Severe Acute Respiratory Syndrome (SARS): An Overview

N. U. Okubadejo and E. O. Bandele
Department of Medicine
College of Medicine, University of Lagos,
P. M. B. 12003, Lagos, Nigeria.

Correspondence: **N. U. Okubadejo**

SUMMARY

Background: Severe acute respiratory syndrome (SARS) is an emerging infectious disease recognized in March 2003. From its original location, the disease has rapidly spread globally, leaving in its wake, considerable anxiety, morbidity and mortality.

Objective: To review existing literature on SARS, and provide an overview of what is currently known of the epidemiology, clinical features, diagnosis, treatment and prognosis of SARS.

Findings: Much information has become available on SARS, and this is largely credited to international collaboration, expedition of information flow via the world wide web and global press, and the leading roles of the World Health organization (WHO), Centres for Disease Control and Prevention (CDC), governmental health authorities, and non-governmental organizations. The causative agent has been sequenced, preliminary short-term clinical features described, and interim prevention measures identified. The probability of resurgence, the gold standard for diagnosis, and specific treatment regimes, are actively being investigated.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a new communicable disease that apparently first manifested in humans in the Guangdong province of China, in November 2002 [1]. In late February 2003, the attention of the World Health Organization (WHO) was drawn to an outbreak of atypical pneumonia of unknown aetiology in a hospital in Hanoi, Viet Nam [2-4]. Consequently, in March 2003, the WHO issued a global alert and travel advisory on Severe Acute Respiratory Syndrome (SARS), describing it as a "worldwide health threat" and indicating that possible cases had been identified in Canada, Indonesia, Philippines, Singapore, Thailand and Vietnam [3,4]. The disease outbreak rapidly spread worldwide, with probable cases reported from virtually every continent [5]. In the wake of the alert, the international press, governments and non-governmental organizations, scientific journals, and the global health community (comprised of collaborating laboratories, affected health institutions staff, national ministries of health, etc.) arose to their responsibilities[6]. With the dramatic speed only attainable in this information age, and the world wide web serving as a medium for expediting information spread [7], emerging information was rapidly disseminated on the epidemiology, presumed aetiology, clinical manifestations, diagnosis, management and prognosis of this infectious disease. This article provides an overview of current knowledge regarding SARS.

EPIDEMIOLOGY

An appraisal of the cumulative number of reported probable cases of SARS posted by the WHO for the period 1 November 2002 to 6 June 2003, showed that 8404 persons had been affected [8]. Of these, 779 deaths had occurred, while 5937 persons had, so far, recovered [8]. The epidemic curves between 1 March and 5 June 2003 showed that the number of cases gradually increased from early March 2003, reached a peak around mid April 2003, with a somewhat steady decline of reported cases thereafter [8]. The WHO, which is continuously providing information as to the current status as regards ongoing local transmission, believes the outbreak appears to have slowed considerably, with cautious optimism that it is well on its way to being contained globally [9]. For instance, the last probable cases reported from Viet Nam, Brazil and Australia were on 8 April, 10 April, and 12 May respectively, though these are regions with fewer cumulative cases [8]. Some uncertainties however, still remain relating to information flow from health authorities in a few affected countries, poor infrastructure, and the possibility of resurgence as a result of relaxed surveillance [9]. For instance, Canada, initially taken off the list of areas with local transmission in late May, thereafter experienced a fresh outbreak of probable cases of SARS [10].

At the outset of the SARS epidemic, the aetiologic agent was unknown. However, following laboratory evaluation of the lungs and sputum of probable cases conducted by several investigators collaborating internationally [11], the causative agent, which fulfils Koch's postulate, has been identified, sequenced and named the SARS-associated coronavirus (SARS-CoV) [12-17]. The diameter of the virus is about 50nm without envelope or 100nm with envelope, and the virus responds positively to convalescent-phase serum specimen from SARS patients, providing further evidence that it is aetiologically linked to the outbreak of SARS [13]. Prior to the discovery of the SARS-CoV, the two previously known human coronaviruses had only been associated with often seasonal (winter), predominantly mild, self-limited upper respiratory infections, rarely causing lower respiratory tract infections (perhaps in part due to their poor growth at 37°C) [18-20]. In contrast, animal coronaviruses (such as feline, swine, avian, mouse, and porcine types) have been known to cause fatal systemic diseases in animals [20, 21].

The origin of the SARS-CoV remains conjectural. Available evidence implies that the virus is new to humans, based on the finding that human sera collected for other purposes prior to the outbreak of SARS do not contain antibodies directed against the SARS-CoV [20]. Genetic sequencing has shown that the new SARS-CoV is only distantly related to the known coronaviruses, and probably did not arise either as a mutation of known human

coronaviruses or recombination of other known coronaviruses[20]. The possibility of animals being the original source of the SARS-CoV [22] has culminated in the banning, in Guangdong province, China, of the sale of wild animals, including the civet cat, one of a range of wild animals that are a delicacy in southern China, and a suspected source of SARS-CoV [9].

The pattern of transmission of the SARS-CoV is similar to that of other viral respiratory pathogens. It spreads predominantly by droplets and contact with contaminated objects, but may spread by the air-borne route as well [24, 25]. Most patients identified so far have been previously healthy adults aged 25 -70 years, with only a few suspected cases reported among children below 15 years [26, 27]. The risk of contacting SARS is greatest in persons having direct contact with SARS patients (health-care workers, other admitted patients, and household contacts) [2,28]. High attack rates have consistently been documented among health care workers caring for SARS patients in foci of infection in Hanoi, Hong Kong Special Administrative Region, and Toronto [2,28-31]. Although nosocomial transmission of SARS has been well documented, experience has demonstrated that spread among health care workers can occur despite knowledge about the epidemiology and transmission of SARS [30-32]. The best protection shown to curtail spread within hospitals appears to be derived from increased vigilance and the proper application of generally accepted infection control measures such as use of N95 face masks, hand hygiene (frequent hand washing or use of alcohol-based hand rubs), double gloves, and eye protection while caring for suspect or probable cases [33, 34]. Preventive measures recommended in households with a SARS patient are similar, and should be continued for 10 days after resolution of fever and respiratory symptoms. The measures include limiting outsiders contact with the patient, hand hygiene for all household members, use of disposable gloves in patient care, and avoiding the sharing of personal items (towels, beddings, etc) with the patient [33, 34]. Public –health interventions have included encouragement to report to hospital promptly after the onset of clinical symptoms, contact tracing for confirmed and suspected cases, and quarantining, monitoring, and restricting the travel of contacts [33, 34].

CLINICAL FEATURES

The clinical presentation of SARS is relatively consistent across all nations affected [35-38]. However, a full description of the clinical spectrum of SARS can only be expected with long-term experience. The case definitions for surveillance of SARS as posted by the WHO [1] are shown in Table 1. It is important to note that these are subject to modification as new information becomes available, and updated versions can be accessed on the WHO website [1]. Table 2 provides a summary of frequency of various initial features of SARS at presentation in some published series [28, 35-38].

The symptoms of SARS resemble those of atypical pneumonia which can be of diverse aetiology. The incubation period is typically 2-7 days, but may occasionally be as long as 10 days [2, 39]. There are generally three recognized phases of SARS thereafter: the prodromal phase, the lower respiratory phase, and the recovery or progression phase [2, 37].

The prodromal phase is characterized by onset of high fever (>38°C) often associated with chills and rigors, and accompanied by myalgia, headache, and malaise [28, 35-39]. Occasionally, but less commonly, mild respiratory symptoms such as cough, runny nose and sore throat may occur [28, 35-39]. Diarrhea has been reported, although it is present in less than one-third of patients in most series reported [28, 35-38]. Peiris et al reported that despite an initial low frequency of diarrhea on admission (1%), 73% of their cases subsequently developed diarrhea while on admission [37]. They opine that this may be related to the possible route of infection (faeco-oral) in their cohort of patients [37]. Their cases were residents of the Amoy Gardens, a high-rise housing estate in Hong Kong, in which there was a purported point-source outbreak, linked to a faulty sewage system, initially contaminated by the excreta of the index case [37]. Skin rashes are rare [28, 36]. Neurologic findings have not been reported at presentation.

The lower respiratory phase usually begins after 3-7 days, with the onset of dry, often unproductive cough or dyspnea, which might be accompanied by, or progress to hypoxaemia [2, 36-39]. Physical examination reveals a high body temperature in most patients [28, 35-38]. Other occasional findings include tachycardia, tachypnea, and crepitations.

As regards subsequent disease progression, SARS patients generally fall into one of two categories. The majority (80-90%), at day 6 or 7, begin to show gradual improvement in signs and symptoms [2, 36-38]. A smaller group (10-20%) progress to a more severe form of SARS characterized by ARDS necessitating ventilatory support, and sometimes complicated by nosocomial sepsis (related to end-organ damage and severe lymphopenia)[36-38]. There is some evidence that the severe clinical worsening may be due to immunopathological damage as a result of overexuberant host response, rather than uncontrolled viral replication [37].

Certain prognostic indicators associated with an increased risk of more severe disease and death from SARS have been reported. These include old age [28, 35, 37], chronic hepatitis B infection [37], and the presence of co-morbid disease (diabetes, chronic obstructive pulmonary disease, cancer or cardiac disease) [28]. Booth et al showed that, although age of 60 years or older, diabetes, and presence of other comorbidities are all positively associated, statistical comparisons from univariate and multivariate models indicated that collinearity was not a problem [28].

The estimation of case fatality rates in the situation of an emerging epidemic is not simple, because the disease is just evolving [38]. Another reason is that most figures will be based on in-hospital mortality, excluding milder cases that have not been admitted. Donnelly et al reported an estimated case fatality rate of 13.2% and 43.3% for patients younger than 60years, or aged 60 and above respectively [38], while Peiris et al and Booth et al found 21-day mortality rates of 6.7% and 6.5% respectively [37, 38]. The case-fatality rate among persons with SARS meeting the current WHO case definition is approximately 9.3% (based on 8404 cases and 799 deaths as at June 6) [8].

LABORATORY FEATURES

The definitive diagnosis of SARS depends on demonstration of the SARS-CoV in a suspect or probable case. The presence of features of atypical pneumonia not

attributable to any other cause and a history of exposure to a suspect or probable case of SARS is usually the basis of the presumptive diagnosis. In evaluating suspected cases, the CDC recommends that initial testing should include chest radiographs, pulse oximetry, blood cultures, sputum Gram's stain and culture, and testing for viral respiratory pathogens, notably influenza A and B and respiratory syncytial virus. A specimen for Legionella and pneumococcal urinary antigen testing should also be considered [40]. Clinicians are also advised to save any available clinical specimens (respiratory, blood and serum) for additional testing until a specific diagnosis is made [40]. Acute and convalescent (greater than 21 days after onset of symptoms) serum samples should be collected from each patient who meets the case definition. Samples can be forwarded to the CDC for coronavirus antibody testing, through state and local health authorities [40]. A few commercially available systems for reverse transcriptase polymerase chain reaction (RT-PCR) testing of samples for SARS-CoV have been developed [41].

Chest radiograph findings may vary depending on the phase of disease. At the onset of the febrile prodrome, most patients have abnormal findings [35, 37]. The initial radiographic features are not distinguishable from other causes of bronchopneumonia and usually comprise of small, unilateral, focal and predominantly peripheral, interstitial infiltrates, which slowly progress to bilateral or multi-zonal, generalized shadows, with interstitial infiltrates [35,37]. Peiris et al found abnormality in initial chest radiographs in 71% of their patients, with unilateral involvement in 49% and multizonal changes in 21% [37]. Lower-zone infiltrates or consolidation occurred in 60% [37]. They also describe a shifting pattern of initial improvement of pulmonary lesions associated with appearance of new radiological lesions at other sites in 45% of patients [37]. Some patients (<1/3rd) progress to a diffuse ground-glass appearance, and most of these subsequently develop ARDS [37]. Spontaneous pneumomediastinum (unrelated to intubation and positive-pressure ventilation) and pneumothorax have also been reported as an occasional complication [28, 37]. Computerised tomographic (CT) scans have also been used, but SARS has been found to share features with other conditions that result in subpleural air-space disease [42]. CT features include subpleural focal consolidation with air bronchograms and ground-glass opacities, usually in the posterior aspects of the lower lobes [37, 42].

Lymphopenia, thrombocytopenia, elevated creatine kinase, lactate dehydrogenase, and aspartate and alanine aminotransferase enzyme levels are frequently reported [28,35,37,42,43]. Booth et al also report a high frequency (>50%) of electrolyte and biochemical abnormalities (hypocalcemia, hypomagnesemia and hypophosphatemia), during hospitalization, often associated with worsened hospital course [28].

With respect to the virology of SARS, Peiris et al documented that IgG seroconversion was documented in 93% of their patients at a mean (SD) of 20 (5.1) days [37]. SARS-CoV was detected in nasopharyngeal aspirates by RT-PCR in only 32% of patients at initial presentation (mean (SD) 3.2 (1.3) days after onset), but this value rose to 68% at day 14. In addition, viral RNA was detected in 42% and 97% of stool and urine samples (respectively) collected later in the illness (day 14-15) [37]. As such, serology, respiratory and faecal samples can be used to confirm the diagnosis of SARS-associated coronavirus infection in most SARS patients [37].

TREATMENT

Several treatment regimes have been tried with variable results in SARS patients [28, 31, 37]. The therapeutic options depend on the severity of the illness. A number of antibiotics have been tried to presumptively treat known bacterial agents of atypical pneumonia, but with little clear effect [6,28,37,39]. Antiviral drugs such as oseltamivir and ribavirin, with or without steroids have been increasingly used, but their efficacy is not yet proven [28,37,39]. The vast majority of patients (95%) in the series by Booth et al received empirical antibiotic therapy during the course of their illness. while ribavirin and steroids were used in 88% and 40% of cases respectively [28]. They however commented that, given the retrospective nature of their study, it would be difficult to determine the therapeutic benefit of the treatment regimens used, particularly in the face of numerous adverse effects associated with these treatments [28]. There are recent reports to the effect that most patients recover from SARS despite not receiving either ribavirin or steroids [44]. Currently, the most appropriate management measures are general supportive therapy, ensuring adequate hydration, and treatment of subsequent infections [39].

Emerging knowledge regarding the causative coronavirus has led to proposals for potential targets for antiviral drugs and vaccines [20]. Many steps unique to coronavirus replication could be targeted for development of antiviral drugs. These include molecules capable of blocking the binding of the coronavirus spike protein(S) on the viral envelope to specific receptors on the host cell membrane, protease inhibitors to inhibit cleavage of SARS-CoV polymerase protein and viral RNA synthesis, and nucleoside inhibitors to block viral replication [20].

Table I

Case definitions for surveillance of SARS (revised 16 March 2003)

Category	Definition
Suspect case	A person presenting after 1 February 2003 with history of: * High fever (>38°C) AND * *One or more respiratory* symptoms including cough, shortness of breath, difficulty breathing AND one or more of the following: * Close contact* within 10 days of symptoms, with a person who has been diagnosed with SARS * History of travel, within 10 days of onset of symptoms to an area in which there are reported foci of transmission of SARS
Probable case	A suspect case with chest x-ray findings of pneumonia or respiratory distress syndrome OR A person with an unexplained respiratory illnessresulting in death, with an autopsy examination demonstrating the pathology of Respiratory Distress Syndrome without an identifiable cause.

* Close contact means having cared for, having lived with, or having had direct contact with the respiratory secretions and body fluids of a person with SARS

Table II

Clinical features at presentation (%) in SARS in some reported series

Clinical feature	Lee et al[35] (Hong Kong) n = 138	Peiris et al[36] (Hong Kong) n = 50	Booth et al[28] (Toronto) n = 144	Peiris et al[37] (Hong Kong) n = 75	Donnelly et al[38] (Hong Kong) n = 1425
Fever	100	100	99	100	94
Cough	57	62	74	29	50
Myalgia	61	54	49	68	51
Breathlessness	Not available	20	42	4	31
Headache	56	20	35	15	50
Malaise	Not available	50	31	Not available	64
Chills and/or (rigors)	73	74	28	65 (56)	65 (44)
Rhinorrhea	22	24	2	Not available	25
Sore throat	23	20	12	11	23
Diarrhea	20	10	24	1	27
Abdominal pain	Not available	Not available	3	Not available	12
Nausea or vomiting	20	Not available	19	Not available	14
Anorexia	Not available	20	Not available	Not available	55

Cough predominantly unproductive, e.g. Sputum production in 29% [35], 69.4% (productive) v. 4.9% (unproductive)[28]

CONCLUSION

This paper attempts (but is by no means exhaustive) to summarise what is currently known about SARS. The concept of the world as a global village has been well demonstrated by the SARS epidemic. Globalization will, over the years, take its toll, and this will include epidemics of this nature, starting in somewhat obscure, previously relatively unknown regions of the world, but transmitted far and wide due to the mobility of contemporary society. However, the unprecedented spirit of international collaboration demonstrated, the speed with which information has become rapidly available, and the ethical considerations conceded by international journals in expediting publication and providing many original publications freely accessible to the public online is remarkable, and definitely a plus for the concept of globalization.

The SARS epidemic has posed several challenges to all stake-holders in the health sector. One such challenge is the need for authorities to be prompt and truthful in reporting the health-care situation and epidemic-preparedness in their countries, so as to limit extent of spread of communicable diseases. Another sphere is the economic and social impact of such epidemics including imposition of travel restrictions, closure of work places, and mandatory quarantine. In addition, the specific impact of SARS on healthcare workers brings to the fore the occupational hazards faced by this group of employees and the need for pro-activeness in routinely ensuring adequate protection while delivering care.

Regarding the long-term effects of SARS, and the question as to whether it will re-emerge in epidemic proportions, only time will provide the answers. Three priority tasks have been identified in the global response to SARS [28]. First, the identification of the causal agent and development of tests to detect the virus and allow rapid confirmation of cases. Secondly, the development and assessment of treatment protocols. Lastly, the determination of key epidemiological processes and parameters that affect the spread and persistence of infection to aid the formulation of appropriate public-health interventions. Gladly, efforts are ongoing in all these areas, and will hopefully result in eventual victory over this new, unwanted foe.

REFERENCES

1. World Health Organization. Case definitions for surveillance of severe acute respiratory syndrome (SARS). Available at: http://www.who.int/csr/surveillance/casedefinition/en.
2. Pan American Health Organization. Severe Acute Respiratory Syndrome (SARS). Available at: http://www.paho.org/.
3. World Health Organization. WHO issues a global alert about cases of atypical pneumonia. Available at: http://www.who.int/csr/sarsarchive/2003_03_12/en/.
4. World Health Organization. Severe acute respiratory syndrome (SARS): multi-country outbreak. Available at:http://www.who.int/csr/don/2003_03_16/en/.
5. Centers for Disease Control and Prevention. Update: outbreak of severe acute respiratory syndrome-worldwide, 2003. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a1.htm.
6. Gerberding JL. Faster...but fast enough? Responding to the epidemic of severe acute respiratory syndrome. N Engl J Med 2003;348:2030-2031
7. Larkin M. Web serves as conduit for SARS information. Lancet Infect Dis 2003 Jun;3(6):388-9.
8. World Health Organization. Cumulative number of reported probable cases of severe acute respiratory syndrome (SARS). Available at: http://www.who.int/csr/sarscountry/2003_06_06/en/.
9. Parry J. Spread of SARS slows. BMJ 2003;326(7401):1232.

10. Kondro W. SARS back in Canada. Lancet 2003;361(9372):1876
11. Stohr K. A multicentre collaboration to investigate the cause of severe acute respiratory syndrome. Lancet 2003;361(9370):1730-3.
12. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953-1966
13. Zhang QF, Cui JM, Huang XJ, Lin W, Tan DY, Xu JW, et al. Morphology and morphogenesis of severe acute respiratory syndrome (SARS)-associated virus. Acta Pharmacol Sin. 2003 Jun;24(6):505-11.
14. Fouchier RAM, Kuiken T, Schutter M, van Amerongen G, van Doornum GJJ, van den Hoogen BG, et al. Aetiology: Koch's postulates fulfilled for SARS virus. Nature 2003;423(6937):240
15. Poon LL, Wong OK, Luk W, Yuen KY, Peiris JS, Guan Y. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). Clin Chem 2003 Jun;49(6):953-5.
16. Centers for Disease Control and Prevention. SARS coronavirus sequencing. Available at:http:// www.cdc.gov//ncidod/sars/sequence.htm.
17. Marra MA. The genome sequence of the SARS-associated coronavirus. Science 2003. doi:10.1126/ science.1085953.(epub ahead of print).
18. Bradburne AF and Tyrrell DAJ. Coronaviruses of man. Prog. Med. Virol. 1971;13:373-403.
19. Chilvers MA, McKean M, Rutman A, Myint BS, Silverman M, and O'Callaghan C. The effects of coronavirus on human nasal ciliated respiratory epithelium. Eur Respir J. 2001;18(6):965-970.
20. Holmes KV. SARS coronavirus: a new challenge for prevention and therapy. J Clin Invest 2003;111:1605-1609.
21. Herrewegh AA, Mahler M, Hedrich HJ, Haagmans BL, Edgerink HF, Horzinek MC, et al. Persistence and evolution of feline coronavirus in a closed cat-breeding colony. Virology 1997;234(2):349-363.
22. Abbott A. Pet theory comes to the fore in fight against SARS. Nature 2003;423(6940):576.
23. Cyranoski D, Abbot A. Virus detectives seek source of SARS in China's wild animals. Nature 2003 May 29;423(6939):467.
24. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L et al. Transmission Dynamics and Control of Severe Acute Respireatory Syndrome. Science 2003; May 23 (Epub ahead of print). Available at: http:// www.sciencemag.org.
25. Riley S, Fraser C, Donnelly CA, Ghani AC, Abu Raddad LJ, Hedley AJ et al. Transmission Dynamics of the etiological agent of SARS in Hong Kong: Impact of Public Health Interventions. Science 2003; May 23 (Epub ahead of print). Available at: http:// www.sciencemag.org.
26. Centers for Disease Control and Prevention. Preliminary clinical description of severe acute respiratory syndrome. Available at: http://www.cdc.gov/ /mmwr/preview/mmwrhtml/m2d321.htm.
27. Hon KLE, Leung CW, Cheng WTF, Chan PKS, Chu WCW, Kwan YW, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 2003;361(9370):1701-3.
28. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto area. JAMA 2003;289(21):1-9.
29. Dwosh HA, Hong HH, Austgarden D, Herman S, Schabas R. Identification and containment of an outbreak of SARS in a community hospital. CMAJ 2003;168(11):1415-20.
30. Centers for Disease Control and Prevention. Cluster of severe acute respiratory syndrome cases among protected health-care workers –Toronto, Canada, April 2003. JAMA 2003;289(21):2788-9.
31. Centers for Disease Control and Prevention. Severe Acute Respiratory Syndrome-Taiwan, 2003. JAMA 2003:289(22):2930-2932.
32. Seto WH, Tsang, D, Yung WR, Ching TY, Ng TK, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory distress syndrome (SARS). Lancet 2003;361:1519-29.
33. Federal Ministry of Health (Nigeria). Severe acute respiratory syndrome (SARS). Health Alert for Medical Facilities.
34. Centers for Disease Control and Prevention. Updated interim domestic infection control guidance in the health-care and community setting for patients with suspected SARS. Available at: http://www.cdc.gov// ncidod/sars/infectioncontrol.htm.
35. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986-1994.
36. Peiris JSM, Lai S, Poon LLM, Guan Y, Yam LYC, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361(9366):1319-1326.
37. Peiris JSM, Chu CM, Cheng VCC, Chan KS, Hung IFN, Poon LLM, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361(9371):1767-1772.
38. Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003;361(9371):1761-6.
39. World Health Organization. SARS-Worldwide (09): Clinical Features. Available at: http//www.who.int/csr/ sars/cliniciansconference/en/.
40. Centers for Disease Control and Prevention. Collecting specimens. Available at: http://www.cdc.gov/ncidod/ sars/specimen_collection_sars2.htm.
41. McIntosh K. The SARS coronavirus: Rapid diagnostics in the limelight. Clin Chem 2003;49(6):845-846.
42. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, Chan-Yeung M, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1977-1985.
43. Chan-Yeung M, Yu WC. Outbreak of severe acute respiratory syndrome in Hong Kong Special Administrative Region:case report. BMJ 2003;326:850-2.
44. Centers for Disease Control and Prevention. SARS and coronavirus testing –United States. Available at www.cdc.gov/mmwrhtml/mm5214a1.htm.