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SARS

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Abbreviations

ACE2 angiotensin-converting enzyme 2
CoV coronavirus
CSR Communicable Disease Surveillance & Response
EIA enzyme immunoassay
PEDV porcine epidemic diarrhea coronavirus
PRCV porcine respiratory corona
RSV respiratory syncytial viruses
RT-PCR reverse transcriptase-polymerase chain reaction
SARS severe acute respiratory syndrome
TGEV transmissible gastroenteritis virus
WHO World Health Organization

A New Infectious Disease Emerges

On 11 February 2003, the World Health Organization's (WHO) Communicable Disease Surveillance & Response (CSR) unit published a report from the Chinese Ministry of Health of an outbreak of acute respiratory syndrome in Guangdong Province with 300 cases and 5 deaths. At the same time, mass media reported that a pneumonia epidemic in Guangdong was causing considerable fear and disruption among the local population, but provided no details about the etiology of the apparently infectious disease.

One week later, CSR reported the detection of an avian influenza A (H5N1) virus in a child from Hong Kong. Following a visit to mainland China, several members of the family had presented with a similar illness, to which two of the child's relatives had succumbed.

Although many observers were tempted to see a possible causal link between the two reports relating to adjacent geographic areas, the Chinese Ministry of Health stated on 20 February that the atypical pneumonia outbreak in Guangdong was probably caused by *Chlamydia pneumoniae*.

Days later, a doctor who had treated patients with the disease in Guangdong booked into a Hong Kong hotel for a family reunion. In the days until he himself succumbed to the disease in a Hong Kong hospital, he unwittingly infected 2 family members, 10 other hotel guests, and 4 health care staff. He thus became the epicenter for the international spread of the illness: Traveling hotel guests infected by him brought the disease within days to Vietnam, Singapore, Canada, Ireland, the USA and, indirectly, Germany.

On 12 March 2003, WHO issued a 'global alert' about cases of atypical pneumonia spreading to hospital staff. The alert had been raised by a WHO doctor working in Vietnam, Dr. Carlo Urbani, who recognized this was a novel infectious disease with an enormous potential for nosocomial transmission; tragically, he himself became infected and later succumbed to it. An 'emergency travel advisory' followed on 15 March 2003, reporting the worldwide spread of what was for the first time termed severe acute respiratory syndrome (SARS).

Identifying the Etiological Agent

In an unprecedented move, WHO initiated a collaborative multicenter research project to identify the causative agent of SARS. Avian influenza was quickly ruled out. Several laboratories diagnosed active infections with Chlamydia or paramyxoviruses in some – but far from all – patients suffering from SARS. However, there was good evidence that neither of these were plausible etiological agents for the novel infectious disease.

The network comprised laboratories with access to SARS patient samples and those with particular expertise on emerging or respiratory viruses. For several weeks, a spirit of cooperation rather than competition prevailed. Samples were exchanged and results and findings shared continuously via daily telephone conferences and a password-protected website.

Within weeks, groups in Hong Kong, Germany, Canada, and the United States of America found a hitherto unknown member of the coronavirus family in SARS patients. This was achieved through independent studies but certainly benefited greatly from the real-time sharing of interim results. Although different approaches were employed, including cell culture, electron microscopy,

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and molecular techniques, sequencing data showed all laboratories had identified the same coronavirus, previously unknown to human and veterinary virology (Figure 1).

It was shown that SARS patients seroconverted against this virus in the course of their illness; healthy, unexposed control individuals lacked antibody reactivity. However, it remained to be proven that this novel coronavirus was indeed the etiological agent for SARS rather than an 'innocent bystander' newly discovered by thorough studies.

After experimental infection of macaques with the newly isolated agent was shown to cause a SARS-like illness, and subsequent reisolation of the agent, all of Koch's postulates had been fulfilled. On 16 April 2003, WHO officially announced that the provisionally termed SARS-associated coronavirus (SARS-CoV) was the causative agent of SARS.

Based on this breakthrough, tests for the detection of viral sequences and specific antibodies were quickly developed and made available to affected countries. In addition, numerous scientists embarked on programmes to develop vaccines and drugs or antibodies for prophylactic or therapeutic use.

Controlling the Outbreak

Within a few months, the SARS outbreak was brought under control. On 5 July 2003, WHO declared that the last chain of person-to-person transmission had been interrupted. Measures including source isolation of patients – who only became infectious after onset of clinical symptoms – strict infection control in health care facilities, timely identification and quarantining of exposed contacts, and perhaps also measures to increase social distance, such as travel warnings and screening of travelers, had led to this remarkable and remarkably rapid success.

Thorough and consistent implementation of these measures eventually brought an end to the SARS outbreak even in the worst affected areas. In the meantime, however, several areas – different Chinese provinces other than Guangdong, most prominently the capital, Beijing, but also Toronto in Canada, and Taiwan – paid a high price for not implementing adequate countermeasures in a timely fashion. Typically, a so-called 'superspreader,' that is, a highly contagious SARS patient, would seek treatment at a poorly prepared facility, and by the time the danger was realized, scores of staff and patients had become infected and themselves become sources of spread.

Interestingly, despite the rapid identification of the agent and laboratory tests becoming available almost immediately, these formidable achievements did not contribute much to the containment of the outbreak. Instead, it was the prudent and thorough use of 'old-fashioned' measures such as isolation and quarantine that proved to be the key to success. Identification of suspected cases was based on clinical and epidemiological criteria: high fever (>38°C) plus symptoms of respiratory tract infection plus an exposure history, the details of which depended on each location's SARS status at the time. An additional positive SARS-CoV test result or radiological or pathological evidence of pneumonia or respiratory distress syndrome would make it a probable case.

The final case count from 1 November 2002 until 31 July 2003 is 8096, with 774 deaths. Since mid-2003, SARS has reappeared on four occasions. Three involved laboratory-acquired infections, which demonstrates the dangers of breaching biosafety procedures and the risks of subsequent further spread in the community by secondary transmission outside of the laboratory. The fourth SARS outbreak was due to reintroduction from the reservoir.

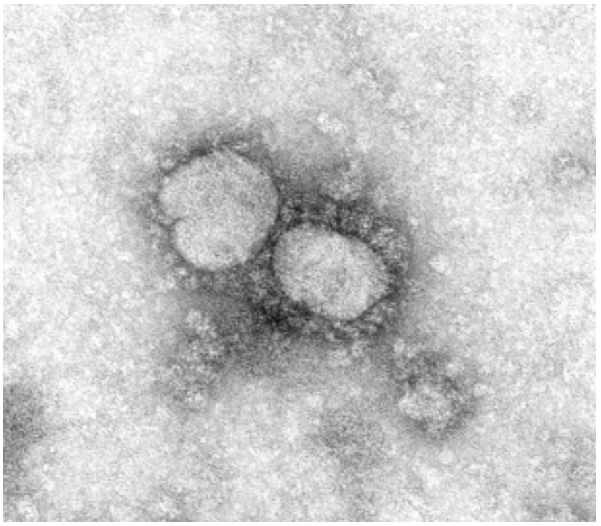

Figure 1 Electron microscopy image of SARS-CoV particle from infected cell culture supernatant after ultracentrifugation, 2% formalin fixation, and negative staining with uranyl acetate (photograph by H. R. Gelderblom, Robert Koch Institute, Berlin, Germany). Reproduced with permission from Berger A, Drosten Ch., Doerr HW, Stürmer M, and Preiser W (2004) Severe acute respiratory syndrome (SARS) - paradigm of an emerging viral infection. *Journal of Clinical Virology* 29: 13–22.

To minimize the risk of reemergence, WHO has issued guidelines for the surveillance of possible SARS cases. Risk categories to guide adequate national surveillance strategies to guard against the possible (re-)emergence of SARS are emergence from wildlife or other animal reservoirs, emergence or introduction from laboratories or via international travel, or low risk of SARS-CoV emergence or introduction.

WHO also urges all countries to conduct an inventory of all laboratories working with or storing SARS-CoV and to ensure strict enforcement of biosafety procedures.

Finding Its Source

Before SARS, only two coronaviruses (HCoV-229 E and HCoV-OC43) were known to infect humans. Because they both cause only relatively minor disease and are difficult to propagate in the laboratory, they received relatively little attention by diagnostic and research laboratories. In contrast, several coronaviruses were recognized as animal pathogens, infecting pigs, dogs, rabbits, cats, mice, rats, turkeys and chicken. Some of these had for some time played important roles in veterinary medicine.

It was obvious that the majority of human SARS cases were acquired through transmission from other SARS sufferers (which proved key to its eventual control). However, it seemed highly unlikely that this was a previously existing disease entity that was only then being recognized; its propensity to cause nosocomial outbreaks, often in hospital settings, would not have been overlooked for long.

The very first SARS cases were identified retrospectively in various localities in Guangdong Province. The first of these early cases occurred in Foshan in November 2002, and several more over the following weeks in nearby places. Interest soon focused on these early index cases: was there any characteristic these patients had in common that could point to a source of their SARS-CoV infection?

There was indeed; many of these early index patients either worked in kitchens or at markets or lived nearby where they were constantly exposed to a multitude of species of domestic and wild animals that were being traded, kept in captivity, and finally slaughtered and prepared for consumption.

This provided the impetus for studying animals being sold at Guangdong markets. Infection with coronaviruses closely related to SARS-CoV was identified in different species, most commonly in the masked palm civet (*Paguma larvata*) but also in the Chinese ferret badger (*Melogale moschata*) and the raccoon dog (*Nyctereutes procyonoides*). A further, small SARS outbreak occurred again in Guangdong in late 2003/early 2004; molecular analysis of virus isolates from human cases and animals sampled at the same place and time confirmed that this was zoonotically acquired from *Paguma larvata*.

However, further investigations revealed that this widely consumed species is most likely not the animal reservoir, as most populations studied were uninfected. Later research identified a multitude of coronaviruses in different species of bats in Asia and elsewhere, among them what is probably the progenitor of SARS-CoV.

Studies by different groups demonstrate that SARS was the result of spillover from a wildlife reservoir – most likely bats – into an intermediate host (or hosts; most importantly *Paguma larvata*) and from there to the human population. Rapid viral evolution was demonstrated and most likely was the pivotal factor that allowed SARS-CoV to rapidly adapt to nonreservoir species. **Table 1** shows the distribution of several different coronaviruses in humans and animals and their classification into different groups.

Laboratory Testing

Disease caused by SARS-CoV may present with rather nonspecific clinical signs and symptoms. The differential diagnosis is therefore wide and may include various common respiratory pathogens, including influenza, parainfluenza, and respiratory syncytial viruses (RSV)

The laboratory diagnosis of SARS remains a challenge; in fact, despite the rapid identification of SARS-CoV as the etiological agent, testing contributed little to the successful control of the 2003 outbreak. Insufficient test specificity on occasions caused false-positive results, leading to considerable confusion. In many viral diseases, virus shedding is greatest during the early symptomatic phase, that is, around, and immediately following the onset of symptoms. Unfortunately, virus excretion is comparatively low during the initial phase of SARS. It peaks in respiratory specimens and in stools at around day 10 after the onset of the clinical illness.

In addition, there are currently no laboratory tests available to reliably diagnose SARS in the first few days of illness. The highest test sensitivity is achieved with bronchoalveolar lavage fluid or lung biopsy tissue at the onset of illness. Because of the invasiveness of such procedures and the associated risk of transmission, nasopharyngeal aspirates and throat washings, taken with respiratory precautions and preserved in viral transport medium, remain the most important diagnostic specimens.

Most commonly, viral genome detection, usually by reverse transcriptase-polymerase chain reaction (RT-PCR), is used diagnostically. Nucleic acid amplification tests have been designed targeting the Orf1b or nucleoprotein genes; it has not been clearly proven in clinical studies that they are superior.

Real-time RT-PCR of nasopharyngeal aspirates is the most sensitive and rapid method. Furthermore, the determination of viral load in nasopharyngeal specimens or serum has been shown to be of clinical value, as it is an important prognostic factor.

To avoid false-positive results, WHO stipulates that the following should be tested: At least two different clinical specimen types (e.g., nasopharyngeal aspirate and stool), or the same type of clinical specimen but collected on at least two occasions during the

Table 1 Coronaviruses in humans and animals and their phylogenetic relation to distinct groups within the virus family

Group	*Virus*		*Types of infection*
1a	TGEV	porcine transmissible gastroenteritis virus	Enteric
	PRCoV	porcine respiratory coronavirus	Respiratory
	PEDV	porcine epidemic diarrhea virus	Enteric
	FIPV	feline infectious peritonitis virus	Systemic, peritonitis
	FeCoV	feline enteric coronavirus	Enteric
	CCoV	canine coronavirus	Enteric
1b	Bat CoV	bat coronavirus	Asymptomatic
	HCoV-NL63	human coronavirus NL63	Respiratory
	HCoV-229E	human coronavirus strain 229E	Respiratory
2a	MHV	murine hepatitis virus	Respiratory, enteric, hepatitis, neurologic
	SDAV	rat sialodacryoadenitis virus	Neurologic
	RCoV	rat coronavirus	Respiratory
	HEV	porcine hemagglutinating	Respiratory, enteric, neurologic
	BCoV	encephalitis virus	Enteric
	HCoV-OC43	bovine coronavirus	Respiratory
		human coronavirus strain OC43	
2b	Bat SARS-like CoV	bat SARS coronavirus	Asymptomatic
	Civet SARS-like CoV	civet SARS coronavirus	?
	Human SARS CoV	human SARS coronavirus	Respiratory, enteric
2c	Bat CoV HKU4	bat coronavirus	Asymptomatic
	Bat CoV HKU5	bat coronavirus	Asymptomatic
2d	Bat CoV HKU9	bat coronavirus	Asymptomatic
3	IBV	avian infectious bronchitis virus	Respiratory, hepatitis, urologic

Source: Cheng VC, Lau SK, Woo PC, and Yuen KY (2007) Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clinical Microbiology Reviews* 20: 660–694.

course of the illness (e.g., sequential nasopharyngeal aspirates), or the same original clinical sample but two different assays or by repeating the same assay but using a new RNA extract for each test.

SARS-CoV is cultivable on Vero and Caco2 cells not only from respiratory materials but also from fecal samples (**Figure 2**). Once isolated, the virus must be identified as SARS-CoV using further tests. Cell culture is a very demanding test, but currently (with the exception of animal trials) the only means to show the existence of a live virus.

Antigen detection in respiratory and fecal specimens using enzyme immunoassay (EIA) is generally less sensitive than RT-PCR. However, antigen detection in serum specimens with monoclonal antibodies or monospecific polyclonal antibody against the viral N protein was found to be a sensitive and specific test for the diagnosis of SARS. As serum antibody levels start to rise from day 7 after onset of illness, the sensitivity of the serum antigen assay progressively decreased to 0% at day 21.

Antibody testing allows the indirect diagnosis of SARS-CoV infection and is unsuitable during the acute illness. Positive antibody test results indicate previous infection with SARS-CoV. Seroconversion from negative to positive or a fourfold rise in the antibody titer from acute to convalescent serum indicates a recent infection. A negative antibody test result later than 21 days after the onset of illness is likely to indicate that no infection with SARS-CoV has taken place.

Virus-specific serum IgG, IgM, and IgA antibodies against SARS-CoV appear at around the same time, between days 5 and 17 after the onset of symptoms. Antibody testing is therefore generally not useful during the first week of illness. For antibody testing, the indirect immunofluorescent antibody test is more commonly performed than the neutralizing antibody test in cell cultures that

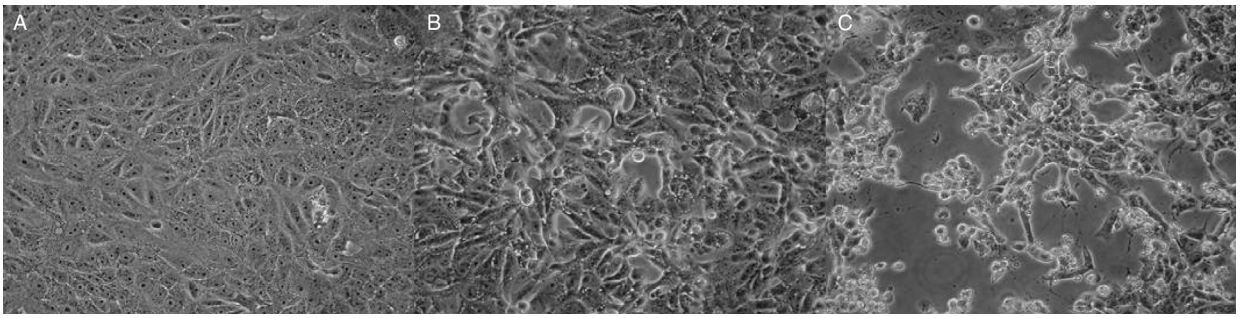

Figure 2 Cytopathic effect (CPE) caused by SARS-CoV in Vero cell culture A: 0 h, B: 24 h, and C: 48 h after inoculation (photographs by G. Bauer, Institute of Medical Virology, Frankfurt, Germany). Reproduced with permission from Berger A, Drosten Ch., Doerr HW, Stürmer M, and Preiser W (2004) Severe acute respiratory syndrome (SARS) – paradigm of an emerging viral infection. *Journal of Clinical Virology* 29: 13–22.

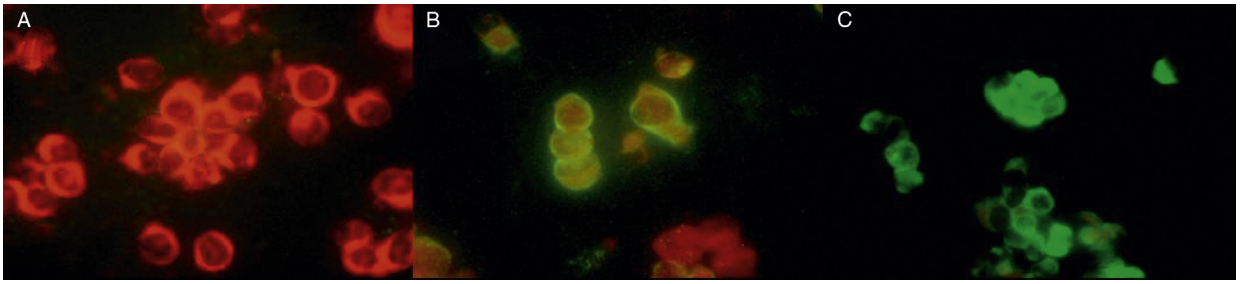

Figure 3 Seroconversion during the course of SARS demonstrated by immune fluorescence antibody assay using SARS-CoV-infected Vero cells. Follow-up of serum samples diluted 1:50. A: 9 days, B: 12 days, and C: 14 days after hospitalization (photographs by G. Bauer, Institute of Medical Virology, Frankfurt, Germany). Reproduced with permission from Berger A, Drosten Ch., Doerr HW, Stürmer M, and Preiser W (2004) Severe acute respiratory syndrome (SARS) – paradigm of an emerging viral infection. *Journal of Clinical Virology* 29: 13–22.

again requires a biosafety level 3 laboratory (**Figure 3**). A recombinant nucleocapsid EIA may be used as a rapid screening test and possesses a higher sensitivity, with detection as early as day 5 after onset of illness. Single low-titer positive antibody results can be due to cross-reactivity with other human coronaviruses and require confirmation by more specific Western blotting or neutralization assays. WHO regards seroconversion or an at least fourfold rise in antibody titer between an acute and a convalescent serum as proof of infection.

The updated WHO Guidelines for the Global Surveillance of SARS of October 2004 replace all previous WHO guidance on SARS surveillance and response. One key recommendation is that independent of the test used, WHO strongly recommends that during the interepidemic period all countries seek verification of laboratory-confirmed cases of SARS ('preliminary positive' cases), preferably by an external laboratory that is part of the WHO SARS International Reference and Verification Laboratory Network (**Figure 4**).

Clinical Symptoms

Human SARS-CoV are no longer circulating in the human population, nevertheless the virus is still present in the animal reservoir and virological laboratories and can reemerge anytime. There is no single test that can be used to diagnose SARS with a reasonable degree of accuracy. Diagnosis, therefore, continues to rely on the clinical examination, supported by case definitions that include the risk assessment according to the 2004 updated WHO guidelines (**Tables 2 and 3**). The initial symptoms of SARS are nonspecific, complicating the differential diagnosis. The mean incubation period is 5 days with the range of 2–10 days although there are isolated reports of longer incubation periods. Unlike influenza virus, where the patients are most infectious in the first 2 days of illness, transmission from symptomatic SARS patients usually occurred on or after the fifth day of onset of disease, which is in line with the rising viral load in nasopharyngeal secretions that peaked at around day 10. There have been no reports of transmission occurring before the onset of symptoms. The typical clinical presentation of SARS is that of viral pneumonia with rapid respiratory deterioration. Patients initially develop influenza-like prodromal symptoms. Fever, malaise, myalgia, headache, rigors, and nonproductive cough are the major presenting symptoms, whereas rhinorrhea and sore throat are less frequently seen. Clinical deterioration, often accompanied by watery diarrhea, commonly occurs 1 week after the onset of illness. Although history of fever is the most frequently reported symptom, it may be absent on initial measurement. Severe cases develop rapidly progressing respiratory distress and oxygen desaturation with approximately 20% requiring intensive care. Chest radiographs typically show ground-glass opacities and focal consolidations, especially in the periphery and subpleural regions of the lower zones. Progressive involvement of both lungs is not uncommon. Features during the later stages have sometimes included spontaneous pneumothorax, pneumomediastinum, subpleural fibrosis and cystic changes. Nosocomial transmission of SARS-CoV has been a striking feature of the SARS outbreak. The majority of the cases have occurred in adults. Children are less commonly affected than adults and usually have a milder illness. The overall mortality rate was approximately 10%. Age and the presence of comorbidities are poor prognostic indicators.

Treatment and Prevention

Although the SARS outbreak was still ongoing during the first half of 2003, significant funding was made available for SARS-related research.

Immunomodulators (i.e., corticosteroids, intravenous immunoglobulins, thymosin, and anti-TNF) were empirically used for the treatment of SARS during the initial epidemic. The correlation between viral load and clinical outcome suggests that suppression of viral replication by effective antiviral drugs should be the key to preventing morbidity and mortality. Numerous potential antiviral agents have been identified using different approaches. *In vitro* susceptibility test results demonstrate that IFN-alpha and IFN-beta have some potential activity. Ribavirin has good activity when tested in human Caco-2 cells despite its lack of activity in Vero cells.

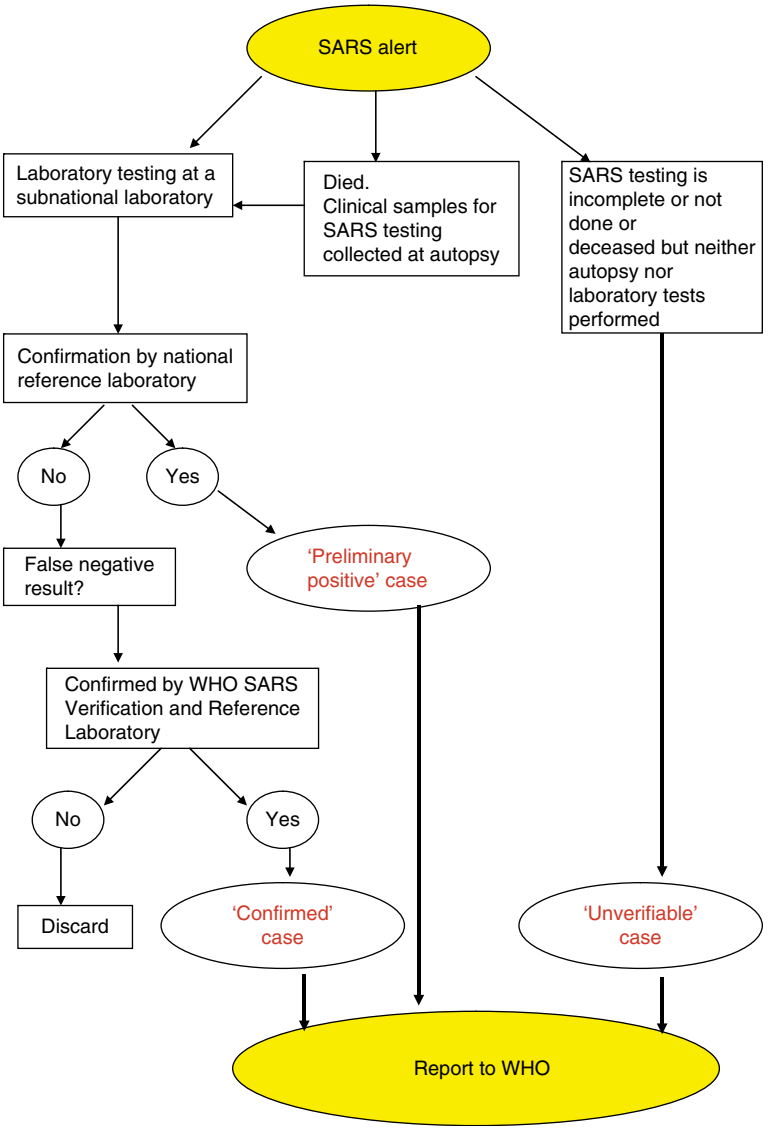

Figure 4 SARS testing and report algorithm in the interepidemic period according to the WHO guidelines (October 2004).

Table 2 Risk categories for the emergence of SARS

Emergence of SARS-CoV-like viruses from wildlife or other animal reservoirs
– Countries/areas identified as source(s) of the epidemic in 2002–03 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
– Countries/areas at potentially higher risk of SARS-CoV emergence or introduction due to the presence of laboratories in which SARS-CoV or SARS-CoV-like viruses are being studied or in which clinical specimens infected with SARS-CoV are being processed or stored.
OR
– Countries/areas with entry of large numbers of persons from areas in which wildlife or other animal reservoirs of SARS-CoV-like viruses are found.
Low risk of SARS-CoV emergence or introduction
– Countries/areas that never reported cases or reported only imported cases during the 2002–03 epidemic, and that do not conduct research using live SARS-CoV-like viruses or store clinical samples from SARS cases.

Source: Reproduced with permission from WHO, updated recommendations, October 2004.

The viral proteases are important targets for the development of antiviral drugs. Protease inhibitors like nelfinavir, glycyrrhizin, chloroquine, and many others as well as many herbal formulations have been found to possess some antiviral activity against SARS-CoV *in vitro*. In addition, the use of nitric oxide (S-nitro-N-acetylpenicillamine) inhalation as an experimental form of rescue therapy for SARS appeared to have inhibitory activity against SARS-CoV. Screening of chemical libraries has identified several inhibitors of the viral protease and helicase. Identification of angiotensin-converting enzyme 2 (ACE2) as an obligatory cellular receptor for

Table 3 Clinical evidence for SARS for surveillance purposes

A clinical case of SARS is an individual with
1. A history of fever, or documented fever $\geq$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.

Source: Reproduced with permission from WHO, updated recommendations, October 2004.

SARS-CoV contributed to understanding of the SARS-CoV entry process, and helped to characterize two targets of antiviral therapeutics: the SARS-CoV spike protein and ACE2. However, most of the chemicals or approaches have not been evaluated in human or animal models.

Various approaches toward producing a vaccine against SARS have been pursued, including the use of inactivated SARS-CoV, plasmid DNA, and adenovirus vectors. One obvious problem any vaccine would face is whom it should be given to, in the absence of SARS-CoV transmission. However, waiting until a renewed outbreak occurs before commencing vaccination means that precious weeks would be lost until individuals at risk become immune.

The administration of preformed antibodies (obtained from human or animal donors or, more recently, produced *in vitro*) is effective in preventing a number of different infections, such as hepatitis B, varicella, and RSV. Similarly, it could be shown that neutralizing antibodies against SARS-CoV can protect experimental animals from infection.

Using screening of a large naive antibody library by antibody phage display technology, neutralizing antibodies were identified and produced that were protective *in vitro*. There was no evidence of enhancement of SARS-CoV infection by subneutralizing concentrations of these antibodies, and immune escape mutants were not generated.

In theory, this could be an ideal tool: If sufficient stocks of such human monoclonal antibodies could be procured, they would be ready for use when and wherever SARS reemerges. One could then passively immunize anyone in contact with the source or patients, affording immediate protection.

Résumé and Lessons to be Learnt from SARS

In summary, SARS was a novel severe infectious disease that presumably originated in Guangdong in southern China. Large-scale wildlife trade and consumption favored the emergence of this zoonosis from a hitherto unrecognized animal reservoir. After its zoonotic origins, the new agent quickly spread within the human population, being transmitted mostly via the respiratory route through close human-to-human contact.

SARS was rapidly disseminated via the metropolis Hong Kong through international air travel. Its important potential for nosocomial transmission in the community and in hospitals was soon recognized and allowed for appropriate measures to be instituted in most places.

There was an unprecedented rapid gain of knowledge through global networking and international collaboration, led by WHO. Unfortunately it took some major outbreaks, some of them affecting industrialized countries with modern health care systems, until the first SARS epidemic was controlled. Thus in the end rapid success was achieved through 'traditional' sanitary measures, mainly rapid identification of suspect cases and isolation of the diseased.

Fortunately, SARS-CoV has – at least so far – not established itself permanently in the human population. Its relatively low transmissibility (with the exception of 'superspreaders') led to a low basic reproduction number R_0; together with the fact that infected individuals only become infectious themselves once they have developed clinical disease, this made 'traditional' public health measures very effective.

Is the fact that the first pandemic of the twenty-first century was quickly contained reason to take comfort in the knowledge that the history of humankind has reached a phase in which biomedical sciences and information technology are able to deal with such threats? Probably not.

First, the rapid success was remarkable. Unfortunately, though, this does not reflect preparedness. In 1998, Donald Burke proposed the following criteria for identifying virus families with a high pandemic risk: (1) those that had caused pandemics in human populations in the recent past; (2) those with the proven ability to cause larger epizootics; and (3) those with an intrinsic propensity to rapidly undergo evolution on the basis of high mutation rate or genome organization favoring recombination ('intrinsic evolvability').

Interestingly, even before the SARS outbreak (which obviously fulfills the first criterion), the coronavirus family should clearly have been regarded as high risk: Starting in the late 1970s, the porcine epidemic diarrhea coronavirus (PEDV) caused a severe swine epizootic in Europe and Asia (second criterion). The high evolvability of the coronavirus family had also been demonstrated: the porcine respiratory coronavirus (PRCV) evolved through a deletion mutation in the S gene from the transmissible gastroenteritis virus (TGEV); the mutant has a different tissue tropism and is less virulent.

Second, infectious disease emergence from zoonotic sources was a well-recognized threat long before SARS. Nevertheless, it took another – fortunately minor – SARS outbreak before decisive steps were taken to control at least the trade in the directly implicated *Paguma larvata* in southern China.

Starting shortly after SARS had been controlled, another agent with pandemic potential has caused an ongoing epizootic of unprecedented proportions: highly pathogenic influenza A (H5N1) virus. Transmission to humans occurs almost exclusively through close contact with infected – and sick – poultry. Despite the possibility that this avian influenza virus will become fully 'humanized' and trigger the next influenza pandemic, even activities recognized as high risk, such as 'wet markets,' have mostly not been curtailed.

Finally, the lessons from SARS – particularly the experiences of Beijing, Toronto, and Taiwan that suffered devastating SARS outbreaks during the later phase of the outbreak – emphasize over and over again the enormous importance of open and timely communication. At times, this may mean admitting to problems that (at least initially) reflect negatively on the country or territory concerned. In the medium to long term, however, such openness is the only way to prevent consequences that would be much worse. Although this was widely accepted in the wake of the SARS experience and has had a strong influence on the new International Health Regulations that entered into force in June 2007, the information policies of some countries during the H5N1 epizootic unfortunately do not attest to this at all.

Notwithstanding its grave consequences in humanitarian, political, and economic terms, SARS should serve as an example what can be achieved through international cooperation, modern science, and rigorous use of 'traditional' approaches. Even if prudent precautions were suddenly adopted, SARS will certainly not have been the last highly pathogenic novel infectious agent that crosses the species barrier into the human population.

Although bats must be very high on the list of 'culprits' for emerging viral diseases, having been identified as reservoir hosts for a number of emerging viruses, there is no reason why other groups of animals should not figure as prominently in future. The mechanisms behind emergence have been studied. These may be linked to the agent, the new host species (i.e., human beings and in certain cases also the intermediate hosts) or to the connection between those. Many of the factors and determinants of disease emergence are related to human activities.

Although this has accompanied humankind throughout history, and in fact may have helped shape human history, the speed and the extent of human-induced changes has accelerated markedly in recent times. Although in the case of SARS people were lucky in the end, this may be quite different next time round. It will be important to improve understanding of emergence to minimize the risks of what is a natural phenomenon but much aggravated by human behavior.

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