SARS: Current overview, Aetiology and Epidemiology

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At this moment, public health authorities, physicians and scientists around the world are struggling to cope with a severe and rapidly spreading new disease in humans called severe acute respiratory syndrome, or SARS. According to World Health Organisation (WHO) this appears to be the first severe and easily transmissible new disease to emerge in the 21st century. Though much about the disease remains poorly understood, including the details of the causative virus, we do know that it has features that allow it to spread rapidly along international air travel routes.

As of 10 May 2003, a cumulative 7296 probable SARS cases with 526 deaths have been reported from 30 countries on three continents (WHO, ProMED). In the past week, more than 1000 new probable cases and 96 deaths were reported globally. This represents an increase of 119 new cases and 8 new deaths compared with 9 May 2003 (China (85), Taiwan (23), and Hong Kong (7) represented the overwhelming majority, with one additional case each reported from France, Malaysia, Singapore, and the United States). Only in China, as of 10 May 2003 (WHO) total of 4884 with 235 deaths have been reported. Some outbreaks have reassuring features.

SARS historical overview

Severe Acute Pulmonary Syndrome (SARS) was first identified in Viet Nam on 28 Feb 2003, when Dr Carlo Urbani, an epidemiologist from the Hanoi WHO office, examined a patient with a severe form of pneumonia for which no aetiology could be found. On 10 Mar 2003, 22 hospital workers in Hanoi French Hospital were ill with a similar acute respiratory syndrome, and by 11 Mar 2003, similar outbreaks were reported among hospital workers in Hong Kong.

SARS occurred at a time of heightened surveillance for atypical respiratory disease. From 10 Feb 2003 the WHO office in Beijing, which reinforced its staff with 2 epidemiologists, had been working with the government of China to learn more about an outbreak of atypical respiratory disease that affected health workers, their families and contacts in Guangdong Province, with (at that time) 305 cases and 5 deaths reported from 16 Nov 2002 to 7 Feb 2003. Approximately 30 percent of cases were reported to occur in health care workers. Surveillance was heightened further when a 33-year-old man who had travelled with his family to Fujian Province in China died in Hong Kong on 17 Feb 2003. The next day, Hong Kong authorities announced that avian influenza A (H5N1) virus, the cause of "bird flu", had been isolated from both the man and his 9-year-old hospitalized son. Another member of the family, an 8-year-old daughter, died in Fujian and was buried there.

On 12 Mar 2003, after an assessment of the situation in Asia with WHO teams in Hanoi, Hong Kong, and Beijing, *a global alert was issued about cases of severe atypical pneumonia with unknown aetiology that appeared to place health workers at high risk.*

Two days later, on 14 Mar 2003, WHO received a report from the government of Canada that health authorities had taken steps to alert hospital workers, ambulance services, and public health units across the provinces that there were four cases of atypical pneumonia within a single family in Toronto that had resulted in two deaths.

At 0200h Geneva time 15 Mar 2003, the government of Singapore notified WHO, by urgent telecommunication, of a similar illness in a 32-year-old physician who had treated hospital workers with a severe respiratory syndrome in Singapore, including one from the French Hanoi hospital who had self-evacuated to Singapore. This Singapore physician had travelled to the United States for a medical conference, and at the end of the conference boarded a return flight to Singapore in New York. Before departure, he had indicated to a colleague in Singapore by telephone that he had symptoms similar to the patients he had treated in Singapore. The colleague notified health authorities and WHO identified the airline and flight, and the physician and his accompanying family members were removed from the flight at a stopover

in Frankfurt, Germany, where he was immediately isolated and placed under hospital care, as were his 2 accompanying family members when they developed fever and respiratory symptoms several days later. As a result of this prompt action, *Germany experienced no further spread linked to the three imported cases*.

Later in the morning of 15 Mar 2003, with this background and chronology of events, a decision was made by WHO to increase the level of the global alert issued on 12 Mar 2003. The decision was based on 5 different but related factors:

- *First*, the aetiology, and therefore the potential for continued spread, of this new disease were not yet known.
- *Second*, the outbreaks appeared to pose a great risk to health workers who managed patients, and to the family members and other close contacts of patients.
- *Third*, many different antibiotics and antiviral agents had been tried empirically and did not seem to have an effect.
- *Fourth*, though the numbers were initially small, a significant percentage of patients (25 of 26 hospital staff in Hanoi, and 24 of 39 hospital staff in Hong Kong) had rapidly progressed to respiratory failure, requiring intensive care and causing some deaths in previously healthy persons.
- *Finally*, the disease had moved out of its initial focus in Asia and appeared to have spread to North America and Europe.

At this time, the epidemiology of SARS was poorly understood. A virulent strain of influenza had not been ruled out as a possible cause, even though transmission patterns were not characteristic for influenza. There was also some hope that the new disease, like many other new diseases of the recent past, would fail to maintain efficient person-to-person transmission, or that it might attenuate with passage and eventually self-contain. Despite the lack of understanding about the disease, its cause, and future evolution, the need was great to introduce a series of emergency measures to contain SARS outbreaks in the affected areas and prevent further international spread, thus reducing opportunities for the new disease to establish endemiology. *WHO thus decided, on 15 Mar 2003, to issue a rare emergency travel advisory as a global alert to international travellers, health care professionals, and health authorities?*

At the same time, the global alert recommended no change in patterns of international travel, but that passengers notify their health authority if they should develop signs and symptoms and have a history of travel to areas reporting cases of SARS. Following this alert, awareness increased immediately, and many potential new outbreaks were prevented by the prompt isolation and strict management of suspected cases.

By 27 Mar 2003, however, it was evident that international spread of SARS had continued after the 15 Mar 2003 advisory at 2 of the earliest outbreak sites, namely Viet Nam and Hong Kong. Persons on the same airplanes as persons with symptoms consistent with SARS, and sitting in close proximity to them, had developed signs and symptoms compatible with SARS. On this date, it was decided to recommend new measures related to international travel, still with the intent of preventing the international spread of the infectious agent. These recommendations were that SARS-affected areas, where chains of human-to-human transmission were known to occur, institute measures to identify international passengers who had signs, symptoms and history compatible with SARS, and to recommend that such persons postpone international travel and seek medical advice. These recommendations were instituted in most of the affected areas shortly after 27 Mar 2003.

Concern however, continued to mount. An urgent investigation of the Amoy Gardens, outbreak in Hong Kong began on 29 Mar 2003, and the following day, health officials announced that 213 Amoy residents were probable cases of SARS. This followed an unusual cluster of cases, closely linked in time and place, among guests and visitors who had stayed on the same floor of a hotel located in the same district (Kowloon) as Amoy Gardens. By this same date, nine business travellers and tourists had returned to Singapore, Beijing, and Taiwan from Hong Kong, either sick or in the incubation period of SARS.

Outbreaks in the hotel and housing estate indicated that SARS was showing an unusual pattern of transmission in Hong Kong, probably involving an environmental component that would place persons at risk outside the confined health care settings associated with outbreaks in most other countries. The nine cases of probable SARS that occurred in Singapore, Beijing, and Taiwan associated with travel in Hong Kong, indicated that the risk of international spread was continuing.

Cases of possible transmission in airplanes continue to be reported and investigated. As recently as 5 Apr 2003, notification of a SARS patient travelling internationally by sea from Hong Kong to Vladivostok (Russian Federation) was received, opening a possible second route of international travel for the virus.

WHO travel recommendations are kept under constant review and will be amended as more data about the evolution of SARS become available.

Aetiology of SARS

On 17 Mar 2003, a network of 11 leading laboratories around the world was set up as a mechanism for expediting identification of the SARS causative agent. Today, after joining of two more laboratories from China during first part of April, there are total 13 laboratories from 10 countries all around the World who are working on SARS virus research. Laboratories were selected based on three criteria:

- outstanding scientific expertise,
- facilities at biosafety level III, and
- capacity to contribute to the battery of tests and experiments that would be needed to fulfil Koch's four postulates[1] for the identification of an infectious agent as the cause of a specific disease.

The network was set up on the model of the influenza network and provides another important lesson: models and systems set up for one health emergency can be rapidly adapted to serve others.

Collaboration is virtual. Members of the network confer in daily teleconferences coordinated by WHO and use a secure web site to post electron microscopic pictures of candidate viruses, sequences of genetic material for virus identification and characterization, descriptions of experiments, and results. The well-guarded secret techniques that give each laboratory its competitive edge have been immediately and openly shared with others. Laboratories also quickly exchange various samples from patients and post-mortem tissues. These arrangements have allowed the analysis of samples from the same patient simultaneously in several laboratories specialized in different approaches, with the results shared in real time. This collaboration has resulted in the identification of the suspected causative agent, and the development of three diagnostic tests, with unprecedented speed.

Recent findings in China show that with seven investigated fatal cases both Chlamydia like and Coronavirus like agents were found in all seven cases of atypical pneumonia collected in Guangdong province. Since the Chlamydia-like agents presenting in both organs and cell cultures could not react with the genus specific antibodies against Chlamydia and monoclonal antibodies against C. pneumoniae and C. psittaci, the results might well be suggestive of a novel Chlamydia-like agent (Hong T. et al, 2003), and not only a new Coronavirus.
Virus isolation continues from patients with SARS, and at the same time virus has been isolated from tears and faeces. Publications on these various findings are being prepared by members of this collaborating group, but the need remains for a highly sensitive and specific PCR test to diagnose acute infections.

New coronavirus discovered

Through new mechanisms set up by WHO, progress in research has been unprecedented, particularly in the rapid discovery of a new coronavirus and development of diagnostic tests. The best scientists from around the world are working on these problems around the clock, and in an unprecedented spirit of collaboration against a threat of as-yet-unknown dimensions. Nonetheless, we still do not have conclusive proof that the new virus is indeed the cause of SARS. The results of animal experiments, which are currently being conducted by a laboratory in a WHO network, will be available soon and may provide the last pieces of evidence needed for definitive proof that SARS is caused by the newly discovered coronavirus. The family of Coronaviridae consists of enveloped, generally spherical virions with helical nucleocapsids containing a single, positive stranded RNA genome. Coronavirus are shown to show a high mutation rate, thus rapidly producing new, genetically differing variants or subspecies. This special behaviour may complicate the development of valuable diagnostic test systems showing sufficient sensitivity and specificity. Furthermore, the findings will provide additional evidence to understand the role of metapneumovirus as a possible "helper virus" in persons co-infected with the new coronavirus.

Diagnostic tests
The development of a diagnostic test has proved more problematic than hoped. Three tests are now available and are helping to improve understanding of how the virus causes disease in humans. However, all three tests have limitations as tools for bringing the SARS outbreak quickly under control.

The ELISA detects antibodies reliably but only from about day 20 after the onset of clinical symptoms. It therefore can not be used to detect cases at an early stage before they have a chance to spread the infection to others.
The second test, an immunofluorescence assay (IFA), detects antibodies reliably as of day 10 of infection, but is a comparatively slow test that requires the growth of virus in cell culture.

[1] These postulates stipulate that to be the causal agent, a pathogen must meet four conditions:
1. it must be found in all cases of the disease,
2. it must be isolated from the host and grown in pure culture,
3. it must reproduce the original disease when introduced into a susceptible host, and
4. it must be found in the experimental host so infected.

The current RT-PCR molecular test for detection of SARS virus genetic material is useful in the early stages of infection but produces many false negatives. This means that many persons who actually carry the virus may not be detected - creating a dangerous sense of false security in relation to a virus that is known to spread easily in close person-to-person contact.

Present role of tests in diagnosis

A positive test result indicates that a person is (RT-PCR), or recently was (ELISA, IFA), infected with the coronavirus. However, a negative test result does not guarantee that the person is not infected with the virus.

At present, reporting to WHO of probable SARS cases is based on an assessment of clinical symptoms, history -- including travel history -- of possible exposure to an infected person, and distinctive chest X-rays. The 10 countries in the WHO laboratory network, namely Canada, France, Germany, Japan, Hong Kong SAR, the Netherlands, Singapore, the United Kingdom, and the United States of America, are beginning to conduct routine laboratory testing of suspect and probable SARS cases. WHO has posted on its web site details about the test methodology that allows other countries to perform tests. However, more work is needed to produce a robust test that is capable of rapidly and reliably detecting cases at an early stage of infection.

Epidemiology of SARS

Modes of transmission

A collaborative group on epidemiology, made up of investigators from all sites with local transmission of SARS, continues to confirm person-to-person transmission as the major route of transmission. Based on the latest findings of virus survival in the environment (See Table 1.) there probably is more then one way of SARS transmission.

The WHO team also found evidence of "super-spreaders" in Guangdong, including one who is thought to have infected as many as 100 other persons. The outbreak dates back to 16 November 2002, when an initial case was reported in Foshan City. The phenomenon of a "super-spreader", which is not a recognized medical condition, also dates back to the early days of the outbreak. At that time, when SARS was just being recognized as a severe new disease, many patients were thought to be suffering from atypical pneumonia from other causes, and were therefore not treated as special cases requiring special precautions of isolation and infection control. In SARS outbreaks, a "super-spreader" is a source case who, for yet unknown reasons, has infected a large number of persons. It remains unknown whether such "super-spreaders" are persons secreting an exceptionally high amount of infectious material or whether some other factor, perhaps in the environment, is working to amplify transmission at some key phase of virus shedding (WHO).

Incubation period

SARS appears to be less infectious than influenza. The incubation period is short, estimated to range from 2-7 days, with maximum of 10 days (WHO), with 3-5 days being more common. However, the speed of international travel creates a risk that cases can rapidly spread around the world. One recently published analysis of data from Hong Kong estimates a longer maximum incubation period in a group of 57 patients. The longer incubation period could reflect differences in methodology, specificity of diagnosis, route of transmission, infectious dose, or other factors. Reliable diagnosis - determining that all cases diagnosed as SARS are true cases of the disease - has been particularly difficult to establish in this outbreak, as diagnosis is based on a set of non-specific symptoms and clinical signs that are seen in several other diseases.

Case fatality ratio

On 7 May 2003 WHO revised its initial estimates of the case fatality ratio[2] of SARS. The revision is based on an analysis of the latest data from Canada, China, Hong Kong SAR, Singapore, and Viet Nam. On the basis of more detailed and complete data, and more reliable methods, WHO estimates that the case fatality ratio of SARS ranges from 0% to 50% depending on the age group affected, with an overall estimate of case fatality of 14% to 15%. Based on data received by WHO until 7 May, the case fatality ratio is estimated to be less than 1% in persons aged 24 years or younger, 6% in persons aged 25 to 44 years, 15% in persons aged 45 to 64 years, and greater than 50% in persons aged 65 years and older.

One method of overcoming this difficulty is to calculate the case fatality ratio using only those cases whose final outcomes - died or recovered - is known. However, this method, when applied before an outbreak is over, gives an overestimate because the average time from illness

[2] A case fatality ratio measures the proportion of all people with a disease who will die from the disease. In other words, it measures the likelihood that a disease will kill its host, and is thus an important indicator of the severity of a disease and its significance as a public health problem. The likelihood that a person will die of SARS could be influenced by factors related to the SARS virus, the route of exposure and dose (amount) of virus, personal factors such as age or the presence of another disease, and access to prompt medical care. Many factors complicate efforts to calculate a case fatality ratio while an outbreak is still evolving. Deaths from SARS typically occur after several weeks of illness. Full recovery may take even longer. While an epidemic is still evolving, only some of the individuals affected by the disease will have died or recovered. Only at the end of an epidemic can an absolute value be calculated, taking into account total deaths, total recoveries and people lost to follow-up. Calculating case fatality as the number of deaths reported divided by the number of cases reported irrespective of the time elapsed since they became ill gives an underestimate of the true case fatality ratio.

onset to death for SARS is shorter than the average time from illness onset to recovery. With these methods, estimates of the case fatality ratio range from 11% to 17% in Hong Kong, from 13% to 15% in Singapore, from 15% to 19% in Canada, and from 5% to 13% in China.
A more accurate and unbiased estimation of case fatality for SARS can be obtained with a third method, survival analysis. This method relies on detailed individual data on the time from illness onset to death or full recovery, or time since illness onset for current cases. Using this method, WHO estimates that the case fatality ratio is 14% in Singapore and 15% in Hong Kong. In Viet Nam, where SARS has been contained and measurement is more straightforward, case fatality was comparatively low, at 8%. One explanation for this is the large number of total cases that occurred in younger, previously healthy health care workers.

Prevention

A high awareness of SARS symptoms among travellers and the medical and nursing professions has often resulted in good management of imported cases - prompt isolation of patients and management according to strict procedures of infection control. WHO continues to recommend the earliest possible isolation of all suspect and probable cases of SARS. A short time between onset of symptoms and isolation reduces opportunities for transmission to others. It also reduces the number of contacts requiring active follow-up, and thus helps relieve some of the burden on health services. In addition, prompt hospitalization gives patients the best chance of receiving possibly life-saving care should their condition take a critical course. As a result, many countries having only a single or a few imported cases have experienced no further spread to hospital staff, families of patients and hospital visitors, or the community at large. SARS patients should be placed in an isolation unit. Strict respiratory and mucosal barrier nursing is recommended. It is very important that suspected cases are separated from other patients and placed in their own hospital room. Health care workers and visitors should wear efficient filter masks, goggles, aprons, head covers, and gloves when in close contact with the patient. (WHO: Hospital Infection Control Guidance).

On 1 May 2003, WHO updated SARS case definition (WHO). The surveillance case definitions, based on available clinical and epidemiological data, are now being supplemented by a number of laboratory tests and will continue to be reviewed as tests currently used in research settings. They will become more widely available as diagnostic tests. Preliminary clinical description of Severe Acute Respiratory Syndrome summarizes what is currently known about the clinical features of SARS. Countries may need to adapt case definitions depending on their own disease situation. Retrospective surveillance is not expected. Clinicians are advised that patients should not have their case definition category downgraded while awaiting results of laboratory testing or on the bases of negative results (WHO: Use of laboratory methods for SARS diagnosis).

Suspect case

1. A person presenting after 1 November 2002[3] with history of:
   - high fever (>38 °C)

   AND
   - cough or breathing difficulty

   AND one or more of the following exposures during the 10 days prior to onset of symptoms:
   - *close contact*[4] with a person who is a suspect or probable case of SARS;
   - history of travel, to an area with recent local transmission of SARS
   - residing in an area with recent local transmission of SARS

2. A person with an unexplained acute respiratory illness resulting in death after 1 November 2002, but on whom no autopsy has been performed

IN ADDITION, one or more of the following exposures during to 10 days prior to onset of symptoms:
- *close contact*[4], with a person who is a suspect or probable case of SARS;
- history of travel to an area with recent local transmission of SARS
- residing in an area with recent local transmission of SARS

Probable case

1. A suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray (CXR).
2. A suspect case of SARS that is positive for SARS coronavirus by one or more assays. (WHO Use of laboratory methods for SARS diagnosis).
3. A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause.

3 The surveillance period begins on 1 November 2002 to capture cases of atypical pneumonia in China now recognized as SARS. International transmission of SARS was first reported in March 2003 for cases with onset in February 2003.

4 Close contact: having cared for, lived with, or had direct contact with respiratory secretions or body fluids of a suspect or probable case of SARS.

Exclusion criteria

A case should be excluded if an alternative diagnosis can fully explain their illness.

Reclassification of cases

As SARS is currently a diagnosis of exclusion, the status of a reported case may change over time. A patient should always be managed as clinically appropriate, regardless of their case status.

- A case initially classified as suspect or probable, for which an alternative diagnosis can fully explain the illness, should be discarded after carefully considering the possibility of co-infection.
- A suspect case that, after investigation, fulfils the probable case definition should be reclassified as "probable".
- A suspect case with a normal CXR should be treated, as deemed appropriate, and monitored for 7 days. Those cases in which recovery is inadequate should be re-evaluated by CXR.
- Those suspect cases in whom recovery is adequate but whose illness cannot be fully explained by an alternative diagnosis should remain as "suspect".
- A suspect case who dies, on whom no autopsy is conducted, should remain classified as "suspect". However, if this case is identified as being part of a chain transmission of SARS, the case should be reclassified as "probable".
- If an autopsy is conducted and no pathological evidence of RDS is found, the case should be "discarded".

Reporting procedures

- All probable SARS cases should be managed in the same way for the purposes of infection control and outbreak containment (WHO: Management of Severe Acute Respiratory Syndrome (SARS)).
- *At this time, WHO is maintaining surveillance for clinically apparent cases only i.e. probable and suspect cases of SARS*. (Testing of clinically well contacts of probable or suspect SARS cases and community based serological surveys are being conducted as part of epidemiological studies which may ultimately change our understanding of SARS transmission. However, persons who test SARS CoV positive in these studies will not be notified as SARS cases to WHO at this time).
- Where laboratory tests are not available or not done, probable SARS cases as currently defined above should continue to be reported in the agreed format.
- Suspect cases with positive laboratory results will be reclassified as probable cases for notification purposes *only if the testing laboratories use appropriate quality control procedures.*
- No distinction will be made between probable cases with or without a positive laboratory result and suspect cases with a positive result for the purposes of global surveillance. WHO will negotiate sentinel surveillance of SARS with selected partners to collect detailed epidemiological, laboratory and clinical data?
- Cases that meet the surveillance case definition for SARS should not be discarded on the basis of negative laboratory tests at this time.

Rationale for retaining the current surveillance case definitions for SARS

The reason for retaining the clinical and epidemiological basis for the case definitions is that at present there is no validated, widely and consistently available test for infection with the SARS coronavirus. Antibody tests may not become positive for three or more weeks after the onset of symptoms. It is currently undetermined if all patients will mount an antibody response. Molecular assays may not be positive in the early stages of illness using currently available reagents. No one is yet able to define the optimal specimen to be tested at any given stage of the illness. This information is accruing as more tests are being performed on patients with known exposures and/or accompanied by good clinical and epidemiological information. It is hope that in the near future an accessible and validated diagnostic assay(s) will become available which can be employed with confidence at a defined, early stage of the illness.

First data on stability and resistance of SARS coronavirus compiled by members of WHO laboratory network (WHO)

Virus survival in stool and urine

- Virus is stable in faeces (and urine) at room temperature for at least 1-2 days.
- Virus is more stable (up to 4 days) in stool from diarrhoea patients (which has higher pH than normal stool).

Disinfectants and fixatives (for use in laboratories)

- Virus loses infectivity after exposure to different commonly used disinfectants and fixatives.

Virus survival in cell-culture supernatant

- Only minimal reduction in virus concentration after 21 days at 4°C and -80°C.
- Reduction in virus concentration by one log only at stable room temperature for 2 days. This would

indicate that the virus is more stable than the known human coronaviruses under these conditions.
- Heat at 56°C kills the SARS coronavirus at around 10000 units per 15 min (quick reduction).

Full research results from four different hospitals are presented in Table 1.

SARS: a particularly serious threat to international health

Although the last decades of the previous century witnessed the emergence of several new diseases, SARS needs to be regarded as a particularly serious threat for several reasons. If the SARS virus maintains its present

Table 1. Research results from four different hospitals on virus survival time in an environment

Lab*	**Substrate**	**Initial viral count log_{10PFU}**	Condition	Survival time	Method of testing viability
Government Virus Unit, Department of Health, Hong Kong, SAR China	virus spiked in baby stool	1.00E+03	pH 6-7	3 hr	Virus isolation in cell culture
	virus spiked in normal stool	7.50E+03	pH 8	6hr	Virus isolation in cell culture
	virus in diarrhoeal stool	7.50E+03	pH 9	4days	Virus isolation in cell culture
Queen Mary Hospital, The University of Hong Kong, Hong Kong, SAR China	stool	1.00E+03	Room Temperature	at least 2 days	Virus isolation in cell culture
	urine	1.00E+03	Room Temperature	at least 24 hr	Virus isolation in cell culture
	Virus culture medium+ 1% bovine serum	1.00E+03	on plastic surface in room temperature	at least 2 days	Virus isolation in cell culture
	Virus culture medium+ 1% bovine serum	1.00E+04	30-37°C	at least 1hr	Virus isolation in cell culture
	Virus culture medium+ 1% foetal calf serum	1.00E+04	56°C	degradation of titre over time (10 000 infectious virus units in 15 min)	Virus isolation in cell culture
	virus in Acetone, 10% Formaldehyde and Paraformaldehyde, 10% Clorox, 75%ethanol, 2% phenol	1.00E+06	Room Temperature	less than 5 min	Virus isolation in cell culture
National Institute of Infectious Diseases, Tokyo, Japan	Virus culture+ 2% bovine serum	1.00E+06	minus 80°C	at least 4 days	Virus isolation and RT-PCR
	Virus culture+ 2% foetal calf serum	1.00E+06	4°C	at least 4 days	Virus isolation and RT-PCR
	Virus culture+ 2% foetal calf serum	1.00E+06	37°C	less than 4 days	Virus isolation and RT-PCR
	Virus culture+ 2% foetal calf serum	1.00E+05	56°C	less than 30min	
University Marburg, Germany	Virus culture	1.00E+06	4°C	at least 21 days	Virus isolation
	Virus culture	1.00E+06	minus 80°C	at least 21 days	Virus isolation

Source: WHO

pathogenicity and transmissibility, SARS could become the first severe new disease of the 21st century with global epidemic potential. As such, its clinical and epidemiological features, though poorly understood, give cause for particular alarm. With the notable exception of AIDS, most new diseases that emerged during the last 2 decades of the previous century or established endemiology in new geographical areas have features that limit their capacity to pose a major threat to international public health. Many
(Avian influenza, Nipah virus, Hendra virus, Hanta virus) failed to establish efficient human-to-human transmission. Others (Escherichia coli O157:H7, variant Creutzfeldt-Jakob disease) depend on food as a vehicle of transmission. Diseases such as West Nile Fever and Rift Valley Fever that have spread to new geographical areas require a vector as part of the transmission cycle and are associated with low mortality, often in high-risk groups, such as the elderly, the immunocompromised, or persons with co-morbidity. Still others (Neisseria meningitidis W135, and the Ebola, Marburg, and Crimean-Congo haemorrhagic fevers) have strong geographical foci. Although outbreaks of Ebola haemorrhagic fever have been associated with case-fatality rates in the range of 53 percent (Uganda) to 88 percent (Democratic Republic of the Congo), person-to-person transmission requires close physical exposure to infected blood and other bodily fluids. Moreover, patients suffering from this disease during the period of high infectivity are visibly very ill and too unwell to travel.

In contrast, SARS is emerging in ways that suggest great potential for rapid international spread under the favourable conditions created by a highly mobile, closely interconnected world. Anecdotal data indicate an incubation period of 2 to 10 days (average 2 to 7 days), allowing the infectious agent to be transported, unsuspected and undetected, in a symptomless air traveller from one city in the world to any other city having an international airport. Person-to-person transmission through close contact with respiratory secretions has been demonstrated. The initial symptoms are non-specific and common. The concentration of cases in previously healthy hospital staff and the proportion of patients requiring intensive care are particularly alarming. This "21st century" disease could have other consequences as well. Should SARS continue to spread, the global economic consequences -- already estimated at around USD 30 billion -- could be great in a closely interconnected and interdependent world.

A third collaborative group - clinical, which unites 80 clinicians from 13 countries treating SARS cases, has consistently provided anecdotal information about the lack of efficacy of treatment with specific antibiotics and antiviral agents, and has begun to develop systematic clinical trials of Ribavirin at 2 sites. Their discussions have shed light on features of the disease at presentation, treatment and progression of the disease, prognostic indicators, and discharge criteria. No therapy has been shown to demonstrate any particular effectiveness. The clinicians agreed that a subset of SARS patients, perhaps 10 percent, decline, usually around day 7, and need mechanical assistance to breathe. The care of these people is often complicated by the presence of other diseases. In this group, mortality is high. Age over 40 years also appears to be associated with a more severe form of disease. Countries have made travel recommendations for their citizens, using the guidance provided by WHO and other considerations such as feasibility of medical evacuation of their citizens and their insurance coverage should they become infected.

Lessons

Probably the most important lesson learned form this outbreak is the value of innovation and international collaboration. The knowledge obtained in the first 3-week period started 15 Mar 2003 has been remarkable. It demonstrates the value of international cooperation on emerging infections and the importance of early detection and rapid introduction of emergency measures to prevent further international spread and help ensure that imported cases are not allowed to cause disease in others.

When WHO began to set up emergency plans on 15 Mar 2003, identification of the SARS causative agent and the development of diagnostic testing were given paramount importance in the overall containment strategy. Detection of the disease in its early stage, confirmation of cases, understanding modes of transmission, development of protocols for targeted treatment, vaccine research and development, and implementation of disease-specific preventive measures would all depend upon swift progress and results in etiological and diagnostic research. Sound public health measures would also require understanding of the presence and concentration of the pathogen in different tissues and secretions, and patterns of excretion throughout the course of illness and convalescence. So long as the etiological agent remained poorly known, specialists in infectious disease control would be forced to resort to control tools dating back to the "Middle Ages" of microbiology: isolation and quarantine.

Key questions that should be answered in the near future include the exact points during the course of incubation and infection when transmission occurs and whether asymptotic cases are capable of spreading SARS. These questions must be answered in order to evaluate better the extent of SARS spreading, and the success of containment activities.

The SARS response is the rollout of a global alert and response activity under the revision of the International Health Regulations, which provide the legal framework for the surveillance and reporting of infectious disease and for the use of measures to prevent their international spread. SARS is showing how the alert and response activity works in practice for a newly identified disease. It also indicates how the system now in operation could apply to other highly significant infectious disease events, including the next influenza pandemic, the next emerging infection, and the deliberate release of a biological agent in an act of warfare or terrorism.

The scientific community is now contending with an outbreak caused by a new virus. This creates an extra step in the containment response: identification and characterization of the causative agent, which then allows development of a diagnostic test, treatment protocols, and a scientifically sound basis for recommending control measures. This is a step that would not be needed should a biological attack occur using a well-known pathogen such as anthrax or smallpox. The response to an influenza pandemic would likewise not be dealing with an entirely new and poorly understood virus.

The next weeks and months will tell whether the global alert and response will contain the current SARS outbreaks, preventing SARS from becoming yet another endemic infectious disease in human populations, or whether SARS will remain confined to its origins in nature, to re-emerge at yet another time and place. It is clear that the responsibility for containing the emergence of any new infectious disease showing international spread lies on all countries. *In a world where all national borders are porous when confronted by a microbial threat, it is in the interest of all populations for countries to share the information they may have as soon as it is available. In so doing, they will allow both near and distant countries -- all neighbours in our globalising world - to benefit from the understanding they have gained*

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