

EPIDEMIC
ALERT &
RESPONSE

WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS)

*Updated recommendations
October 2004*

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Executive summary

This document sets out revised guidelines for the global surveillance and reporting of SARS as an ongoing strategy for rapidly detecting cases and preventing further national or international spread. Addressed to national health authorities, the guidelines respond to the need for a sustainable long-term approach to SARS surveillance that maintains an adequate level of sensitivity yet does not overburden health system capacity. With this objective in mind, the document adopts a phased approach to surveillance and preparedness, with different levels of activity recommended for each of four phases. These phases move from the absence of evidence that the SARS coronavirus (SARS-CoV) is circulating in human populations, to the detection of human chains of transmission, to evidence of international spread, to the post-epidemic period.

The revised guidelines, which replace a previous document issued in August 2003¹, draw on experiences during four recent incidents in which cases of SARS occurred following breaches in laboratory biosafety, or human exposure to an animal reservoir or other environmental source. Apart from demonstrating the importance of continued vigilance, these incidents revealed the need for more precise guidance on laboratory testing and on the requirements for official reporting to WHO. Throughout the document, specific recommendations take into account the high demands of a disease with non-specific symptoms and a diagnosis that requires multiple test results and rigorous procedures for quality assurance. Particular emphasis is given to the prevention of secondary transmission from sporadic cases and common source outbreaks as a strategy for reducing the risk of another international outbreak.

Document structure

The document has five main sections. The **first section** gives the background to the 2002-2003 SARS epidemic, discusses the potential sources of the SARS coronavirus since the global interruption of human transmission in July 2003, and presents the case for continued vigilance for the reappearance of SARS as a threat to human health.

Section 2 describes the clinical and laboratory criteria recommended by WHO for the diagnosis of SARS for the purposes of global surveillance i.e. the clinical and laboratory case definitions used by WHO to assess, verify or discard reported cases of SARS-like illness. Extensive experience during the 2002–2003 epidemic is used to provide advice on clinical symptoms, the differential diagnosis, recommended laboratory tests, and the interpretation of results.

Section 3 presents and explains a revised definition of the WHO SARS Alert which applies globally in the inter-epidemic period and for countries/areas free of SARS after its re-emergence elsewhere. The Alert, which operates as an early warning and preparedness mechanism, is based on what has been learnt about the potential sources of human exposure to SARS-CoV and the early epidemiological indicators that this may have occurred. Based on recent experiences, the Alert has been expanded to include additional epidemiological risk factors that should raise the level of suspicion and prompt investigation. The section also includes advice on assessing the risk within a given country or area that SARS might emerge or be introduced, and the indications for testing during the inter-epidemic period. Situations in which WHO recommends testing are set out in a table. Further information includes advice on the public health management of a SARS Alert, and a series of 11 enhanced surveillance activities that could help detect cases in groups at particular risk.

¹ World Health Organization. *Alert, verification and public health management of SARS in the post-outbreak period, 14 August 2003*. <http://www.who.int/csr/sars/postoutbreak/en/>

Section 4 presents revised guidance for the global surveillance of SARS during an outbreak. In view of the inherent difficulties with diagnostic tests, the section describes "preliminary positive", "confirmed", "probable" and "unverifiable" cases of SARS on the basis of the clinical, laboratory and epidemiological evidence for SARS coronavirus-associated infections in a population. Procedures for verifying an outbreak of SARS are followed by diagnostic and reporting algorithms for use during the inter-epidemic and epidemic periods.

Section 5, on international reporting of SARS, outlines information about cases that should be officially reported to WHO, and suggests additional information that can assist in the rapid investigation of rumours and the accurate dissemination of information to other governments, the media, and the public.

What's new

The *WHO Guidelines for the Global Surveillance of SARS. Updated Recommendations October 2004* replaces all previous WHO guidance on SARS surveillance and response.^{1,2} The present document introduces a number of important changes to the global risk assessment and case definitions for SARS to ensure that the response to a case of acute febrile respiratory disease is commensurate to the risk posed to the patient, their contacts, health care workers, and local and international communities. The document should be used together with the *WHO SARS Risk Assessment and Preparedness Framework*. The aims, objectives and underlying assumptions of the *WHO SARS RAPF* have been summarized in Annex 1.

Definitions

Key epidemiological concepts have been defined in the introduction.

Changes to the risk assessment for SARS

In recognition that human exposure to SARS-CoV since July 2003 has occurred in laboratories working with the virus or from wildlife sources of SARS-like coronaviruses, WHO has replaced the previous risk categories for the emergence of SARS¹ to better reflect the current situation, noting that some countries/areas may fall into two categories. The new risk categories are:

- Emergence from wildlife or other animal reservoirs
- Emergence or introduction from laboratories or via international travel
- Low risk of SARS-CoV emergence or introduction.

These risk categories are intended to assist national health authorities in determining the most cost-effective surveillance strategy for SARS in their country.

Clinical criteria for surveillance purposes and indications for testing for SARS-CoV

Clear distinction has been made between the comprehensive clinical assessment made by clinicians in the differential diagnosis of acute febrile respiratory disease and the clinical evidence required to define a **clinical case of SARS for surveillance purposes**. This section provides a detailed description of:

- The indications for testing for SARS-CoV in the inter-epidemic period

¹ World Health Organization. *Alert, verification and public health management of SARS in the post-outbreak period*, 14 August 2003. <http://www.who.int/csr/sars/postoutbreak/en/>

² World Health Organization. *Case Definitions for Surveillance of Severe Acute Respiratory Syndrome (SARS)*, revised 1 May 2003. <http://www.who.int/csr/sars/casedefinition/en/>

- The laboratory investigations, their interpretation and test quality assurance required for the diagnosis of SARS.

The SARS Alert – Vigilance for SARS in the inter-epidemic period

The SARS Alert remains a tool to raise the possibility of SARS in health-care settings. Individuals under investigation for SARS should be placed in respiratory isolation and transmission-based precautions, including the use of personal protective equipment, implemented while investigations to confirm the diagnosis are ongoing. Individuals at higher risk of SARS through their occupation, close contact with another person under investigation for SARS, or by travel to, or residence in, an area with an outbreak of SARS have been added to the SARS Alert. Clustering of SARS-like illness in health-care workers or others exposed to a health-care facility remain important sentinel events that may indicate the re-emergence of SARS. During the inter-epidemic period, WHO will utilize highly specific laboratory criteria for the diagnosis of SARS and requests that countries investigating a SARS Alert seek independent verification of positive results at one or more WHO International SARS Reference and Verification Network laboratories. A single negative test result is insufficient to confidently exclude SARS when there is compelling clinical and/or epidemiological evidence of SARS due to the risk of false negative test results.

The global surveillance of SARS during an outbreak

Once an outbreak of SARS has been independently verified as above, the laboratory requirements for case confirmation will be less specific than those recommended for the inter-epidemic period.

New surveillance case definitions have been developed for use once one or more individuals with a SARS-like illness test positive at a national SARS reference laboratory ("**preliminary positive case**") and independently verified by a WHO International SARS Reference and Verification Network laboratory ("**confirmed case**"). Indications for the independent verification of positive SARS tests by a WHO International SARS Reference and Verification Network laboratory during an outbreak are listed.

If secondary transmission occurs the following two categories of patients epidemiologically linked to a laboratory-confirmed chain of transmission will also be considered "**confirmed**" for the purposes of global surveillance:

- "Preliminary positive" cases
- Individuals with clinical evidence for SARS and with a single positive SARS test (serological test or RT-PCR).

Individuals with clinical evidence for SARS who are epidemiologically linked to a confirmed chain of transmission will be regarded as "**probable**" cases.

Finally during an outbreak a living or deceased individual with clinical evidence for SARS but for whom laboratory evidence is lacking will be considered an "**unverifiable**" case of SARS.

Testing and reporting algorithms for SARS in the inter-epidemic period and during an outbreak have been included in this document to assist in the investigation of individuals with clinical evidence for SARS. As with previous guidance, only cases of clinically apparent SARS need be reported to WHO. National health authorities should report the first "preliminary positive" case(s) of SARS in their country to WHO within 24 hours of the receipt of positive test results from their national SARS reference laboratory.

WHO will continue to assist with the independent verification of testing in national laboratories and for primary diagnosis for countries without laboratory capacity for SARS testing if requested.

The period for heightened vigilance for SARS has been extended to **28 days** after the last reported case of SARS globally has been placed in isolation or died and the source(s) and routes(s) of transmission have all been identified and contained. The extended period of vigilance for SARS after an outbreak arises from the lessons learnt during the 2002–2003 epidemic and is recommended to reduce the risk of ongoing transmission arising from missed SARS-CoV infections and from prematurely stepping down respiratory precautions.

1. Introduction

1.1 Rationale for the continued vigilance for SARS

Severe acute respiratory syndrome (SARS) was first recognized as a global threat in mid-March 2003. The first known cases of SARS occurred in Guangdong province, China, in November 2002 (1,2) and WHO reported that the last human chain of transmission of SARS in that epidemic had been broken on 5 July 2003. The etiological agent, the SARS coronavirus (SARS-CoV) (3,4,5) is believed to be an animal virus that crossed the species barrier to humans recently when ecological changes or changes in human behaviour increased opportunities for human exposure to the virus and virus adaptation, enabling human-to-human transmission (6). By July 2003, the international spread of SARS-CoV resulted in 8098 SARS cases in 26 countries, with 774 deaths (7). The epidemic caused significant social and economic disruption in areas with sustained local transmission of SARS and on the travel industry internationally in addition to the impact on health services directly. While much has been learnt about this syndrome since March 2003, our knowledge about the epidemiology and ecology of SARS-CoV infection and of this disease remains incomplete.

The natural reservoir of SARS-CoV has not been identified but a number of wildlife species – the Himalayan masked palm civet (*Paguma larvata*), the Chinese ferret badger (*Melogale moschata*), and the raccoon dog (*Nyctereutes procyonoides*) – consumed as delicacies in southern China have shown laboratory evidence of infection with a related coronavirus (2,8). Domestic cats living in the Amoy Gardens apartment block in Hong Kong were also found to be infected with SARS-CoV (9). More recently, ferrets (*Mustela furo*) and domestic cats (*Felis domesticus*) were infected with SARS-CoV experimentally and found to efficiently transmit the virus to previously uninfected animals housed with them (10). These findings indicate that the reservoir for this pathogen may involve a range of animal species. The masked palm civet is the wildlife species most often associated with animal-to-human transmission; however, whether the civet is the natural reservoir of SARS-like coronaviruses remains unproven. The modes and routes of inter-species transmission from animals to humans or to other animal species need further investigation.

At the time of writing in October 2004, the world is in an inter-epidemic period for SARS. At this time, the most probable sources of infection with SARS-CoV are exposure in laboratories where the virus is used or stored for diagnostic and research purposes, or from animal reservoirs of SARS-CoV-like viruses. It remains very difficult to predict when or whether SARS will re-emerge in epidemic form.

Since July 2003, there have been four occasions when SARS has reappeared. Three of these incidents were attributed to breaches in laboratory biosafety and resulted in one or more cases of SARS (Singapore (11–13), Taipei (14) and Beijing (15,16)). Fortunately only one of these incidents resulted in secondary transmission outside of the laboratory. The most recent incident was a cluster of nine cases, one of whom died, in three generations of transmission affecting family and hospital contacts of a laboratory worker. For this reason, WHO strongly urges countries to conduct an inventory of all laboratories working with cultures of live SARS-CoV or storing clinical specimens actually or potentially contaminated with SARS-CoV. WHO also recommends that each country ensures that the correct biosafety procedures are followed by all laboratories working with the SARS coronavirus and other dangerous pathogens (17) and that appropriate monitoring and investigation of illness in laboratory workers is undertaken.

The fourth incident (Guangzhou, Guangdong province, China (18–20) resulted in four sporadic, community-acquired cases arising over a six-week period. Three of the cases were attributed to exposure to animal (20) or environmental sources while the source of exposure is unknown in the other case. There was no further community transmission.

These events demonstrate that the resurgence of SARS leading to an outbreak remains a distinct possibility and does not allow for complacency. In the inter-epidemic period, all countries must remain vigilant for the recurrence of SARS and maintain their capacity to detect and respond to the re-emergence of SARS should it occur.

1.2 Using *WHO guidelines for the global surveillance of SARS* and linked documents

This document replaces all previous WHO guidance on SARS surveillance and response.

It includes a surveillance strategy for the inter-epidemic period, once chains of human transmission of SARS-CoV have occurred, and for the period after an epidemic when human SARS-CoV transmission has been interrupted.

The WHO guidelines are aimed at the early detection and investigation of individuals with clinically apparent SARS-associated coronavirus infection i.e. **symptomatic cases only**.

These guidelines are based on the most common clinical features of SARS and the most important risk factors for infection with SARS-CoV and SARS-CoV-like viruses. WHO recognizes that SARS-CoV causes a spectrum of clinical illness from the severe form of respiratory disease after which the syndrome was named, to milder or atypical presentations of SARS which may not meet the clinical criteria defined by WHO (see section 2.4). Such cases are likely to be missed unless there is supportive epidemiological and laboratory evidence suggesting a SARS-CoV infection, and a high level of awareness about the spectrum of disease caused by the SARS coronavirus among clinicians, laboratory staff and public health professionals. Early clinical recognition of SARS poses significant challenges. Cases of SARS can easily escape early detection particularly as acute respiratory infections account for the majority of diagnoses in adults presenting to primary care. In many regions, febrile illness is also a common complaint. SARS may be initially missed due to the non-specific nature of presenting symptoms, the possibility of absence of fever on initial measurements, atypical presentations, co-morbidities masking SARS and the recognized difficulties of clinically diagnosing an atypical pneumonia.

However, adopting more sensitive (inclusive) criteria for raising the clinical suspicion of SARS (i.e. using clinical criteria for SARS that do not include radiological evidence of pneumonia) would require that SARS be considered in the differential diagnosis of a potentially large number of acute respiratory infections (ARIs) when the real risk is low. WHO is concerned that such an approach would quickly overwhelm alert, verification and response systems, especially in countries at higher risk of SARS and with a high incidence of ARIs.

The decision to exclude asymptomatic infections from global surveillance is based on epidemiological evidence that SARS-CoV is transmitted by symptomatic individuals and that asymptomatic infection poses no significant public health risk (21–22). Accordingly, WHO requests that countries report only symptomatic cases of SARS.

This document refers to four categories of cases – "preliminary positive", "probable", "confirmed" and "unverifiable" cases of SARS to be used in accordance with diagnostic certainty and during relevant epidemiological phases (see section 4.1). Only individuals fulfilling one of these case definitions should be officially reported to WHO.

Note: National public health authorities may choose to use additional operational categories to describe persons under investigation for SARS before the definitive results of testing are available.

Linked documents

This document should be used in conjunction with the following publications:

1. The *WHO SARS Risk Assessment and Preparedness Framework (WHO SARS RAPF)* which recommends preparedness and response activities for WHO, areas with local transmission of SARS and areas free of SARS during the inter-epidemic, epidemic and post-epidemic periods as defined for SARS. The aims, objectives and underlying assumptions of the *WHO SARS RAPF* have been summarized in Annex 1.
2. *Infection Control and Clinical Management of Severe Acute Respiratory Syndrome (SARS) - A Continuing Concern for all Health Care Workers*. This document is under development and will be published in December 2004. Refer to the WHO web site on Severe Acute Respiratory Syndrome (SARS) on which new documents are published.¹
3. *The SARS minimum global data dictionary*. This document is under development. Refer to the WHO web site on Severe Acute Respiratory Syndrome (SARS) on which new documents are published.¹

This guidance has been prepared for the global surveillance of SARS and should be used in conjunction with national surveillance and response guidance. WHO recognizes that the risk of SARS varies between and within countries and regions of the world so that strategies for maintaining vigilance for SARS, and the resources allocated, will vary based on the national risk assessment and should be commensurate with the level of risk.

1.3 Definitions

Inter-epidemic period (Phases 0–1 of the *WHO SARS Risk Assessment and Preparedness Framework, RAPF*)

Defined as the absence of human chains of SARS-CoV transmission worldwide.

- Sporadic (isolated) cases of SARS or a common source outbreak may occur but do not result in secondary transmission.
- The risk of secondary transmission of SARS-CoV has been shown to fall significantly if cases are identified and isolated within 3 days of illness onset (23,24). Preventing secondary transmission from sporadic cases and common source outbreaks is a measure of health system preparedness in detecting and managing SARS-like illness and implies rapid case identification, case containment and contact tracing.
- These events are unlikely to have international public health implications unless they are the result of a previously unknown route(s) of transmission, or the route(s) of transmission cannot be determined, or the clinical findings are suggestive of increased SARS-CoV virulence.

¹ <http://www.who.int/csr/sars/en/index.html>

SARS cluster

Defined as two or more epidemiologically linked "preliminary positive" and/or "probable" and/or "confirmed" cases of SARS (see section 4.1).

SARS epidemic (Phases 3–4 of the WHO SARS RAPF)

Evidence of international spread of SARS, considered a global public health emergency.

Note: A single exported case of SARS constitutes international spread.

Global interruption of SARS-CoV transmission (Phase 5 of the WHO SARS RAPF)

Defined as **twenty-eight (28) days** after the last reported case of SARS globally has been placed in isolation or died AND the source(s) and route(s) of transmission have all been identified and contained.

- Corresponds to the post-epidemic period of the *WHO SARS RAPF*.

The last reported case would be one of the following:

1. A "probable" or "confirmed" case of SARS

OR

2. A death from acute respiratory disease in:

- a) an area with human chain(s) of SARS-CoV transmission where autopsy findings are consistent with the pathology of pneumonia or acute respiratory distress syndrome (ARDS) without an identifiable cause

OR

- b) a close contact of a "preliminary positive" or "confirmed", infectious case of SARS within the 10 days before the onset of symptoms or death in whom an autopsy was not done (verbal autopsy only) AND/OR in whom laboratory testing was not done or was incomplete.

Note: The extended period of vigilance for SARS arises from the lessons learnt during the 2002–2003 epidemic and is recommended to reduce the risk of new outbreaks arising from missed SARS infections (25,26) or incubation periods beyond 10 days (27–31). [The second wave of SARS transmission in Canada was attributed to the inherent difficulties in diagnosing SARS when the clinical presentation is atypical and prematurely stepping down respiratory precautions in hospitals (25,26)].

A new (independent) chain of human transmission

A new transmission tree that cannot be linked to an existing chain of human transmission after an epidemiological investigation.

SARS-CoV infection

The term "SARS-CoV infection" is used when referring to the transmission of the SARS coronavirus and includes both symptomatic and asymptomatic infections.

Definitive laboratory testing completed

Testing meets the requirements for the laboratory diagnosis of SARS and almost always involves two or more different tests or the same assay on two or more occasions during the course of the illness or from different clinical sites. See sections 2.3 and 2.5 for the tests and quality assurance required for the confirmation of SARS.

Note: A single test result is insufficient for the definitive diagnosis of SARS-CoV infection because both false negative and false positive results are known to occur.

Contacts

A contact is a person who is at greater risk of developing SARS because of exposure to a SARS case. Risky exposures include having cared for, lived with, or having had direct contact with the respiratory secretions, body fluids and/or excretions (e.g. faeces) of cases of SARS.

2. Clinical and laboratory criteria for the global surveillance of SARS

2.1 Clinical case description of SARS

The case description (see Annex 2) provides details of the spectrum of disease including atypical presentations, the clinical evolution of SARS, and radiological and laboratory findings to assist clinicians with their diagnosis. All health-care workers should be aware of the clinical symptoms and signs of SARS and the appropriate transmission-based precautions that should be applied (see Annex 3).

2.2 The differential diagnosis of SARS

The clinical symptoms and signs of disease caused by SARS-CoV are non-specific. The differential diagnosis therefore may include a range of common respiratory pathogens including influenza virus, parainfluenza viruses, respiratory syncytial virus (RSV), *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia* species, *Legionella* species, and *Coxiella burnetii*. In addition, there are currently no laboratory tests that reliably diagnose SARS in the first few days of illness. Other human coronaviruses (e.g. OC43 and 229E) and animal coronaviruses can also cause diagnostic confusion.

Clinical algorithms incorporating clinical and epidemiological criteria can assist in the systematic assessment of patients presenting with an ARI, particularly when linked to testing algorithms using the panel of common respiratory pathogens. Clinicians and public health professionals should be familiar with the epidemiology of other diseases that have presentations similar to the symptoms and signs of SARS, including the common causes of community-acquired and hospital-acquired ARI.

Caution should be exercised in diagnosing non-specific viral pneumonia without detailed inquiry to ascertain risk factors for SARS in the 10 days before the onset of illness. These include determining whether other family members and/or other close social or occupational contacts have had a similar illness (particularly in a laboratory or hospital setting), or a relevant history of travel to an area at risk of SARS-CoV transmission from animal reservoirs or a recent outbreak of SARS.

Establishing an alternative diagnosis should not delay the triggering of a SARS Alert (see section 3) and the timely implementation of patient isolation and stringent infection control measures if a SARS diagnosis cannot be confidently excluded. Indications for testing during a SARS Alert are given in section 3.4.

2.3 The laboratory diagnosis of SARS

The following tests are recommended for the laboratory diagnosis of SARS. A single test result is insufficient for the definitive diagnosis of SARS-CoV infection because both false negative and false positive results are known to occur (see below, "The interpretation of laboratory results for SARS-CoV").

Nucleic acid tests

Reverse transcription polymerase chain reaction (RT-PCR), positive for SARS-CoV using a validated method from:

1. At least two different clinical specimens (e.g. nasopharyngeal and stool)
OR
2. The same clinical specimen collected on two or more occasions during the course of the illness (e.g. sequential nasopharyngeal aspirates)
OR
3. Two different assays or repeat RT-PCR using a new RNA extract from the original clinical sample on each occasion of testing.

Seroconversion by ELISA or IFA

- Negative antibody test on acute state serum followed by positive antibody test on convalescent phase serum tested in parallel.
OR
- Fourfold or greater rise in antibody titre between acute and convalescent phase sera tested in parallel.

Note: Virus neutralization should be conducted to exclude serological cross-reactions with other human and/or animal coronaviruses. Virus neutralization should only be conducted in a specialized laboratory under the appropriate biosafety level (BSL3). It is recommended in the inter-epidemic period and for at least one case in each new (independent) chain of human transmission when an outbreak is being verified to exclude serological cross-reactions. Once SARS-CoV transmission is well established, virus neutralization will not usually be required but may be used when the results of RT-PCR and serology are difficult to interpret.

Virus isolation

Isolation in cell culture from any clinical specimen and identification of SARS-CoV using a validated method such as RT-PCR.

The interpretation of laboratory results for SARS-CoV

The reliability of the results of diagnostic tests for SARS-CoV infection depends crucially on the type of clinical specimens collected, the time of collection and the method of collection. WHO has established a network of international reference and verification laboratories for SARS to assist with independent verification of testing in national laboratories and for primary diagnosis if requested. Guidance on the clinical specimens for the laboratory diagnosis of SARS-CoV and the timing of their collection can be found in *WHO SARS International Reference and Verification Laboratory Network : Policy and Procedures in the Inter-Epidemic Period* (32).

Serological testing is improving, although quality assurance has indicated a significant level of missed positive specimens and of false positive results. Where acute and convalescent phase sera show a fourfold or greater rise in titre when tests are carried out in parallel, but no PCR

product is available or virus isolated, viral neutralization assays should be performed. This test should be performed by the national reference laboratory and, depending on whether the case occurs in the inter-epidemic period or during an outbreak, by a WHO SARS International Reference and Verification Laboratory for final confirmation and to ensure that the rising titre is not due to a second human coronavirus.

In the inter-epidemic period, WHO strongly recommends that all countries seek verification of laboratory-confirmed cases of SARS ("preliminary positive" cases), preferably by an external laboratory which is part of the WHO SARS International Reference and Verification Laboratory Network.

Virus isolation and sequencing should be undertaken wherever possible to monitor the evolution of SARS-CoV in human populations and the frequency of interspecies transmission. Virus isolation requires BSL3 conditions and practices.

WHO will facilitate testing at one of the Network laboratories for national health authorities without their own SARS-CoV testing facilities. All laboratories should adhere to the biosafety levels recommended for diagnostic work on clinical specimens actually or potentially infected with SARS-CoV and research on SARS-CoV.

Biosafety guidance for handling SARS-CoV safely is found in *Laboratory Biosafety Manual, third edition (33)* and the *WHO biosafety guidelines for handling of SARS specimens (34)*.

2.4 Clinical evidence for SARS

The following clinical criteria for SARS, presented in Table 1, are used for public health (surveillance) purposes only. Clinicians are advised to refer to the clinical case description for further details of the symptoms and signs of SARS.

Table 1. Clinical evidence for SARS for surveillance purposes

Clinical evidence for SARS	
A clinical case of SARS is an individual with:	
1.	A history of fever, or documented fever ≥ 38 °C (100.4 °F).
	AND
2.	One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath)
	AND
3.	Radiographic evidence of lung infiltrates consistent with pneumonia or ARDS or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause.
	AND
4.	No alternative diagnosis can fully explain the illness.

2.5 Laboratory case definition for SARS

An individual who tests positive for SARS-CoV by any of the testing procedures described above in section 2.3 using validated testing methods and appropriate quality assurance mechanisms, including positive and negative controls.

See section 4.1 for further details of how "laboratory confirmation" is interpreted in the inter-epidemic period and once human transmission of SARS has been established.

3. The inter-epidemic period – The SARS Alert

3.1 Objectives of the SARS Alert

1. Provide early warning of the potential recurrence of SARS to:
 - rapidly implement appropriate infection control measures in a health-care setting
 - expedite diagnosis
 - activate the public health response
2. Raise a global alert if indicated.

3.2 Definition of the SARS Alert

Table 2. The SARS Alert

Definition of the SARS Alert	
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: <ul style="list-style-type: none">• 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.

Notes

- In the context of a SARS Alert, the term “health-care worker” includes ALL hospital staff.
- A jurisdiction may choose, based on its national SARS risk assessment and local experience of acute respiratory disease, to increase the minimum number of ‘alert’ cases defining a cluster. The definition of the health care unit in which the cluster occurs will depend on the local situation. Unit size may range from an entire health care facility if small, to a single department or ward of a large tertiary hospital.
- All laboratories that propagate SARS-CoV/SARS-CoV-like viruses, or use clinical materials from SARS patients or infected animals, infectious clones and/or replicons should implement a health monitoring programme for staff.
- Personnel with an occupational risk of SARS should be informed of their responsibility to volunteer details of their occupational history when seeking health care for an acute febrile illness.
- It is important that clinicians ask patients about risk factors for SARS if they present with a clinically compatible illness. This includes determining whether other family members and/or close social or occupational contacts (particularly in a laboratory or hospital setting) have had a similar illness, or a relevant history of travel to an area at risk of SARS-CoV transmission from animal reservoirs or a recent outbreak of SARS.
- Following the last reported case in an outbreak of SARS, an individual fulfilling the clinical case definition for SARS should be asked about travel to the outbreak area(s) in the preceding 28 days before illness onset (25–31).

3.3 Assessing the risk of the emergence or introduction of SARS-like coronaviruses during the inter-epidemic period

In recognition that the risk of SARS-CoV emergence or introduction varies between and within countries, WHO has developed a staged approach to SARS surveillance in the inter-epidemic period based on a global risk assessment.

The responsibility for the management of SARS rests primarily with national authorities. Ideally, each national government should determine the intensity of its surveillance for SARS in the inter-epidemic period on the basis of a risk assessment.

Accordingly, WHO strongly recommends that all countries undertake an analysis of their risk of SARS emergence or introduction and develop a contingency plan for the detection and management of SARS should it recur in epidemic form.

Three of the four SARS incidents since July 2003 have been attributed to breaches in laboratory biosafety. WHO strongly recommends Biosafety Level 3 (BSL3) as the minimum containment level to work with live SARS-CoV. WHO also urges countries to maintain a thorough inventory of laboratories working with and/or storing live SARS coronavirus and to ensure that necessary biosafety standards are in place.

WHO has defined three risk categories (see Table 3) that take into account the experience during the 2002–2003 SARS epidemic and the potential for emergence of SARS-CoV.

Table 3. Risk categories for the emergence of SARS

Risk category	Definition
Emergence of SARS-CoV-like viruses from wildlife or other animal reservoirs	<ul style="list-style-type: none"> ▪ 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.
Emergence or introduction of SARS-CoV from laboratories or international travel	<ul style="list-style-type: none"> ▪ 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. <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ 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.

Note: Some countries/areas may fall into two risk categories.

3.4 Indications for testing for SARS-CoV in the inter-epidemic period

The risk of false positive results from SARS-CoV testing will be high in the inter-epidemic period given the limitations of currently available laboratory tests and without any evidence that the virus is circulating in human populations. In addition, other common respiratory infections causing pneumonia or ARDS may stimulate testing for SARS-CoV. Experience from the 2002–2003 SARS epidemic and the four SARS incidents since July 2003 indicates that certain human and animal populations are at higher risk of infection and disease from SARS-CoV and SARS-CoV-like viruses (see section 3.7).

Confidence in the accuracy of a positive or negative test result will vary with the risk that SARS-CoV is present in different settings, i.e. the predictive value of the test varies with changes in the prevalence of the aetiologic agent/disease. WHO recommends that clinicians, epidemiologists, public health and laboratory experts consult together on persons under investigation for SARS in the inter-epidemic period. In low risk settings where false positive results for SARS-CoV are most likely, the triage process should ensure that testing for SARS-CoV is considered in the context of clinical and epidemiological evidence that the virus may be the etiological agent causing an individual case or cluster of cases of ARI. Such an approach will help to limit the inappropriate use of resources and the risk of overwhelming the health system by unnecessary activation of hospital-based and public health SARS responses.

Thus, WHO recommends testing in the situations described in Table 4.

Table 4. Risk of SARS emergence and indications for testing

Situation	Indication for testing
Emergence of SARS-CoV-like viruses from wildlife or other animal reservoirs	<ul style="list-style-type: none"> ▪ In the investigation of a SARS Alert ▪ As part of enhanced surveillance for SARS in populations at risk ▪ As part of special studies for evidence for SARS-CoV-like viruses in wildlife and other animal reservoirs
Emergence or introduction of SARS-CoV from laboratories or international travel	<ul style="list-style-type: none"> ▪ In the investigation of a SARS Alert ▪ As part of enhanced surveillance for SARS in human populations at risk
Low risk of SARS-CoV emergence or introduction	<ul style="list-style-type: none"> ▪ In the investigation of a SARS Alert

3.5 Public health management of a SARS Alert

Public health actions when a SARS Alert is raised

- Patient(s) should be immediately isolated and transmission-based precautions instituted, if not already in place (35).
- The diagnosis should be expedited. WHO will assist in the investigation of SARS alerts as appropriate, including facilitating access to laboratory services (17).
- Contacts of persons under investigation for SARS should be traced and placed on twice daily fever monitoring until SARS has been ruled out as the cause of the illness.
- All contacts should ideally be given written information on the clinical picture, transmission and other features associated with SARS, as well as written information on respiratory hygiene and contact precautions.

Reporting to WHO

- National public health authorities should report every laboratory-confirmed case of SARS to WHO.
- However, in view of the global attention given to SARS rumours, informing WHO of clusters of acute respiratory disease and/or high-risk individuals under investigation for SARS will facilitate rapid verification and the accurate dissemination of information to other governments, the media and the public.

Management of contacts within a health-care setting following a SARS Alert

- Inpatient contacts should be isolated or cohorted away from unexposed patients and transmission-based precautions instituted. They should be placed on active fever surveillance.
- Exposed staff should be placed on active fever surveillance, and either cohorted to care for exposed patients (“work quarantine”) or redeployed to non-clinical duties depending on local circumstances.

Management of community contacts following a SARS Alert

Community contacts should:

- Be informed that the most consistent first symptom that is likely to appear is fever and instructed on how to self-monitor for fever. Fever monitoring should be performed twice daily for 10 days from the last contact with a person under investigation for SARS.
- Should report the onset of fever and/or other symptoms to health authorities immediately and place themselves in isolation pending medical care.
- Be visited or telephoned daily by a member of the public health-care team to ascertain their clinical status.
- Be investigated locally at an appropriate health-care facility if they develop symptoms. Informing the health-care facility before presenting for medical care will minimize the risk of nosocomial transmission.

3.6 Indicators of the quality of the SARS Alert mechanism

WHO recommends that national public health authorities monitor the quality of the SARS alert mechanism, e.g. by establishing indicators based on:

- the number of alerts expected and reported by health facilities over time
- the time taken to implement transmission-based precautions and expedite diagnosis
- the time taken to alert local public health authorities, national public health authorities
- the time taken to complete contact tracing and quarantine contacts.

This list is not meant to be exhaustive but rather a suggested approach to monitoring the alert mechanism.

3.7 Enhanced surveillance and special studies in human and animal populations at higher risk of SARS-CoV infections

Depending on risk assessment and available resources, areas at risk of the re-emergence of SARS-like coronaviruses from wildlife and other animal reservoirs and areas at higher risk of SARS-CoV emergence or introduction from other sources may undertake one or more of the following activities:

- Fever surveillance of occupational risk groups e.g. laboratory workers in the inter-epidemic period; health care workers during an outbreak of SARS.
- 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 health care workers caring for patients with SARS and laboratory staff working with SARS-CoV and products of experimental work on SARS-CoV or potentially infected clinical materials.
- 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 (health care workers, laboratory staff working with SARS-CoV or in laboratories storing clinical samples infected with SARS-CoV, etc.).
- Serological surveys to detect new infections (seroincidence studies) and the prevalence of serological markers for SARS-CoV-like virus infections (seroprevalence) surveys of wildlife handlers, market vendors and/or hunters. Care must be taken in such studies to exclude serological cross-reactions with other animal and human coronaviruses.
- Community-based serological surveys to monitor changes in the seroprevalence of SARS-CoV infection.
- Seroincidence and seroprevalence surveys among wildlife populations thought to be the reservoir(s) of SARS-CoV transmission.

This list is not meant to be exhaustive but rather a suggested approach to enhanced surveillance.

4. The global surveillance of SARS during an outbreak

4.1 Surveillance case definitions for SARS

Only individuals fulfilling one of the following surveillance case definitions should be officially reported to WHO.

However, national public health authorities may choose to use additional operational categories e.g. "persons under investigation for SARS" or "suspect" cases, before the definitive results of testing are available.

Table 5. Surveillance case definitions for SARS during an outbreak

Preliminary positive case of SARS

An individual with clinical evidence for SARS **AND** who meets the laboratory case definition of SARS-CoV infection **where testing has only been performed at a national reference laboratory.**

Confirmed case of SARS

A 'preliminary positive' case where testing performed at a national reference laboratory has been **independently verified by a WHO International SARS Reference and Verification Laboratory.**

OR

A "preliminary positive" case of SARS where at least one case in the first chain of transmission identified in the country/area has been independently verified by a WHO International SARS Reference and Verification Laboratory.

OR

An individual with clinical and epidemiological evidence* for SARS **AND** with preliminary laboratory evidence of SARS-CoV infection based on the following tests performed at a national reference laboratory or a designated sub-national laboratory:

a) A single positive antibody test for SARS-CoV

OR

b) A positive PCR result for SARS-CoV on a single clinical specimen and assay.

*Epidemiological evidence for SARS is linkage to a chain of human transmission where at least one case in the first chain of transmission identified in the country area has been independently verified by a WHO International SARS Reference and Verification Laboratory

Probable case of SARS

An individual with clinical evidence of SARS epidemiologically linked to a 'preliminary positive' or 'confirmed' case of SARS.

OR

An 'unverifiable' case of SARS if epidemiologically linked to a 'preliminary positive' or 'confirmed' case.

Unverifiable case of SARS

An individual with clinical evidence of SARS but in whom initial laboratory results are negative, if done, and the patient is lost to follow up.

OR

A deceased individual with a pre-morbid history of illness compatible with SARS AND

a) whose autopsy findings are consistent with the pathology of pneumonia or ARDS but in whom SARS-CoV testing was not done or was incomplete

OR

b) in whom neither an autopsy nor laboratory testing were performed.

Notes:

- One or more cases in the first chain of human transmission occurring in countries/areas previously free of SARS should **always be independently verified by a WHO International SARS Reference and Verification Laboratory**.
- In the event of a large outbreak where sub-national laboratories may be designated to perform SARS testing by the national health authority, WHO recommends that at least one case in all subsequent new (independent) chains of transmission should be **independently verified by a national SARS reference laboratory**.

4.2 Verifying an outbreak of SARS

During the inter-epidemic period, WHO will utilize highly specific laboratory criteria for the diagnosis of SARS and requests independent verification at one or more WHO International SARS Reference and Verification Network laboratories to reduce the risk of false positive and false negative test results. The laboratory requirements for confirmation imply the use of validated testing methods and appropriate quality assurance mechanisms, including positive and negative controls in all laboratories undertaking diagnostic and reference work for SARS.

Once an outbreak of SARS has been independently verified, the laboratory requirements for case confirmation will be less specific than those recommended for the inter-epidemic period.

National health authorities may wish to devolve laboratory testing to sub-national laboratories which meet the quality standards described above.

WHO also advises that during a sustained outbreak of SARS, countries test a proportion of individuals with clinical evidence for SARS throughout the outbreak as a form of quality assurance. Such testing is recommended to reduce diagnostic confusion with other infectious conditions that mimic SARS clinically, especially as the epidemic wanes.

Table 6 summarizes the indications for independent verification of positive tests performed at national reference laboratories.

Table 6. Indications for the independent verification of positive SARS tests by a WHO International SARS Reference and Verification Network laboratory

In the inter-epidemic period

- All sporadic 'preliminary positive' cases.
- At least one case in each new (independent) chain of human transmission.

During an outbreak or global epidemic of SARS

- At least one case in the first chain of human transmission occurring in countries previously free of SARS, and depending on the size of the country, in areas within countries previously free of SARS.

Note:

In the event of a large outbreak where sub-national laboratories may be designated to perform SARS testing by the national health authority, WHO recommends that at least one case in all subsequent new (independent) chains of transmission should be **independently verified by a national SARS reference laboratory**.

At any time

- In the event of a change in the clinical spectrum of the disease, or when clinical and/or epidemiological evidence suggests increased virulence or that the virus is more readily transmissible or is spreading by previously unknown or uncommon route(s) of transmission.

A higher level of global vigilance, and lower threshold for SARS testing, will be required during another epidemic of SARS. The risk of false positive results from SARS-CoV testing will be lower than during the inter-epidemic period. However, experience during the 2002–2003 epidemic suggests that in areas free of SARS the positive predictive value of clinical and epidemiological evidence for SARS will remain low when assessed against laboratory tests.

Figures 1 and 2 present diagnostic and reporting algorithms for SARS in the inter-epidemic and epidemic periods respectively.

Figure 1. Testing and reporting algorithm for SARS in the inter-epidemic period

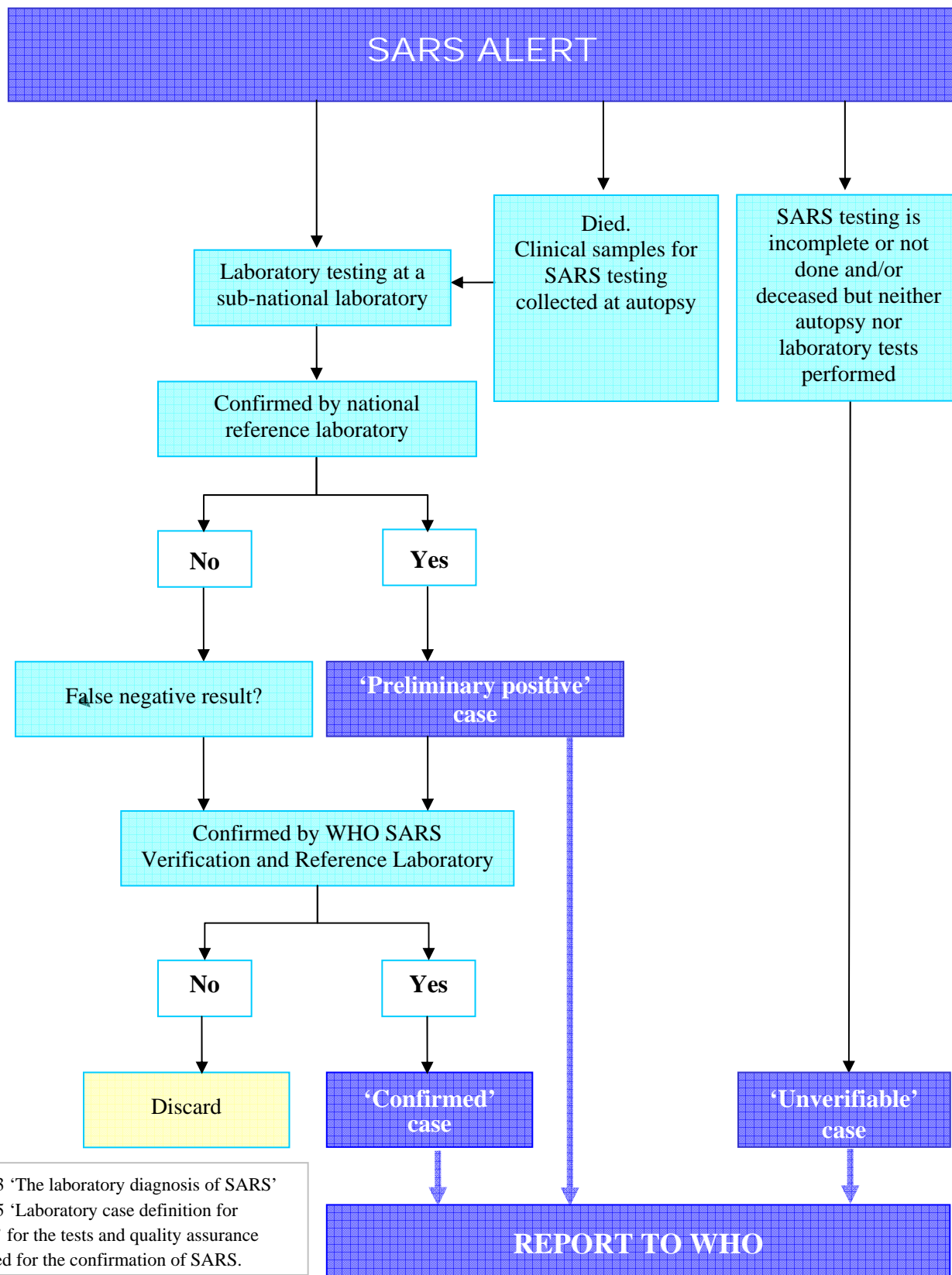
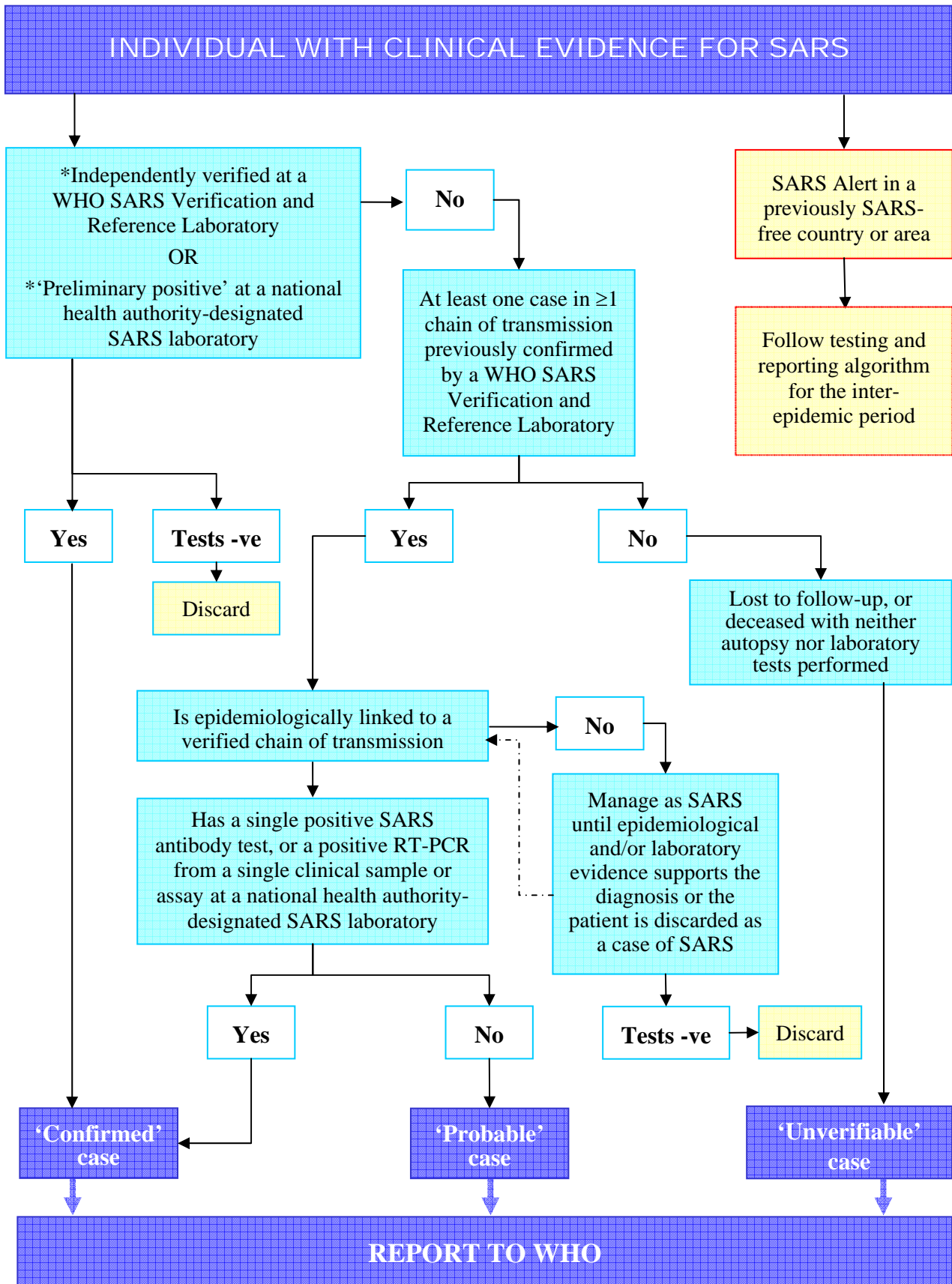


Figure 2. Testing and reporting algorithm for SARS during an outbreak



* See 2.3 'The laboratory diagnosis of SARS' and 2.5 'Laboratory case definition for SARS' for the tests and quality assurance required for the confirmation of SARS.

4.3 Reclassification of SARS cases and exclusion criteria

- A "preliminary positive" case of SARS will be reclassified as a "confirmed case" of SARS under the circumstances described in section 4.1.
- An individual with clinical and epidemiological evidence for SARS AND with preliminary laboratory evidence of SARS-CoV infection will be reclassified as a "confirmed case" of SARS under the circumstances described in section 4.1.
- An "unverifiable" case of SARS will be classified as a "probable case" if epidemiologically linked to a "preliminary positive" or "confirmed" case of SARS.
- National public health authorities should not downgrade or discard individuals as cases while awaiting the results of laboratory tests or on the basis of a single negative result if clinical and/or epidemiological evidence supports the diagnosis.
- A person under investigation for SARS should be discarded as a case if an alternative diagnosis can fully explain the illness OR a validated serological test conducted under appropriate quality assurance mechanisms, including positive and negative controls is negative 28 days or more after the onset of symptoms (32).

5. International reporting of SARS

5.1 WHO global surveillance for SARS

For the purposes of the international reporting of SARS to WHO, national public health authorities are requested to officially report:

- "preliminary positive" cases
- "probable" cases
- "confirmed" cases
- "unverifiable" cases during an outbreak of SARS.

National health authorities should report the **first "preliminary positive" case(s)** of SARS in their country to **WHO within 24 hours** of the receipt of positive test results from their national SARS reference laboratory.

However, in view of the global attention given to SARS rumours, informing WHO of clusters of acute respiratory disease and/or high-risk individuals under investigation for SARS will facilitate rapid verification and the accurate dissemination of information to other governments, the media and the public. See also the *WHO SARS Risk Assessment and Preparedness Framework*.

Reporting to WHO should continue to **exclude asymptomatic SARS-CoV infections**, and individuals with clinically compatible illness but without laboratory confirmation unless the latter are part of a laboratory-confirmed chain of human transmission (i.e. fulfil the "probable case" definition, see section 4.1).

No nil reporting is required

WHO requests that national health authorities inform the focal points at the WHO Country Office, Regional Offices or Headquarters (see Annex 4) of every person meeting WHO definitions of preliminary positive, probable or laboratory-confirmed cases of SARS within 24 hours of the receipt of the positive test results for SARS-CoV infection. This will allow WHO to assess the need for a global alert for SARS on the basis of that notification as appropriate.

In the event of an international traveller being investigated for SARS, all national public health authorities involved in international contact tracing around the case(s) should communicate directly with each other during the investigation. WHO will remain informed on the progress of the investigation and assist as required. Confirmation of the international spread of SARS is a global public health emergency (Phases 3–4 of the *WHO SARS RAPF*).

WHO will continue to identify and verify rumours of events of international public health concern, including rumours about SARS, through its usual well-established mechanisms.

5.2 The minimum global dataset

WHO is developing an expanded minimum global dataset, data dictionary and reporting format for the inter-epidemic period and for reporting during another outbreak of SARS should it occur. The aim of the minimum global dataset is to systematically collect the clinical, laboratory and epidemiological data required to refine estimates of the key distributions for SARS (incubation period, period of communicability, case fatality ratios and basic reproduction number, R_0) as well as improving our knowledge of the risk factors for SARS-CoV infection, the spectrum of disease it causes, and aid in the evaluation of control measures.

This document will be posted on the WHO SARS web site when available.

Annex 1. Summary of the essential aspects of the SARS Risk Assessment and Preparedness Framework (WHO SARS RAPF)

Aims and objectives of the WHO SARS Risk Assessment and Preparedness Framework

The Framework was developed as an aid to national health authorities for the detection and public health management of SARS. The document:

- Outlines different scenarios that might occur at sequential phases of a SARS outbreak.
- Assigns a level of risk as an outbreak occurs or escalates at each phase.
- Suggests activities that areas with local transmission of SARS, SARS-free areas and WHO should undertake.
- Recommends surveillance activities to be established or strengthened as part of national preparedness planning.

Phases of the WHO SARS Risk Assessment and Preparedness Framework

In the assessment framework, the 'phase' refers to sequential stages that might be seen in a SARS outbreak and the recommended public health response. The phases are defined in Table A1.1. The detailed description of the recommended public health actions is found in the *WHO SARS RAPF* document. National public health authorities are encouraged to link their own SARS contingency plans (either existing or future) to the global framework.

Phases 0-1 correspond to the absence of human chains of SARS-CoV transmission worldwide. In these phases, WHO and national health authorities should direct efforts towards assessing preparedness and developing contingency plans.

It is possible to move from one phase to another in a non-sequential fashion during an outbreak of SARS; for example, laboratory confirmation of SARS in a cluster of cases of acute respiratory illness would result in a shift from Phase 0 directly to Phase 2.

The escalation or stepping down of public health activities in response to a phase shift is described in the *WHO SARS RAPF*.

Evaluation of risk

It is important to recognize that the Framework only aims to provide guidance. Many situations will require a risk assessment of the specific circumstances. For example, the stage of illness at which an individual presents, the number of contacts identified, cluster size, the route(s) of transmission and the transmission setting (hospital or community) are all important risk factors for transmission and ease of containment.

Similar situations may present different risks in different settings due to factors that include:

- The relative strength of acute medical and public health infrastructure, especially surveillance and response capacity.

- The level of preparedness, including whether a country has experience in dealing with SARS and whether an appropriate legal framework exists that facilitates the containment of epidemic prone diseases.
- The geographical location, including the risk of SARS-CoV emergence or re-emergence, the mobility of local populations and whether the site is an international hub for travel or trade. See section 3.3 for the assessment of risk of the re-emergence of SARS-like coronaviruses in the inter-epidemic period.

Table A1.1 Preparedness levels for inter-epidemic, epidemic and post-epidemic periods

Phase	Epidemiological situation
Phase 0	No evidence of SARS-CoV transmission to humans worldwide.
Phase 1	Sporadic case(s) of SARS or a common source of transmission that does not result in secondary cases.
Phase 2	Confirmed human-to-human transmission. The magnitude of the outbreak is described in Phase 2, Levels 1 and 2.
Phase 2, Level 1	Chains of transmission in one location.
Phase 2, Level 2	Chains of transmission in two or more locations but with no evidence of international spread.
Phase 3	International spread.
Phase 4	Slowing down of the outbreak.
Phase 5	Global interruption of SARS-CoV transmission (epidemic halted).

Annex 2. Clinical case description of SARS

Etiology

Severe acute respiratory syndrome (SARS) is a disease caused by the SARS coronavirus (SARS-CoV).

Epidemiology

Nosocomial transmission of SARS-CoV has been a striking feature of the SARS outbreak. The majority of the cases are adults. Children are less commonly affected than adults and usually have a milder illness¹.

The mean incubation period is 5 days with the range of 2–10 days although there are isolated reports of longer incubation periods. Cases outside the 2 to 10 day incubation period have not necessarily been subjected to rigorous and standardized investigation, including serological confirmation. There have been no reports of transmission occurring before the onset of symptoms.

Natural history of the disease

Week 1 of illness

Patients initially develop influenza-like prodromal symptoms. Presenting symptoms include fever, malaise, myalgia, headache, and rigors. No individual symptom or cluster of symptoms has proven specific. Although history of fever is the most frequently reported symptom, it may be absent on initial measurement.

Week 2 of illness

Cough (initially dry), dyspnoea and diarrhoea may be present in the first week but more commonly reported in the second week of illness. Severe cases develop rapidly progressing respiratory distress and oxygen desaturation with about 20% requiring intensive care. Up to 70% of the patients develop diarrhoea which has been described as large volume and watery without blood or mucus. Transmission occurs mainly during the second week of illness.

Clinical outcomes

Based on an analysis of data from Canada, China, Hong Kong SAR, Singapore, Viet Nam and the United States during the 2003 epidemic the case fatality ratio (CFR) of SARS is estimated to range from 0% to more than 50% depending on the age group affected and reporting centre, with an crude global CFR of approximately 9.6%.² Higher mortality has also been associated with male sex and presence of co-morbidity in various studies.

¹ Hon KLE, Leung CW, Cheng WTF, Chan PKS, Chu WCW, Kwan YW et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet*, 2003, 361:1701-1703.

² see http://www.who.int/csr/sars/country/table2003_09_23/en/

Elderly and paediatric cases and SARS in pregnancy

Atypical presentations such as afebrile illness or concurrent bacterial sepsis/pneumonia have been highlighted as a particular problem in the elderly. Underlying chronic conditions and their more frequent use of health facilities have both contributed to initially unrecognized nosocomial transmission events.

SARS occurred less frequently and was observed to be a milder illness in the paediatric population.

Known cases of SARS in pregnancy have suggested an increase in fetal loss in early pregnancy and maternal mortality in later pregnancy¹.

Radiological findings

Early chest radiograph or CT changes are observed in most of the patients as early as days 3-4 of illness in spite of the absence of respiratory signs. These typically show patchy consolidation starting with a unilateral peripheral lesion which progress to multiple lesions or ground glass appearance. Some lesions follow a shifting pattern. Features during the later stages have sometimes included spontaneous pneumothorax, pneumomediastinum, sub-pleural fibrosis and/or cystic changes.

Haematological and biochemical findings

There are no haematological or biochemical parameters specific for SARS; however, studies have consistently highlighted the following:

Haematological findings

Lymphopenia is common on presentation and progresses during the course of the illness. Sometimes thrombocytopenia and prolonged APTT are observed.

Biochemical findings

LDH is frequently high and some reports have suggested association with poor prognosis. ALT, AST and CPK elevation are less frequently reported. Abnormal serum electrolytes have also been reported on presentation or during hospitalization including hyponatraemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.

¹ Wong SF, Chow KM, de Swiet M. Severe Acute Respiratory Syndrome and pregnancy. *British Journal of Obstetrics and Gynaecology*, 2003, 110:641–642.

Annex 3. Guidance regarding the diagnosis of SARS in the inter-epidemic period – A concern for all health-care workers (HCWs)

Making a diagnosis of SARS sufficiently early in the disease to implement effective infection control and public health measures will prove a challenge that requires all HCWs to always incorporate risk-based infection control measures in care provision. To prevent or interrupt SARS-CoV transmission all health facilities should ensure they are applying standard precautions at all times, with the adoption of additional transmission-based precautions for the investigation and management of individuals with an acute respiratory illness based on an assessment of the population risk of SARS at the local level and the individual risk of SARS. This will only occur within a culture that treats infection prevention and control as everyone's responsibility. All HCWs should be encouraged to consider the possibility of SARS in a patient under their care. If there are features suggestive of SARS then any concerns should be raised promptly and trigger risk-based infection control measures. There must be monitoring and feedback on this process.

The non-specific nature of the presentation of SARS could lead to concern being raised in a vast number of patients who will ultimately prove to have another diagnosis. In practice, concern about the possibility of SARS may often be expressed at the stage where atypical pneumonia is suspected.

This process should not rely wholly on clinicians but should be responsive to the concerns raised by other HCWs.

Concern of SARS raised by clinicians

For clinicians the process of diagnosis from initial concern to confirmation or exclusion of a SARS diagnosis (see case description) is usually an incremental one following sequential information gathering from various sources that include:

- Clinical history
- Clinical examination
- Epidemiological information obtained from the individual, the health facility or the community
- Bedside monitoring
- Radiology investigations
- Haematology investigations
- Biochemistry investigations
- Microbiology and virology investigations
- Response to treatment

Concern about SARS raised by other health professionals

Concerns regarding SARS may be raised by any HCW. All HCWs need to ensure they are fully aware of what constitutes a clinical concern about SARS and how, in the course of their duties they could be involved in the presentation, investigation or treatment of an unrecognized SARS case.

They should be encouraged to raise concerns with both the clinicians and infection control team who should provide monitoring and feedback on the process.

Some examples are given:

- Infection control staff e.g. noting an increase in hospital acquired pneumonias
- Nursing staff e.g. noting a pattern of deterioration in a patient suggestive of SARS
- Staff involved in care of the elderly e.g. noting an increase in severe illness
- Occupational health staff e.g. noting staff sickness compatible with atypical pneumonia
- Physiotherapists e.g. noting a pattern of atypical pneumonia
- Radiographers e.g. noting a pattern of atypical pneumonia
- Radiologists e.g. noting a pattern of atypical pneumonia
- Haematologists e.g. noting a profile consistent with atypical pneumonia
- Biochemists e.g. noting a profile consistent with atypical pneumonia
- Microbiologists e.g. noting an increase in uncharacterised pneumonias
- Virologists e.g. noting an increase in requests for respiratory investigations
- Pharmacists e.g. noting an increase in prescribing for pneumonia

Atypical pneumonia

Common bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* cause so-called "typical pneumonia". Cases of typical pneumonia present with fever, respiratory symptoms (cough, which is usually early in the illness and often productive, shortness of breath etc.), elevated white cell count and well-defined changes on the chest radiograph. They tend to respond to antibiotic therapy for community acquired pneumonia.

In contrast, "atypical pneumonia" is defined as pneumonia or lower respiratory tract infection with an atypical presentation often with a gradual onset of symptoms such as non-productive, dry cough, a variable white blood cell count and chest radiograph changes. These include patchy, poorly defined changes, which may be often more severe than the clinical picture would suggest. The causative agents include *Mycoplasma pneumoniae*, *Chlamydia* species, *Legionella pneumophila*, and *Coxiella burnetii*.

Diagnosis of atypical pneumonia is in itself challenging but will be assisted by careful clinical assessment (including non-respiratory symptoms), and given the likely absence of auscultatory signs, accurate measurement of respiratory rate and oxygen saturation (where available). Chest radiography is of great use in achieving diagnosis and should be considered even in the absence of respiratory signs.

Table A3.1 Features of SARS that may commonly help with the clinical diagnosis

SARS	Example	Caution
Clinical history	Sudden onset of flu-like prodrome, fever, dry cough, non-respiratory symptoms e.g. diarrhoea, myalgia, headache and chills/rigors.	Take a travel history, occupational history, history of hospitalization and history of contact with health-care facility or person with SARS. The absence of any of these factors in the history should not automatically exclude the diagnosis of SARS.
Clinical examination	Does not correlate with chest radiology changes.	Lack of respiratory signs particularly in groups such as the elderly.
Bedside monitoring	Hypoxia	Temperature may not be elevated on admission. The respiratory rate should be documented.
Haematology investigations	Low lymphocyte count, raised C-reactive protein, prolonged activated partial thromboplastin time.	These changes are non-specific and are not always seen in SARS.
Biochemistry investigations	Raised lactate dehydrogenase, hepatic transaminases, creatine phosphokinase.	These changes are non-specific and are not always seen in SARS.
Radiology investigations	CXR changes poorly defined, patchy, progressive changes.	May present as a lobar pneumonia. Pneumothorax and pneumomediastinum may also occur.
Microbiology investigations	Investigate for community-acquired and hospital-acquired pneumonias including atypical pneumonias.	Concurrent infections may occur.
Virology investigations	Investigate for other causes of atypical pneumonia.	Interpret SARS-CoV test results with caution, based on the assessment of the population risk of SARS at the local level and the individual risk of SARS.
Treatment	Lack of response to antibiotic treatment for community-acquired pneumonia, including atypical pneumonia.	All viral pneumonias and a number of bacterial pneumonias will not respond to standard antibiotic treatments. As yet there is no proven treatment for SARS; supportive measures are recommended.

Annex 4. WHO focal points for SARS

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