fever and respiratory illness; (3) normal or decreased blood leukocyte count; (4) abnormal chest radiograph; and (5) absence of substantial improvement with antibiotic treatment[2]. Once a suspected case was detected serum positive for IgM or IgG antibodies against SARS-CoV by labs in Beijing, he or she was diagnosed as probable SARS case. If a probable case was detected positive for SARS-CoV IgG antibody by an independent external international reference laboratory, he or she was diagnosed as confirmed case of SARS[3]. Actually, diagnoses of all 11 cases were confirmed by the Hong Kong Lab.

RESULTS

Identification of Index Case, Initial Case and Outbreak of SARS

On April 21 2004, RM Hospital affiliated to Peking University reported to Xicheng District Center for Disease Control and Prevention that serum specimen of a hospitalized patient L, a 20 year-old nurse working in JG Hospital, with severe pneumonia was tested positive for anti-SARS-CoV IgG. She had a fever of 37.8℃ on April 6 and visited fever clinic in JG Hospital. Her chest radiograph showed inflammatory infiltration in her right upper lung. Based on her history of having cold before onset, symptoms and signs of fever and respiratory illness, higher blood leukocyte count and inflammatory infiltration in her chest radiogram, L was primarily diagnosed as pulmonary infection and treated with antibiotics. On April 8, L was highly suspected as tuberculosis by a panel consultation based on her chest radiogram, and advised to give both anti-tuberculous and antibiotic agents. But, with all these treatments, her condition had no improvement. On April 14, she was diagnosed as severe pneumonia by another consultation and then referred to RM

Hospital, a tertiary-care hospital in Beijing. In a regular history taking after her admission, no history of contact with SARS case was found. L was then isolated and continued to be treated with antibiotics in an intensive care unit (ICU) of the hospital. On April 16 and 17, her mother and aunt, both of whom took care of her, developed fever (about 37.5℃). On April 19, her chest radiograph suggested SARS-like manifestations in the lungs and SARS was suspected. Her serum anti-SARS-CoV IgG was detected positive on April 21 and she was diagnosed as suspected SARS on April 22, which was later confirmed by the Hong Kong Lab. On the same day, April 22, one of the two initial cases Y was diagnosed as suspected SARS and later confirmed, too. Then, other cases of SARS were diagnosed in Beijing and Anhui Province in succession. Another initial case S was diagnosed as SARS on April 21 in Hefei, Anhui Province after the death of her mother, who cared her for a few days during her hospitalization.

Three Generations of SARS Cases

There were three generations with 11 cases of SARS in total during the outbreak in the spring of 2004 in Beijing, China.

The first generation of cases included two lab workers (S and Y) who worked at NIV, CCDC, reported in April[4]. S was a girl postgraduate student from Anhui Province doing research on respiratory syncytial virus at Diarrhea Virus Laboratory of NIV, and Y was a 31-year-old male doctorate candidate doing research on SARS-CoV at the same unit as S, but he had never worked on SARS-CoV and had no chance to expose to live SARS-CoV since February 2004. No close contact was found between Y and S. There were two additional lab works (R and C) who had been doing experiments on SARS-CoV and appeared to suffer from SARS-like illness in early February 2004. An investigation showed that both R and C were serum positive for antibodies against SARS-CoV by tests performed at a national reference laboratory[5].

Initial case S linked to two cases of the second generation, L and W. L was a nurse who took care of S in JG Hospital during S's hospitalization, and W was S's mother who took care of her after she fell ill. L linked to five cases of the third generation cases, three of them were her family members who took care of her after she fell ill and other two cases were the patients at JG Hospital sharing the same ward room with her.

Detail report of the three generations of cases was published on WHO website[4]. Distribution of the dates of contact, onset and diagnosis of suspected cases is shown in Table 1. All cases developed symptoms of SARS within academic incubation period (14 days).

A brief summary of three generations of nine SARS cases is shown in Figs. 1 and 2.

Tracing and Management of the Contacts

No sooner than the index case L was diagnosed, an investigation was carried out. A total of 747 persons in Beijing[6] during April 23 to May 10, and 115 persons in Anhui Province[7] during April 23 to May 7, who contacted with SARS cases at hospitals or exposed to possible sources of infection at NIV, CCDC, were identified and placed under quarantine for 14 days. NIV of CCDC was blocked on April 23 and an investigation on the cause of the outbreak was carried out there.

TABLE 1

Distribution of Dates of Contact and Onset and Incubation Period

Cases	Generation	Date of Contact	Date of Onset	Incubatory Period (Days)	Date of Diagnosed as Suspected Case
R	1	?	?	?	?
C	1	?	?	?	?
S	1	?	March 25	?	April 23
Y	1	?	April 17	?	April 23
W	2	April 3	April 8	5	April 23
L	2	March 31	April 5	6	April 22
L' s Father	3	April 8	April 19	11	April 25
L's Mother	3	April 8	April 17	9	April 25
L's Aunt	3	April 8	April 16	8	April 25
Z	3	April 12	April 19	7	April 26
X	3	April 12	April 18	6	April 25

Note. ?: unclear.

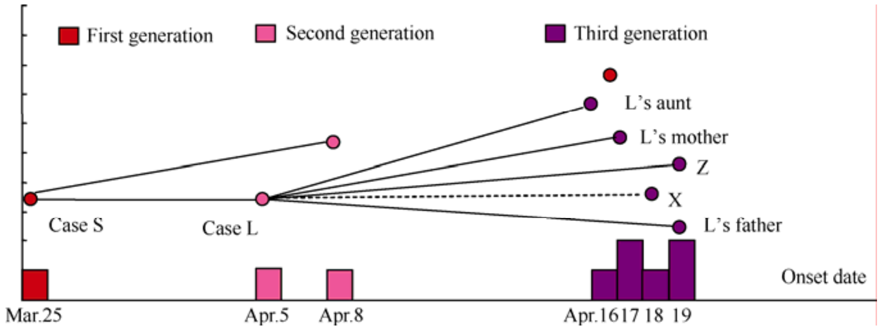

FIG. 1. Chain of transmission during SARS outbreak in 2004, Beijing, China.

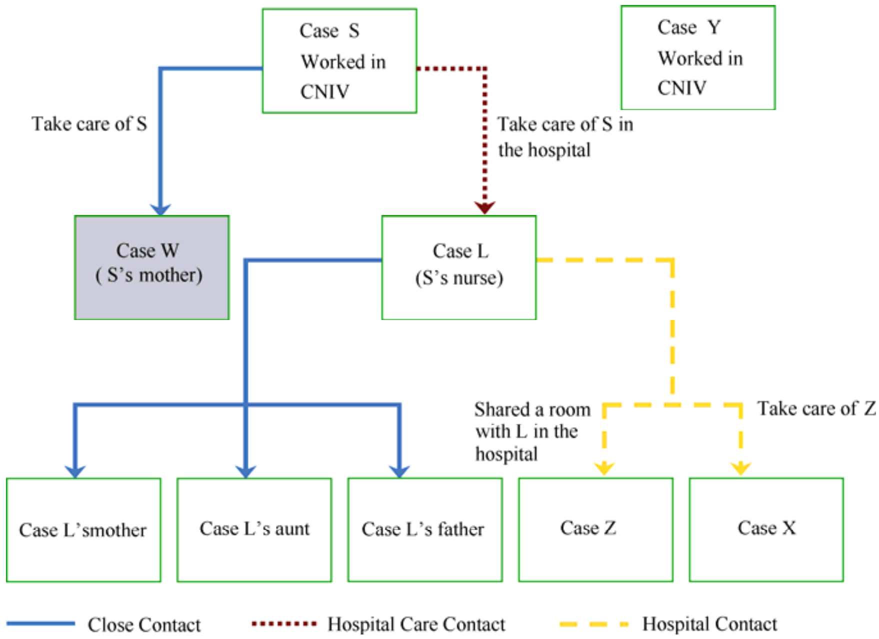

FIG. 2. Mode of SARS transmission in 2004, Beijing, China.

Source of the Outbreak

To look for the cause of SARS outbreak in China, 2004, MOH of China organized a panel of seven experts from AMMS, BCDC and CCDC to start an investigation. With the support from WHO experts, they conducted field investigations and lab experiments on the cause of the outbreak resulting from NIV, CCDC with the following final results.

NIV of CCDC in Beijing was the most likely source of the outbreak. This conclusion was based on evidence of: (1) at least four individuals possibly infected with SARS at NIV, including S and Y reported in April 2004, and two additional lab workers R and C who appeared to suffer from SARS-like illness in early February 2004 and were detected positive for SARS antibodies during the investigation[5]; (2) these four SARS cases were all from the same laboratory, Diarrhea Virus Laboratory at NIV, where studies on live SARS-CoV were conducted[8]; (3) RNA fragment of SARS-CoV was isolated from her pleural effusion specimens of case W of the second generation, highly homologous to the gene sequence of a SARS-CoV strain of HT-S-Cov-2 used at non-bio-safety lab at NIV[8]; and (4) it was almost impossible that infection was from contact with SARS patients outside the lab or infected from wild animals[8].

Use of inactivated SARS CoV at a non-bio-safety lab at NIV appeared the most likely cause of the outbreak. The investigation concluded that: (1) neither S nor Y entered a bio-safety-level 3 (BSL-3) lab at NIV, where studies on live SARS-CoV were involved in 2004[8]; (2) although R who entered a BSL-3 lab and suffered from SARS-like illness in early February 2004 was positive for SARS-CoV antibodies, there was no evidence that she transmitted SARS infection to S and Y leading to the outbreak[8];

(3) no studies involving live SARS-CoV were known to take place at Diarrhea Virus Laboratory at NIV, but its SARS-CoV strain was "inactivated" at a BSL-3 lab and used on several occasions during the early months of 2004 in experiments at Diarrhea Virus Laboratory, and the timing of use of "inactivated" SARS-CoV at a non-bio-safety lab at NIV coincided with the presence of those lab workers with serum positive SARS-CoV antibodies during their possible incubatory periods[8]; and (4) live viruses were inactivated with "0.5% NP40 (one kind of proteolytic agent) plus 1% SDS (sodium dodecylsulfonate) in ice bath for 30 minutes" at NIV[9], which was not evaluated for its inactivation effects, and viruses might not be inactivated completely by such a method, and assessment of effectiveness and quality control procedures were not implemented for each batch of inactivated viruses[8].

So, the investigation concluded that SARS outbreak in Beijing during early 2004 originated from lab leak and contamination, due to poor bio-safety management, flawed implementation of regulations and violation of bio-safety rules by lab workers.

DISCUSSIONS

In 2004 SARS outbreak of Beijing, nine cases were diagnosed as confirmed SARS based on their clinical manifestations, history of contact with SARS cases and lab tests (serum positive IgM or IgG antibodies against SARS-CoV), and two additional cases were identified positive for SARS-CoV antibodies later during a special investigation. Initial case occurred on March 25, 2004 and eight cases occurred sequentially until April 19, and index case was identified on April 21. No new case of SARS occurred in the close contacts and general population. The outbreak was rapidly brought under control through correct strategy and swift measures made by the health authorities and supported by the local government and the public, and ended within a month. In the report on the assessment of effectiveness of outbreak control measure, WHO believed that the Chinese authorities acted swiftly and effectively to control the outbreak once the alarm raised. Extensive contact tracing, effective isolation of cases and identification of contacts appeared to ensure the outbreak containment with remarkable speed[5].

Characteristics of this outbreak could be summarized by officials from Beijing Municipal Health Bureau as follows[10]: 1) chain of transmission was clear, 2) strong infectivity between close contacts, 3) source of the outbreak might be due to failure in lab bio-safety[11], while close contact with SARS patients being the main mode of transmission, 4) SARS cases occurred in limited population and areas, 5) all the cases were diagnosed with strong evidence, including clinical manifestations, history of contact with SARS patients and lab tests for serum antibodies against SARS-CoV, 6) no infection transmitted between health-care workers, except nurse L, and 7) hospitals did not turn into a source of cross-infection.

As compared with SARS outbreak in Beijing during 2003, great success in tracing for source of infection, quarantine of the contacts and avoiding of nosocomial infection was achieved, but outbreak of SARS in Beijing, 2004 still reflected some weakness in management of lab bio-safety, swiftly detecting of SARS cases, and management of fever patients and nosocomial infection, yielding important lessons for global public health, especially for lab bio-safety and the swiftly detecting of highly infectious diseases.

Management of Lab Bio-safety

From November 2002 to June 2003, SARS broke out in Gunagdong, Beijing and other places of China, a large number of specimens were collected from suspected and probable SARS cases and sent to different national and international labs for a variety of pathogen tests. Since then scientists have always concerned inadvertent release of SARS-CoV from a hospital or a lab with very dangerous pathogens[12]. Unfortunately, lab accident of infections occurred. The first lab accident resulted in a laboratory-confirmed cases of SARS-CoV infection in Singapore in September 2003 due to improper experiment procedure[13], and the second lab-failure causing SARS infection in Taiwan, China occurred in December 2003, and the most reasonable explanation for acquiring SARS infection was exposure to an experimental chamber which was considered infected[14]. Since the first lab affection, bio-safety of labs, where SARS-CoV-containing specimens were stored or studied, has ever been a globally important issue. WHO has developed post-outbreak bio-safety guidelines for handling of specimens and cultures of SARS-CoV[15], and a laboratory bio-safety manual[16]. In the manual, guidelines of lab bio-safety are clearly elucidated for different levels of bio-safety and for lab facilities, techniques, safety organisation and training. Several months after the two earlier lab accidents occurred, the third incident revealed in China[1], which was more serious than the two earlier ones as it resulted in spread of seven confirmed SARS cases while the two earlier ones did not result in spread beyond affected workers.

Based on a specific investigation on the cause of the SARS outbreak 2004 in Beijing, MOH of China and WHO reported that use of "inactivated" SARS-CoV not tested to determine the effectiveness of inactivation in a non-bio-safety lab appears to be the most likely cause of the outbreak[4]. This incident has raised lessons on bio-safety in general: (1) Research on highly infective or pathogenic virus should be conducted only by experts. In NIV, CCDC, studies on SARS-CoV were conducted by lab workers, who were working on diarrhea viruses and unfamiliar with SARS-CoV that is prone to cause bio-safety problems. (2) All lab workers involved in studies on highly infective or pathogenic viruses or at risk of contracting a range of infectious diseases must be trained strictly and comprehensively in bio-safety knowledge. (3) Any new methods for inactivation of virus should be adopted only after rigorous evaluation. Scientists working with highly pathogenic viruses such as SARS-CoV, need to handle inactivated material with utmost cautions. In particular, researchers should use appropriate and internationally accepted methods for validating inactivation of live virus, and inactivated material should be handled only in lab at bio-safety level 2 (BSL-2) or above[5].

Through this outbreak, WHO will develop country and regional strategies to strengthen lab bio-safety. Accident from laboratory contamination may yield important lessons for lab bio-safety, not only for SARS CoV, but also for any other highly infective or pathogenic viruses. Bio-safety standards should be carefully strengthened at all labs, and lessons should be learned from this outbreak to avoid further incidents.

Swift Detection of Infectious Cases

Although authorities in Beijing and Anhui acted swiftly and effectively to control the outbreak once the alarm raised, there was a delay in detecting initial cases. Initial case S got high fever on March 25 and was diagnosed as SARS on April 23. Index case L had high fever on April 5, but was diagnosed as SARS on April 23 after diagnosis of severe non-specific pneumonia and tuberculosis. There was a long delay in detecting these two cases with highly infectious disease. As a consequence, two generations of transmission occurred and application of effective hospital and community control measures took place late in this outbreak. There were a number of globally important lessons from this outbreak. (1) Lab workers involved in highly pathogenic viruses or bacteria, such as SARS-CoV, should be under strict health surveillance. Any illness that may be related to pathogenic virus or bacteria involved in studies should be highly concerned and appropriate measures should be taken to deal with them. Strict health surveillance should also be applied to healthcare workers and people in close contact with certain animals who are at risk of contracting a range of infectious disease. (2) Designated hospitals should be available for lab workers in order to detect possible infectious diseases swiftly and in case of transmission of potential infectious diseases into community. (3) Lab workers should be vigilant whether his/her illness is associated with the virus that is studied on in his/her lab. As a lab worker falls ill with fever, especially more than one worker suffer the same symptoms, they should avoid contacting with others utmost as possible and they should visit physicians immediately and tell physicians they are working with virus, as well as notification should be made to the relevant authorities. (4) Healthcare professional's vigilance is most essential for the early identification and early notification of suspected cases of infectious diseases. Healthcare workers need to be aware of risks associated with some occupational exposure (including their own profession) and to be able to take a detail occupational history from a patient. (5) Healthcare workers also need to be aware of importance of asking about the health of close contacts of anyone with a potentially infectious illness. Quickly identifying possible clusters of illness is helpful for detection of an outbreak of infectious disease and is very important for its control.

In general, healthcare and lab workers' vigilance on SARS and other infectious disease should be greatly raised. Management systems of occupational exposure to biological agents and disease surveillance need to be designed to take all risk factors into account so as to be able to detect potential patients with infectious diseases swiftly.

Management of Fever Patients and Nosocomial Infection

Based on experiences and lessons form SARS outbreak in Beijing during 2003, MOH of China and Beijing Municipal Health Bureau have developed a practical manual for emergent public health events, specially for SARS[17]. The manual stresses that fever patients should be screened according to the following procedures: interviewing their previous medical histories, chest X-ray examination, and blood leukocyte count. If a fever patient has a history of contact with SARS cases, with pneumonia in chest X-ray films and decreased blood leukocyte count, he or she should be highly suspected as case of SARS and should be isolated for further diagnosis. In this outbreak, case S got SARS-like symptoms and exposed to a lab engaged in studies on SARS-CoV, but regretfully it did not arouse enough vigilance at her lab and visited hospitals. She still traveled several places between Beijing and Anhui Province by train without immediate isolation while manifesting symptoms of SARS. This seems to be a serious breach of both regulations of management for fever patients and national/ WHO lab bio-safety guidelines. Case L developed SARS-like symptoms six days after she attended a fever patient at hospital ward and was not treated in isolation and shared a room with other patients, which also seriously breaches regulations for management for SARS patients set in the practical manual mentioned above.

In this outbreak of SARS, no wide spread occurred among healthcare workers, suggesting that nosocomial infection is under well control. But two cases X and Z were infected with SARS at hospital due to their sharing a room in JG Hospital with the index case L when she manifested SARS-like symptoms. Fever patient should be isolated strictly before his or her diagnosis is well established to avoid cross infection among patients.

Suggestions

Experiences and lessons from this outbreak of SARS strongly suggest that: (1) Lab bio-safety with different levels should be strengthened according to lab bio-safety manual developed by WHO in all labs, and new methods for virus inactivation should be adopted only after rigorous evaluation. (2) Management system of occupational exposure to biological agents and disease surveillance system need to be designed to take all risk factors into account so as to be able to detect potential patients with infectious diseases swiftly. (3) All fever patients should be attended only by trained nurses with good personal protection and should not be cared by anyone else before its diagnosis is clearly known to avoid unnecessary cross infection through close contact.

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(*Received November* 20, 2005 *Accepted April* 10, 2006)