

## **Disease management strategies in SARS**

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### **Introduction**

Disease management as understood here does not mean therapy or diagnostics; here the focus will be on the public health management.

When the first SARS cases became known, decisions about the management of these cases, but also regarding the management of their contact persons had to be based on very limited evidence. Although an unprecedented cooperation of scientists around the world led to a rapid accumulation of knowledge about key features of the disease and finally the detection of the virus, the first weeks were characterized by uncertainty and fears. Strategies for managing the disease were necessary on each level of the health systems where patients occurred, i.e. the private practices that saw the patients often before they were transferred to a hospital, and the hospitals. In particular the public health service had to develop strategies for the containment of further spread in the absence of an effective vaccine and a therapeutic option.

In the following chapter, the currently available information about management strategies for SARS in the various areas of health systems will be summarized.

### **General considerations**

For the development of an effective management strategy, several epidemiological features of a disease have to be known, e.g. length of the incubation period, period of infectiousness, the stability of the pathogen in the environment, mode(s) of transmission, risk factors for transmission. Length of incubation period for example has implications for recommendations on isolation of cases and their contact persons. The following section describes the facts known so far [1]. The reader should keep in mind that during the first weeks of the SARS outbreak none of these observations were known to the decision makers.

### *Incubation period*

The incubation period of an infectious disease includes the time from infection to the onset of first symptoms. Usually, an average time is given as well as the range from minimal to maximum number of days. Estimation of the incubation period of SARS was based on cases where a single defined contact to a SARS patient has been observed. Table 1 shows the observations compiled by WHO within the epidemiology working group [1]. Median incubation period was 4–5 days, mean 4–6 days. The minimum time reported was 1 day and the maximum were 14 days. The time which all recommendations were based on had a maximum of 10 days. Therefore, these outlier observations exceeding the 10 days raised concern.

Donnelly et al. commented on their data that they were based on a small number of cases resulting in a high variance and which also may be subjected to reporting bias [2]. The group's consensus and one of the recommendations for further research was to investigate these outliers in more detail before extending the incubation period beyond 10 days.

### *Period of infectiousness*

For the assessment of how long patients should be isolated and at which times exposure to patients may have posed a risk for their contact persons, the period of infectiousness has to be known. Particular anxiety was caused by some patients who infected a high number of persons (so-called “super spreading events”).

The infection by sub-clinically ill patients or transmission in prodromal phase has not been reported so far.

Data so far available are based on small numbers of observations, but they offer an orientation. In general, the estimation of the infectious period can be derived from several observations. At which point in the clinical course can virus be detected in which clinical materials? Ideally, consecutive samples of various clinical materials should be taken.

Transmission seems to be greatest from severely ill patients, usually in the second week of their illness [1]. Data from Singapore show that few secondary cases arise when SARS patients are isolated within 5 days of onset of illness [1]. Using RT-PCR, Peiris et al. [3] detected SARS-associated coronavirus RNA in nasopharyngeal aspirates in 24 of 75 patients with a mean of 3.2 days after onset of illness, in 68% this test was positive at day 14. Twenty of the initially positive patients were followed up in 3-day intervals, and their samples were quantitatively investigated. At days 5, 10 and 15 they found mean geometric viral loads of  $2.3 \times 10^5$ ,  $1.9 \times 10^7$ , and  $9.8 \times 10^4$  copies per ml respectively, indicating a peak of viral load around day 10. These data support the epidemiological observations. Single reports of transmission from patients in their early phase of disease seem to contra-

Table 1: Summary of SARS incubation period estimates [1]

Country	Min.	Mean	Median	Max.	Basis
Canada	2	4.8	4.2	10	42 cases
China	1	4	4	12	70 cases; 5 cases > 10 days
Hong Kong	–	6.4	–	16.7	57 cases; 95% of cases $\leq 14.2$ days [2]
China, Taiwan				10–14	Household transmission studies
Singapore	1	5.3	5	10	46 cases
Viet Nam	5	6–7	–	10	Health care associated exposure
WHO Euro	5	7.2	7	10	5 cases

dict these observations. Current guidelines from WHO on the clinical management and discharge of SARS patients are based on a 10-day interval since defervescence and a normal chest X-ray [4], since there are no reports of transmission beyond 10 days of fever resolution (Clinical management document, WHO [5]). Most countries follow these guidelines. Hong Kong, however, discharges patients only 19 days after the end of fever and normal chest X-ray [1].

### *Stability of SARS coronavirus*

SARS-CoV is stable in faeces and urine at room temperature for at least 1–2 days. In stool from patients with diarrhoea it may be stable up to 4 days. The virus has been isolated from stool on various surfaces such as stainless steel and plastic up to 72 hours. It is susceptible to commonly used disinfectants and fixatives (Clinical management document, WHO [5]) [6].

### *Modes of and risk factors for transmission*

It is now understood that SARS emerged in Guangdong in November 2002. More than one third of the first cases with onset dates before February 1, 2003, occurred in food handlers [7], indicating a primary source in wildlife. Despite many efforts and testing of a variety of animals, e.g. palm civets, racoon dogs, rats, hares, beaver, so far the reservoir has not been found [8–11]. It is unclear whether the animals harbouring the virus are the source or just a vehicle from the primary reservoir to humans.

The basic reproduction number  $R_0$ , which is the average number of secondary cases generated by one infected person in a susceptible population, has been estimated to be around 3 [12, 13] which is compatible with moderate transmissibility like the spread by direct contact or larger droplets that travel only a few meters. However aerosolizing procedures during

health care – which may include bronchoscopy, intubation, suction, and nebulised aerosol therapy – or as shown in the Amoy Gardens outbreak, may amplify transmission *via* aerosols also for a longer distance [14, 15].

The primary mode of transmission seems to be direct mucous membrane contact with infectious respiratory droplets or by exposure to fomites [16, 17]. Cases have occurred primarily among persons with close contact to SARS patients during health care or in households [1]. Transmission occurred also during flights when infected persons were on board during the symptomatic phase of their illness [18, 19]. The risk of transmission during flights is difficult to assess, since either active surveillance was not thoroughly done [19] or the flight crew and/or passengers also had other possible exposures.

However, there was evidence [20, 21] that in the case of the unique outbreak of Amoy Gardens, starting from an index patient with extremely high SARS-CoV concentrations in his faeces and urine, the virus was spread via airborne virus-laden aerosols generated in the vertical soil stack of the apartment building due to improperly functioning of the drainage system.

Tsang et al. [15] describe a so-called super-spreading event in Hong Kong: Nine contact persons of an index patient fell ill, some after short contact times (three times for 10 minutes in the ICU) and one after indirect contact while wearing a surgical mask. The Hotel “M” in Hong Kong played a pivotal role in the international spread of SARS. An infected physician spent one night in February 2003 in this hotel and became the index case for four national and international clusters and cases in two countries without further secondary spread. Although sharing the same floor in that night was a risk factor in a retrospective cohort study, the specific mode of transmission within the hotel still remains unclear [22]. It is unclear whether viral factors, environmental factors, host factors or their combination were important for the occurrence of these events ([23]).

## **Strategy for management**

The management should essentially aim at two goals: the early detection of cases and the limitation of further spread. For the early detection it is important to alert health care workers (HCW) to potential cases of SARS. Thus, updated information on clinical symptoms and training in hygiene measures should be continuously given to all HCW [23]. To assure that criteria for defining cases are similarly used in all affected countries, case definitions are necessary. A systematic approach for the management of clinical cases as well as their contact persons should be pursued. While during the outbreak phase in 2003 these approaches sometimes had to be decided upon very limited evidence, meanwhile several studies have been published which tried to assess the effectiveness of control measures (see below).

Although some of them are based on small numbers of study subjects, they provide some guidance.

Involved in the implementation of these goals are the public health service and HCW in a broad sense both in private practices and hospitals.

### *Early detection of cases*

#### Surveillance

##### *Risk assessment on country level*

For assessing the risk of the occurrence of SARS, three categories of risk zones (see Box 1) have been proposed by WHO [24]. The categorization should be done according to the experience during the epidemic in 2002–2003 and the postepidemic phase. Different levels of activities are recommended in the different risk zones. For areas at risk of emerging SARS-CoV-like viruses from wildlife or other animal reservoirs it is recommended to implement the SARS alert, conduct enhanced surveillance in populations at risk and to carry out special studies for SARS-CoV infections in animals and human populations. For areas at a higher risk of SARS-CoV emergence or introduction the implementation of the SARS alert and enhanced surveillance is recommended, while areas at low risk should implement the SARS alert.

Enhanced surveillance and special studies should be done in populations at risk and could include, depending on the area and the risk assessment [24]:

- Surveillance for pneumonia in settings such as nursing homes, rehabilitation units, community health care centres and in private practice.
- Surveillance of persons discharged from hospital with a diagnosis of unspecified atypical pneumonia during and following an outbreak of SARS.
- Surveillance for absenteeism among HCW caring for patients with SARS and laboratory staff working with SARS-CoV.
- Laboratory-based surveillance of SARS-CoV infection.
- Surveillance for requests for laboratory testing for SARS-CoV.
- Surveillance for unexplained deaths following an acute respiratory illness.
- Serological and clinical surveillance of high risk populations (HCW, animal handlers, laboratory staff working with SARS-CoV, etc).
- Community-based serological surveys to monitor changes in the seroprevalence of SARS-CoV infection.
- Sero-surveys among wildlife populations.

##### *Case definition – SARS alert*

During the outbreak phase of SARS (March through July 2003), the case definition for SARS provided by WHO for global surveillance was based

Box 1: Risk categories for the emergence of SARS [24]

*Emergence of SARS-CoV-like viruses from wildlife or other animal reservoirs*

Countries/areas identified as source(s) of the epidemic in 2002-2003 in southern China or areas with an increased likelihood of animal to human transmission of SARS-CoV-like viruses from wildlife or other animal reservoirs.

*Areas at higher risk of SARS-CoV emergence or introduction*

Countries/areas at potentially higher risk of SARS-CoV-emergence or introduction due to the presence of laboratories in which SARS-CoV and/or SARS-CoV-like viruses are being studied or in which clinical specimens infected with SARS-CoV are being processed or stored.

*OR*

Countries/areas with entry of large numbers of persons from areas in which wildlife or other animal reservoirs of SARS-CoV-like viruses are found.

*Low risk of SARS-CoV emergence or introduction*

Countries/areas that never reported cases or reported only imported cases during the 2002–2003 epidemic, and that do not conduct research using live SARS-CoV-like viruses or store clinical samples from SARS cases.

on the clinical picture of a respiratory disease. Important elements to increase specificity were the criteria of a stay in affected areas and having had contact to a SARS patient [25]. Experience with this case definition in Hong Kong and Singapore showed that the specificity of the case definition was 96% in both studies, and the sensitivity was 26 and 27.8%, respectively, indicating that many patients may have atypical presentation of symptoms and a careful examination and observation period is required for persons with an exposure suspicious of SARS ([26, 27]).

For the post-outbreak period the definition of a “SARS alert” ([24], see box 2) was created: According to the observation that many HCW were affected, the SARS alert is based on the detection of clusters of HCW. The recently occurring infections in laboratory workers resulted in a revision to also include persons in the SARS alert who are working in laboratories where SARS-CoV is handled [24]. The observations of atypical clinical presentations mentioned above were included now into the current description of the clinical picture [24]. Beside the symptoms mentioned for the clinical picture it is now clearly stated that no individual symptom or cluster of symptoms has proven to be specific, even fever may be absent on initial measurement.

Particularly the non-specific disease signs and symptoms, the long mean incubation period of 6.4 days, the long time between onset of symptoms and hospital admission from 3 to 5 days, and a lack of a reliable diagnostic test in the early phase of illness can lead to potential transmission to frontline HCW and the community [2, 16].

**Box 2: Definition of the SARS alert [24]**

1. *An individual* with clinical evidence of SARS AND with one or more of the following epidemiological risk factors for SARS-CoV infection in the 10 days before the onset of symptoms:

- Employed in an occupation associated with an increased risk of SARS-CoV exposure (e.g. staff in a laboratory working with live SARS-CoV/SARS-CoV-like viruses or storing clinical specimens infected with SARS-CoV; persons with exposure to wildlife or other animals considered a reservoir of SARS-CoV, their excretions or secretions, etc.).
- Close contact (having cared for, lived with, or had direct contact with the respiratory secretions or body fluids) of a person under investigation for SARS.
- History of travel to, or residence in, an area experiencing an outbreak of SARS.

OR

2. *Two or more health care workers* with clinical evidence of SARS in the same health care unit and with onset of illness in the same 10-day period.

OR

3. *Three or more persons* (health care workers and/or patients and/or visitors) with clinical evidence of SARS with onset of illness in the same 10-day period and epidemiologically linked to a health-care facility.

Once a SARS alert has been raised, the public health management includes immediate isolation of patients and the implementation of transmission-based precautions (see below); the rapid establishment of a diagnosis; the tracing and quarantine of contact persons. Laboratory confirmed cases have to be reported to WHO.

#### *Transit site surveillance*

In affected areas, fever checks of persons leaving or entering affected areas were suggested to prevent international spread. These measures were particularly recommended for airports and ports and were accompanied by recommendations for the management of possible cases on international flights, disinfection of aircrafts after carrying suspect cases and surveillance of persons who have been in contact with suspect cases while undertaking international travel [28]. For the post-outbreak period these measures are of course abandoned.

#### *Limitation of further spread*

##### Management of contact persons

For the assessment of risk of certain exposures of contact persons, it was attempted to categorize this risk according to the closeness and intensity of the contacts resulting in different levels of protection but also in different

levels of control measures for contact persons. Exposures supposed to confer a higher risk were close contacts with a SARS patients while applying no or inadequate protective measures, including direct contact with respiratory secretions, close/intimate contact with a SARS patient, examining or caring for a SARS patient, living in the same household with a SARS patient or staying within the same room.

Exposures involving the aforementioned situations during which appropriate protective measure were applied presumably conferred a lower risk.

Contact persons should be traced and placed under quarantine, mostly at home or in designated sites [29] until SARS is ruled out in the index patient or the maximum incubation period of 10 days since the last contact with the index patient has elapsed. Quarantine means the separation or movement restriction of persons who are supposed to have been exposed but are not (yet) ill. Quarantined persons are required to monitor their temperature twice a day which should be controlled daily by public health authorities. If persons under quarantine develop fever, they should immediately be brought to hospital and be treated in isolation units.

## Strategies for the prevention of transmission in health care settings

In particular in the absence of evidence of SARS transmission in the world, the main challenge is to be sufficiently alert but not to overload the system with unnecessary differential diagnoses and false alarms.

### *Risk assessment in the health care setting*

The risk assessment within the health care setting should be carried out for the different groups within such a facility (type of facility; isolation unit or general ward, HCW: depending on years of experience and training, visitors, the current management strategies) (Clinical management document, WHO [5]).

Experience showed that infections occurred in areas of assumed lower risk due to patients with atypical symptoms who were not suspected to have SARS at initial examination [30]. Thus, this approach should be cautiously viewed in particular for the clinical management.

### *Risk assessment of the individual patient (differential diagnosis)*

Most important is the assessment of patients with symptoms compatible with SARS. A number of flow charts and clinical decision rules have been reported to standardize the decision making process (examples [31–33]) which were used during the SARS outbreak. So far no agreed upon process for risk assessment of patients in the post-outbreak period has been published although WHO is trying to put together a consensus approach. Despite laboratory tests being available, there is still a lack for a rapid, reli-



able and early test. Thus, the risk assessment has to be based mainly on clinical grounds and epidemiological information (Clinical management document, WHO [5]). The indication for a SARS-CoV test should take into account that in low risk areas false positive test results are more likely. Thus the test should be considered only in the context with clinical and epidemiological evidence that SARS-CoV might be the causative agent. The challenge is to have sufficient sensitivity to screen suspected SARS cases out of the group of atypical pneumonia without raising false alarms too often. This is important to reduce the risk of activating unnecessarily response teams in hospitals and public health service.

#### *Standard precautions*

There is no doubt that the application of standard precautions will reduce the nosocomial transmission of infections in general. Standard precautions include hand hygiene after each patient contact or contact with infectious materials, wearing gloves for contact with body fluids, non-intact skin, routine cleaning and disinfection of frequently touched surfaces, safe handling and disposal of needles and other sharp instruments (Clinical management document, WHO [5]).

#### *Risk reduction strategies*

Since the main transmission pathways are droplets, aerosols or direct/indirect contact with patients, clinical material or indirect *via* contaminated surfaces, precautions should be established to reduce or better, to avoid these contacts.

When a patient is admitted to a health care setting (i.e. private practice or hospital), and there is evidence from the clinical picture and the epidemiological information that SARS could be suspected, the patient should be given a surgical mask and be seated and examined in a separate room. The HCW should also be protected with a surgical mask, possibly with a N95 mask which corresponds to FFP2 masks in Europe [34]. Use of these masks depends on the medical procedures to be performed. If the patient has to be admitted to the hospital – either because the suspicion is corroborated or for further evaluation –, he/she should be placed there in an isolation room with own bathroom facilities and if possible an anteroom. In case of several cases, cohort isolation would be a possibility.

Personal protective equipment of staff caring for these patients should consist of N 95 masks, with even higher protection depending on the kind of medical procedures to be performed, gloves, goggles and gown when entering the room. All equipment has to be disposed safely before leaving the room and hands should be disinfected after removing the gloves. All surfaces have to be cleaned and disinfected daily with proven virucidal disinfectants.

Certain aerosol generating procedures should be carried out only if absolutely necessary and in these circumstances, additional precautions

should be employed, i.e. use of N100 or FFP3 masks. If possible these procedures should be carried out by the most experienced staff trained in the use of appropriate protective measures including respiratory protection. Among these high risk procedures are: resuscitation, bronchoscopy, endotracheal intubation, airway suctioning, diagnostic sputum induction, aerosolized medications such as nebulizers) (Clinical management document, WHO [5]).

Access to the isolation unit should be restricted to essential staff only and they should not care for other patients if possible. The number of visitors should also be limited as much as possible [35].

## Effectiveness of measures

### *Quarantine*

This measure got new appreciation during the SARS outbreak due to a lack of vaccine and therapeutic options [36]. However, the effectiveness was difficult to assess, first because only a few of the quarantined persons developed suspect or probable SARS and secondly, because a series of control measures were applied in addition to quarantine which made the evaluation of the relative contribution of each of the measures difficult [37]. In Taiwan, less than 0.5% of the >130,000 persons under quarantine developed suspect or probable SARS [38], whereas in Beijing the attack rate among quarantined persons varied widely from 0.4% in work or school contacts to 15.4% among spouses. There was also a strong dependence of the attack rate among household members according to age, ranging from 5.0% for persons <30 years to 27.6% in 60- to 69-year old persons [29].

### *Precautions against droplets*

Seto et al. showed that all infected staff members of five Hong Kong hospitals omitted at least one of the recommended measures (mask, gloves, gowns, hand-washing); masks being the most important single measure [39].

### *Reasons for nosocomial outbreaks*

As mentioned above, omission of at least one of the recommended personal protective measures was the most frequent cause of staff members getting infected. In addition, atypical clinical presentation of SARS patients was another factor that contributed to the spread of SARS among health care staff and close contacts of patients. In a hospital in Singapore atypical clinical presentation of an index patient led to 51 infections (24 HCW, 15 other patients, 12 family members) [40]. Similarly, Ho et al. described an outbreak among hospital workers in Hong Kong which resulted from exposure of staff to patients with unsuspected SARS in low-risk general wards [30].

*Transit site surveillance*

Pang et al. report the results of this measure from the Beijing area [29]. Fever checks using infrared thermometers were instituted at the Beijing airport, major train stations and all 71 roads connecting Beijing to other areas. A total of almost 14 million people were screened at these sites between late April through end of June 2003, identifying 12 probable SARS cases. The costs of these measures were not reported.

## Lessons learnt for future management

*Strengthening of public health infrastructure*

The SARS epidemic has helped to sensitize health authorities world wide to strengthen the public health infrastructure which is necessary for combating rapidly spreading infections [41].

*Contact tracing and quarantine*

“Old fashioned” public health concepts like contact tracing, quarantine for exposed persons and isolation of cases should be revisited and instituted early in the outbreak

*Infection control measures*

SARS has emphasised the need for strict infection control measures on a routine basis. Therefore, these infection control measures have to be simple, but effective.

Patients suspected with SARS should be isolated, obviously those with probable SARS.

*Continuous training and communication*

Training and education for health professionals at all levels should be continuously offered. Communication efforts for health care professionals, policymakers and the public have to be enhanced [42]. The purpose of informing and warning the public is to increase the risk perception which may lead to an earlier reporting of symptoms as well as improvements in personal hygiene [2].

*Global cooperation*

Another important lesson is the necessity of global cooperation in the containment of infectious diseases. SARS gave an impressive example that diseases which seem to be happening in one part of the world can spread within no time over the world. The rapid exchange of information between public health institutions world wide, coordinated by WHO, was pivotal in being able to contain the outbreak within months.

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