

## Laboratory Containment of SARS Virus

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### Abstract

Following the severe acute respiratory syndrome (SARS) outbreak in 2003, a large number of clinical and environmental samples containing/potentially containing SARS coronavirus (SARS-CoV) as well as SARS-CoV stocks were retained in clinical and research laboratories. The importance of laboratory biosafety was demonstrated by the occurrence of laboratory incidents in Singapore, Taiwan and Beijing. It is imperative that safe practice and techniques, safety equipment and appropriate facility design should be in place to reduce or eliminate exposure of laboratory workers, other persons and the outside environment to SARS-CoV containing materials. Discussion on laboratory containment of SARS-CoV was initiated in Hong Kong in August 2003. It was agreed that an inventory of all specimens with the potential presence of SARS-CoV collected for any diagnostic or research purposes from November 2002 to July 2003 should be established in each laboratory. They should be stored in a secure place at the appropriate biosafety level with access control. Un-needed samples collected during the period should be destroyed. These laboratories should be audited to ensure inventories are updated. The audit should include safety and security measures to detect irregularities. Any laboratory accidents involving materials suspected of containing SARS-CoV should be reported to the authorities and all personnel exposed closely followed medically. A contingency plan should be in place in the laboratory and a drill conducted regularly to test its efficacy. By January 2004, all clinical laboratories performing SARS-CoV testing in Hong Kong set up inventories to document location and types of SARS-CoV containing materials retained in their laboratory. Audits of these laboratories in 2004 showed that laboratory safety and containment requirements as recommended were generally met.

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**Key words:** Contingency plan, Laboratory safety, Virus inventory, Virus survival

### Introduction

Severe acute respiratory syndrome (SARS) emerged in November 2002 in Guangdong Province in China and quickly spread to 26 countries/areas with local transmission in Hong Kong, Singapore, Vietnam and Canada.<sup>1</sup> The causative agent was identified as SARS coronavirus (SARS-CoV), not seen before in human.<sup>2-4</sup>

On 5 July 2003, the World Health Organization (WHO) declared SARS was contained worldwide.<sup>5</sup> However, research on pathogenesis, epidemiology, diagnostics, therapeutics and vaccines relating to SARS causative agent continued to be carried out in wide variety of institutions.<sup>6</sup> Continued vigilance to prevent the re-emergence of this deadly virus from laboratories was repeatedly emphasised

as live SARS-CoV or SARS-CoV containing materials were handled in large number of laboratories worldwide. Although SARS-CoV remained contained in laboratories, inappropriate laboratory standards and practice had so far led to 3 instances of laboratory related SARS cases in Singapore, Taiwan and mainland China in September 2003,<sup>7</sup> December 2003<sup>8</sup> and April 2004.<sup>9</sup>

### Public Health Concerns

SARS-CoV has been detected in various clinical specimens.<sup>10,11</sup> Laboratory safety is a major issue when working with SARS-CoV. This was of concern during the the SARS outbreak when large number of clinical specimens from SARS patients were handled in diagnostic laboratories.

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Soon after its discovery, SARS-CoV was categorised as a biohazard group 3 pathogen.<sup>12</sup> Diagnosis of SARS by reverse-transcription polymerase chain reaction (RT-PCR) and serology was performed in a biosafety level (BSL) 2 laboratory with enhanced safety practices including the use of gloves, masks and eye protection. As of July 2003 when the epidemic was interrupted, there were 8098 cases globally with 774 deaths. In total, 21% of persons affected were healthcare workers (HCWs).<sup>13</sup> Although SARS-CoV infectious materials were handled in large number of diagnostic and research laboratories, it is notable that there was no instance of laboratory acquired infection reported during the SARS outbreak.

Once SARS was eradicated, the laboratory was the only remaining source of the virus. While the animal precursor of SARS-CoV remains in wild animal species in the environment, these viruses appear less efficient in human-to-human transmission without prior adaptation to human. This was illustrated in the 4 cases of SARS in December 2003 to January 2004 that occurred through presumed inter-species transmission from the animal species.<sup>14</sup> These human cases were mild and did not result in secondary transmission. Many clinical and research laboratories in the world retain clinical materials including SARS-CoV isolates that are more adapted for human transmission. Though the laboratory incidents occurred in Singapore and Taiwan did not result in secondary transmission, the laboratory escape of SARS-CoV in China resulted in severe and fatal disease and 3 cycles of person-to-person transmission occurred before it was successfully interrupted.<sup>15</sup>

Recognising the threat of the re-emergence of SARS through laboratory accident, discussion among laboratories in Hong Kong was initiated as early as August 2003 and efforts were made to ensure safe handling of SARS infectious and potentially infectious materials.

### **SARS-CoV Infectious and Potentially Infectious Materials**

SARS-CoV has been detected in different types of specimens including nasopharyngeal aspirates, sputum, throat swabs, stools, urine and serum. The detection rate differed widely between various types of body secretion, and with day of illness. The viral shedding was low in the initial few days of illness, but in nasopharyngeal aspirate, faeces and upper respiratory tract specimens, it rose significantly after 6 days to peak at 12-14 days after onset of disease. The virus load in faeces was much higher than that in nasopharyngeal aspirates.<sup>11</sup>

While SARS-CoV infected materials, including all clinical specimens from probable SARS cases, infected animals and contaminated environmental samples as well

as potentially infected materials were handled in accordance with specific precautions, safety measures were also taken for any clinical and environmental specimens compatible with the potential presence of SARS-CoV collected for diagnostic or research purposes during the SARS outbreak period.

### **Survival of SARS-CoV**

The primary mode of transmission of SARS appeared to be direct mucus membrane contact with infectious droplets and through exposure to fomites. Knowledge of the survival characteristics of the virus was essential for formulating appropriate preventive measures.

Studies demonstrated that SARS-CoV had contaminated a variety of environmental surfaces in healthcare settings.<sup>16</sup> The presence of SARS-CoV on surfaces was a concern, although few studies where live viruses have been successfully isolated from environmental surfaces have been reported. Surfaces could become contaminated by indirect transfer of SARS-CoV through gloves or gowns. The increase in the rate of methicillin-resistant *Staphylococcus aureus* at the intensive care unit of a Hong Kong hospital during the SARS outbreak suggested that increased cross-contamination could occur if gloves and gowns were inappropriately worn all the time.<sup>17</sup>

SARS-CoV can survive in respiratory samples for 5 days at room temperature and up to 3 weeks at 4°C. In diarrhoeal stool, SARS-CoV can also survive for a few days at room temperature.<sup>18</sup> With a high virus load at a concentration of  $10^6$  TCID<sub>50</sub>/mL of SARS-CoV, it is notable that faecal droplets containing SARS-CoV remained infectious for 4 to 5 days. Hence, appropriate precautions must be taken to prevent formation of aerosols because of probable airborne transmission.<sup>19,20</sup>

During the SARS outbreak, contamination of paper documents was a concern for HCWs who frequently had to handle such documents in their daily work. Experiments showed that even with a relatively high virus concentration normally present in respiratory specimens, as long as the paper was dry, no virus activity remained in less than 5 minutes. The risk of infection through contact with droplets contaminated paper is thus minimal (Table 1).<sup>18</sup>

Survival of the virus on various laboratory gowns depended on whether they were made from absorbent or non-absorbent materials. With SARS-CoV concentration commonly found in clinical specimens, rapid loss of infectivity was observed on a cotton gowns (in 5 minutes). However, SARS-CoV could survive much longer on surface of non-absorbent disposable gowns. Hence, droplets containing SARS-CoV hanging on a non-absorbent disposable gown may pose risk of contaminating the environment. A similar conclusion may also be drawn for

Table 1. Survival Time of SARS-CoV on Paper, Disposable Gown and Cotton Gown

TCID <sub>50</sub> /mL	Time taken to inactivate the virus		
	Paper	Disposable gown	Cotton gown
10 <sup>6</sup>	24 hours	2 days	24 hours
10 <sup>5</sup>	3 hours	24 hours	1 hour
10 <sup>4</sup>	<5 minutes	1 hour	5 minutes

Table 2. Major Features of BSL 2 and BSL 3\*

	BSL 2	BSL 3
Good microbiological technique	√	√
Personnel		
Medical assessment		√
PPE	√	√
Facility		
Separation of lab		√
Restricted access	√	√
Sealable for decontamination		√
Negative pressure		√
Airlock		√
HEPA exhaust filters		√
BSC I or II	√	√
Autoclave onsite	√	
Autoclave in room		√
Own equipment		√
Storage requirements	√	√

PPE: personal protective equipment

\* From WHO global action plan for laboratory containment of wild polioviruses<sup>21</sup>

non-absorbent gloves. A specially designed disposable garment with a fluid repellent lamination that has an outer fluid absorbing sheet may offer better protection for personnel and reduce environmental contamination.

### Recommended Biosafety Practice

From the beginning of the SARS outbreak, all the laboratories were advised to adopt safety practices and techniques when handling specimens potentially containing SARS-CoV. Handling of SARS-CoV containing materials required BSL 2 laboratory with BSL 3 practices (Table 2), while any procedures involving replication of SARS-CoV were to be performed in BSL 3 laboratories. Administrative guidelines aside, competency based training with documentation was adopted. More stringent training was necessary for those working in BSL 3 laboratories. Though only those with significant training and experience were allowed to work with SARS-CoV culture, regular audits of their practice as well as training on how to react to laboratory emergencies were emphasised.

Laboratories are designed to minimise risk and while containment measures are generally in good order when commissioned, maintenance of satisfactory functioning

environment may require much greater effort and persistence. Although facility design has been emphasised as a safety requirement, good microbiological practice is essential to ensure the effectiveness of physical containment. Laboratory escapes of SARS-CoV in Singapore, Taiwan and Beijing provided good illustration of the importance of good microbiological practice. They occurred in BSL 3 and BSL 4 laboratories where there had been breach of good laboratory practice rather than the physical failure of the containment laboratory.

It has been reported that SARS-CoV could cause extensive contamination to environmental surfaces, particularly when gloves were inappropriately worn all the time.<sup>17</sup> Fomites should be considered as a possible mode of transmission in laboratories. Laboratory surfaces and equipment should be routinely decontaminated after use or when visible contamination occurs. Common disinfectants used in hospital and laboratory settings have been generally found to be effective in virus inactivation.<sup>18,22</sup> Ordinary household detergent, hypochlorite solution and peroxigen compounds at concentrations normally used in the laboratory were shown to inactivate SARS-CoV within 5 minutes.<sup>18</sup> As contamination of environmental surfaces may play a role in the transmission of SARS-CoV, regular cleaning of common items and surfaces should be undertaken. Notably, household detergent can be used to clean surfaces which are not grossly contaminated.

As previously stated, during the SARS epidemic, diagnostic specimens were handled in a BSL 2 lab with BSL 3 practices including the use of gloves, surgical masks and eye shields. Surgical masks were mostly sufficient for general purpose. N95 respirators, though not indicated in general as procedures that were likely to produce aerosols or spattering were performed in biological safety cabinets, were provided for use when assessed to be appropriate. Due to inadequate design of post-mortem rooms, powered air-purifying respirators were required when performing autopsy on dead bodies of probable SARS cases. As droplets hanging on non-absorbent disposable gowns posed a risk of contaminating the environment, a specially designed disposable garment with a fluid-repellant lamination with an outer fluid-absorbing sheet may offer better protection for the personnel.

### Inventory and Storage of SARS-CoV Materials

The WHO recommended strongly that un-needed clinical and animal specimens containing SARS-CoV should be destroyed and that national governments should maintain a registry of laboratories that were approved to safely and securely hold and work with SARS infectious specimens. In Hong Kong, soon after the containment of SARS, a Working Group comprising 7 laboratories which provided

SARS-related tests including RT-PCR, serology and virus isolation were set up to establish a local quality assurance scheme of RT-PCR tests for SARS to ensure accuracy of RT-PCR testing. All the laboratories providing this service were to participate in an External Quality Assurance Program (EQAP) organised by the Virology Division, Public Health Laboratory Services Branch (PHLSB), Centre for Health Protection, Department of Health. This working group also addressed the safety issues of laboratories handling SARS-CoV or related materials. A protocol on the storage requirements for SARS-CoV infected or potentially infected materials was proposed in September 2003. Briefly, SARS infectious or potentially infectious materials were categorised into the cell culture virus isolates, clinical specimens collected from known SARS patients and clinical specimens collected from non-SARS patients as part of clinical investigations from 1 November 2002 to 31 July 2003 (Table 3). The last category was such defined as the first case of SARS emerged in November 2002 in Guangdong Province of China. Throughout the SARS epidemic until its interruption, there was a heavy population movement every day to and from Guangdong Province. Clinical specimens in this category, although not known or tested to be SARS-CoV positive, were believed to pose some, though minimal, risk to laboratory workers handling the materials. The non-infectious aliquots of RNA extracts were not included in any specimen category of SARS-CoV infected material, however, an inventory of these materials was to be kept in each laboratory with storage in BSL 2 laboratory.

It was the consensus of all in the Working Group that un-needed specimens in all these categories should be destroyed properly. For those to be retained, depending on the specimen category, the materials were to be stored and locked either inside a BSL 3 (for category A, B and C specimens or isolates) or BSL 2 laboratory with access control. In addition, the laboratory was required to maintain and update inventory of these materials. The databases were kept in each designated laboratory using excel format. A programme was installed to allow only designated staff to gain access to the database to ensure the security of the the inventory. This protocol of storage, access control and inventory maintenance were in accordance with the recommendations by WHO in October 2003.<sup>23</sup>

Riding on the experience of laboratory containment of poliovirus,<sup>21</sup> the Department of Health advised all laboratories in the private and public sector, including universities, to destroy all un-needed clinical, animal and environmental samples in the private and public sector including universities. They were requested to submit the inventory of SARS-CoV infectious or potentially infectious materials retained in their institution. Requirements of

Table 3. Storage Requirements for SARS Co-V Infected/Potentially Infected Materials

**Storage and access policy**

Specimen category	Storage and access control	Inventory requirement
A	1	I
B, C	2	I
D	3	II

Category of specimens/isolates:

- A. Cell culture-grown SARS-CoV isolates
- B. Clinical specimens collected from SARS patients. These refer to blood, respiratory samples, stool or rectal swabs, urine, body fluid, lesion swabs, tissues and all other types of specimens collected from 1 November 2002 to 31 July 2003, inclusively.
- C. Specimens collected from animals/environment which were tested and known to contain SARS-CoV
- D. Clinical specimens collected from non-SARS patients as part of clinical investigations from 1 November 2002 to 31 July 2003, inclusively.

Category of storage and access control:

1. Stored and locked in a freezer/liquid nitrogen tank, inside a Biosafety Level 3 laboratory. Entrance and handling of the stored samples requires prior approval of the principal person-in-charge or his/her deputy. An access record should be maintained.
2. Stored and locked in a freezer/liquid nitrogen tank, inside a Biosafety Level 2 laboratory in a securely locked room with restricted access. Entrance and handling of the stored samples requires prior approval of the principal person-in-charge or his/her deputy. An access record should be maintained.
3. Stored in a lockable freezer/liquid nitrogen tank with controlled access

Category of inventory:

- I. Full inventory:
  - This includes name, identification number, specimen type, specimen laboratory number, specimen collection date, number of aliquots, subsequent movement and numbers of aliquots remained, SARS-CoV RT-PCR result, SARS-CoV isolation result and storage location. This inventory is to be maintained and updated by the principle person-in-charge of SARS specimen/isolate storage.
- II. Summarised inventory (clinical specimens):
  - This includes specimen type, corresponding total number of specimens, subsequent movement and number of aliquots remained, and storage location. This inventory is to be maintained and updated quarterly by the principle person-in-charge of SARS specimen/isolate storage.

inventory maintenance, updating and storage of SARS-CoV infectious and potentially infectious materials, as described above, were to be strictly followed. Though no specific regulation pertaining to handling and storage of SARS-CoV and SARS-CoV potentially infected materials were in place, the Quarantine and Prevention of Disease Ordinance (Cap 141), the Code of Practice of Medical Laboratory Technologist Board and the Occupational Health and Safety Regulation in Hong Kong had been there to ensure the safe handling and storage of infectious materials should the need arise.

In conjunction with this, external audits on the compliance on this storage, access control and inventory measures on SARS materials were conducted and would be carried out periodically. In addition, to monitor safe practice in general in clinical laboratories, a thorough safety audit of clinical laboratories in all public hospitals was carried out.

### Safe Transport of Specimens

To eliminate the risk posed to transport workers and the public, the transport of material containing SARS-CoV was to be carried out in accordance with internationally recognised principles. The transport of such materials in and out of Hong Kong was governed by the Regulation of International Air Transport Association (IATA) as well as Trade and Industry Departments' strategic commodities Act. Import or export permits should be obtained as appropriate prior to arranging for such shipment. However, no regulations governing the road transport of such specimens were in place in Hong Kong. With reference to the principles of international air transport of human specimens and culture stocks,<sup>24</sup> specific guidelines on specimen transport were issued to all laboratories addressing the local transport practices within the hospital as well as transport to other local laboratories. The triple packaging system<sup>25</sup> was adopted when specimens had to be transported to another area or laboratory outside of the hospital premises. Seminars and educational sessions were given to relevant frontline staff to enhance their understanding of safe transportation.

### Facility and Equipment

Since the SARS epidemic, the practice of laboratory safety in clinical laboratories in general was further strengthened by audits, training and education. Extra resources were allocated for the purchase of laboratory safety equipment, such as biological safety cabinets and specimen transport accessories. Recognising the inadequacy of facilities in autopsy rooms to perform post-mortem on hazardous dead bodies including probable SARS cases, the Government allocated special funds to improve the design of these facilities. After the setting up of the Working Group on Quality Assurance on SARS RT-PCR, it was agreed to confine the SARS diagnostic testing within the 7 designated laboratories with only 3 laboratories with BSL 3 facilities to handle live SARS-CoV. This is in accordance with the subsequent guidelines from the WHO which strongly recommends BSL 3 as the appropriate containment level for working with live SARS-CoV materials.<sup>26</sup>

### Training

Although facility design, safety equipment and personal protective equipment were important in laboratory safety, physical control measures were underpinned by the

principles of good microbiological practice. Competency based training with adequate documentation should form an integral part of safety management in laboratories. With the provision of special funding from the government for training to prevent and control communicable diseases, many training classes for healthcare personnel including those from laboratories have been conducted. Joint training of laboratory personnel in public and private sector was also organised and public and private interface strengthened. All aspects of safety issues were included in the training. Special training with significant supervision was provided to laboratory personnel working in BSL 3 laboratories.

### Health and Medical Surveillance

As various hazardous biological materials were handled in laboratories, medical and health surveillance among laboratory workers was an important tool to facilitate early detection of laboratory-acquired infections. As part of the employee health programme, an electronic system [Staff Early Sickness Alert System (SESAS)] was set up in hospitals after the SARS epidemic to record the sickness pattern of staff to alert the infection control personnel and hospital or departmental managers to any abnormal staff sickness pattern. Staff with symptoms related to respiratory tract infections including fever, chills, sore throat and myalgia were required to report them as soon as they occurred, even while they were on leave. This reporting system was also applied to the laboratory staff. Abnormal clustering of sick staff and patients were verified and investigated by the hospital infection control team. This helped to alert the laboratory management level to an early detection of outbreak among laboratory staff who might have been involved in certain laboratory incidents.

For staff working in BSL 3 laboratory handling SARS-CoV containing materials, daily body temperature checks were necessary. Any respiratory illness that occurred within 10 days after handling SARS-CoV materials was required to be investigated and medical consultation, if required, would be performed by a designated doctor in a designated clinic. All staff working with SARS-CoV were issued with a medical card that cited the place of work and the hazardous pathogens handled.

### Contingency Plan for the Laboratories

Although only those with experience were allowed to work with dangerous pathogens like SARS-CoV, specific tailored training on how to react to laboratory incidents and accidents should be conducted. As the consequences to the individual and community were significant if SARS-CoV got out of the facility, staff were repeatedly reminded that all incidents should be reported so that corrective actions could be taken before it evolved into a serious situation. Clear chain of commands was established and clear

instructions on how, who and whom to report laboratory incidents were put in place and reviewed regularly. In Hong Kong, it was agreed that all SARS-CoV incidents/accidents should be reported to the Department of Health as soon as feasible so that control measures that have an impact on limiting the spread of infection could be instituted effectively. Staff working in laboratories were encouraged to air any concerns and contribute constructively to safe handling of SARS-CoV. Drills have been carried out regularly to familiarise staff with the necessary procedures to contain the risk of SARS-CoV escape to the community.

### Lessons Learned

Since the interruption of SARS epidemic in July 2003, the world faces the formidable challenge of locating the many laboratories that have SARS-CoV or SARS-CoV potentially infectious materials and ensuring they are adequately contained. Re-introduction of SARS-CoV into the community presents a threat to public health of global proportion. To minimise such risk, activities involving SARS-CoV or SARS-CoV potentially infectious samples should be performed in containment laboratories by personnel trained in the use of BSL 3 practices following significant direct supervision. Adherence to appropriate biosafety practices and procedures should be regularly monitored and enforced.

As with the laboratory containment of wild poliovirus, survey of laboratories is necessary to establish an inventory system for laboratories that retain SARS-CoV or SARS-CoV infectious materials and to ensure safe handling as well as disposal of all such materials. This inventory facilitates regular monitoring and auditing of laboratories working with SARS-CoV.

The requirements of categorisation and access restriction to SARS-CoV cannot be over-emphasised as illustrated in the recent inadvertent distribution of influenza A(H2N2) virus in proficiency panel samples posing threat of global proportion.<sup>27</sup> While the intention is not to restrict necessary research on pathogens posing significant public health threat, laboratories should critically evaluate the considerable personnel and institutional responsibilities inherent in working with such pathogens. To facilitate monitoring and auditing of safety practices, surveys to establish laboratory inventory are advisable for dangerous pathogens likely to spread into the community.

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