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Public health

A multicentre collaboration to investigate the cause of severe acute respiratory syndrome

World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome (SARS) Diagnosis

Severe acute respiratory syndrome is a new disease in human beings, first recognised in late February, 2003, in Hanoi, Vietnam. The severity of the disease, combined with its rapid spread along international air-travel routes, prompted WHO to set up a network of scientists from 11 laboratories around the world to try to identify the causal agent and develop a diagnostic test. The network unites laboratories with different methods and capacities to rapidly fulfil all postulates for establishing a virus as the cause of a disease. Results are shared in real time via a secure website, on which microscopy pictures, protocols for testing, and PCR primer sequences are also posted. Findings are discussed in daily teleconferences. Progress is further facilitated through sharing between laboratories of samples and test materials. The network has identified a new coronavirus, consistently detected in samples of SARS patients from several countries, and conclusively named it as the causative agent of SARS; the strain is unlike any other known member of the genus *Coronavirus*. Three diagnostic tests are now available, but all have limitations.

Severe acute respiratory syndrome (SARS) is a new infectious disease in human beings, first recognised in late February, 2003, in Hanoi, Vietnam.[1] The disease has since spread rapidly around the world, with cases currently reported from 25 countries on five continents.[2] The disease has features that give rise to great concern, including poorly understood epidemiology and pathogenesis, absence of definitive diagnostic tests and specific treatments, an incubation period that allows rapid spread along international air-travel routes, an incompletely understood pattern of nosocomial transmission, mounting evidence that certain source cases make a special contribution to rapid spread of infection, a disturbing concentration of cases in previously healthy hospital staff, an initial case fatality of 3–4%, and an initially unclear causal agent.[3–7]

In developing emergency plans to contain the outbreak and prevent further international spread, WHO worked on the principle that the unidentified causal agent could lead to an exceptionally dangerous outbreak. Rapid development of scientific knowledge would be needed to reduce opportunities for SARS to establish endemicity. Identification of the causal agent and the development of a diagnostic test were given paramount importance in the overall containment strategy.[8,9] In the view of WHO epidemiologists and virologists, as long as the causal agent remained unknown, and no specific interventions against the agent were available, specialists in infectious disease control would be forced to resort to the control tools of isolation and quarantine.

Members of the WHO Global Influenza Surveillance Network (112 national influenza centres in 83 countries and four WHO collaborating centres) had already increased their vigilance for a novel influenza virus after reports received in early February, 2003, from Guangdong Province, China, of 305 cases and five deaths caused by atypical pneumonia of unknown cause.[10] Laboratory analyses for influenza viruses were reported as negative.[11] On Feb 19, WHO and its influenza network activated emergency pandemic response plans after receiving a report from the Department of Health in Hong Kong confirming the presence of avian influenza virus A, subtype H5N1, in a boy aged 9 years whose family had travelled to Fujian Province, China, in January.[12]

Laboratories in the influenza network ruled out all influenza virus strains and other known causes of pneumonia from samples taken in Hanoi, Singapore, and Hong Kong. SARS looked increasingly like a new disease. Epidemiological evidence suggested person-to-person transmission as the major route.[13] If the causative agent maintained its pathogenicity and transmissibility, SARS could become the first severe new disease of the 21st century, with global epidemic potential.

With the exception of AIDS, most new diseases that emerged in the past two decades or that established endemicity in new geographical areas have features that limit their capacity to pose a major threat to international public health. For example, avian influenza, Nipah virus, Hendra virus, and hanta virus did not establish efficient human-to-human transmission.[14–18] Other diseases, such as *Escherichia coli* O157:H7 and variant Creutzfeldt-Jakob disease, depend on food as a vehicle of transmission.[19,20] Diseases such as West Nile fever and Rift Valley fever that have spread to new geographical areas require a vector as part of the transmission cycle and are associated with low mortality, although they frequently occur in high-risk groups, such as the elderly, the immunocompromised, or people with comorbidity.[21,22] Still others, such as *Neisseria meningitidis* W135, and the Ebola, Marburg, and Crimean-Congo haemorrhagic fevers, have strong geographical foci.[23,24] Although outbreaks of Ebola haemorrhagic fever have been associated with case fatalities of 53% in Uganda, up to 88% in Democratic Republic of the Congo, person-to-person transmission requires close physical exposure to infected blood and other bodily fluids.[25,26] Moreover, patients who are infected with Ebola virus during the period of high infectivity are visibly very ill and too unwell to travel.[27]

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Response to the outbreak

On March 15, 2003, the day WHO issued emergency travel advice in response to SARS, it set up a network of scientists from 11 leading laboratories around the world to expedite identification of the causative agent of SARS and rapidly develop a robust and reliable diagnostic test. The network was modelled partly on the global influenza network. However, the urgency of what was increasingly being seen as a public-health emergency called for rapid adaptation to meet unique needs and ensure virtual collaboration. Laboratories were approached by telephone throughout the weekend of March 15–16, 2003. The objective was to secure the participation of laboratories with outstanding experience in the detection of a wide range of viruses and other micro-organisms, a history of collaboration in international investigations coordinated by WHO, access to SARS samples, and capacity to fulfil the six criteria of Koch's postulates required to establish a virus as the cause of a disease.[28]

All laboratories asked to join agreed to do so and to work according to a set of rules on confidentiality of data. These rules specified that data and information shared among the members of the research project would be used only to advance the project in a collaborative way. Specific scientific data could be shared outside the network with the approval of the laboratory from which the data or other information originated. To avoid discrepancies between official national case notification and laboratory information, data on cases and samples were treated separately from epidemiological information. Such open sharing among academic competitors required trust and willingness to work together.

The collaboration is continued through daily teleconferences and use of a secure WHO website to post electron microscopy pictures of candidate viruses, protocols for testing, phylogenetic trees, PCR primer sequences, and results of various diagnostic tests. These arrangements allow the simultaneous analyses of samples from the same patient in several laboratories with different approaches, and real-time sharing of results. Laboratories in areas with SARS cases, including Canada, Germany, France, Hong Kong, the UK, the USA, and Singapore, regularly exchange samples with each other and despatch materials to laboratories in the Netherlands and Japan, which were initially spared SARS cases. In early April, laboratories from Beijing and Guangdong Province, China, joined the network.

Outcomes of testing

On March 17, 2003, the network laboratories reported on available samples, reviewed past and planned intervention strategies, and catalogued available laboratory experience and capacities. Initially, bacterial, viral, rickettsia, and chlamydia pathogens primarily associated with respiratory disease, and pathogens for which respiratory symptoms might be secondary, were targeted for detection. Methods used include light and electron microscopy, immunohistochemistry, animal inoculation, bacterial and cell-culture isolation techniques, serology, and PCR analyses.

On March 18, participating laboratories in Germany reported paramyxovirus of Singaporean origin on electron microscopy isolated in respiratory samples from a SARS patient in Frankfurt and directly linked to Singapore's index case. Simultaneously, the Chinese University of Hong Kong shared equivocal results from generic and more specific human metapneumovirus PCR primers in samples from patients who had developed SARS after contact with Hong Kong's index case. PCR primers were tested in three additional patients and the findings were positive for human metapneumovirus. Sequences of all primers were shared electronically on the network's secure website.

The next day, the Singapore laboratory noted a pleiomorphic virus on electron microscopy in respiratory samples from SARS patients. The Rotterdam laboratory, where human metapneumovirus was first discovered, sent a car to Frankfurt overnight to obtain samples from SARS patients.[29] The Japanese laboratory reported negative results of PCR for bronchoalveolar lavage and of serum antibody obtained from the index case in Hanoi. The laboratory found no evidence for influenza A and B viruses, respiratory syncytial virus, parainfluenza viruses, human metapneumovirus, Nipah virus, Hendra virus, hanta virus, and Lassa, Ebola, Marburg, and Crimean-Congo haemorrhagic fever viruses.

On March 20, human metapneumovirus primers were tested in four additional laboratories. The Chinese University of Hong Kong found paramyxovirus-like particles in respiratory samples. The Rotterdam laboratory detected no human metapneumovirus in samples from Frankfurt. The Rotterdam laboratory sent test kits for human metapneumovirus to Singapore and Hong Kong laboratories and shared, via the website, the phylogenetic tree of the isolated paramyxovirus. The laboratory in Canada shipped convalescent sera to Rotterdam for further testing of isolates. During the daily conference call, the Singapore laboratory reported round pleomorphic structures in samples, and scientists in Germany and Hong Kong described similar findings.

During the March 21 teleconference, the laboratory in Rotterdam established that all respiratory samples from the cluster tested in Germany (Singapore patients) were negative for human metapneumovirus on PCR. The laboratory also isolated an agent that caused a cytopathogenic effect in Vero and monkey kidney cell lines. Laboratories in the UK also detected H3N2 influenza virus in two suspected SARS cases. The laboratory in Canada detected human metapneumovirus by PCR in samples from two patients and provided an electron-microscopy picture of small virus particles (around 20 nm) seen in bronchoalveolar lavage. At the same time, a German laboratory isolated the agent in Vero cells and in the murine cell line L929. The laboratories also ruled out the presence of respiratory pathogens, such as influenza A and B viruses, respiratory syncytial virus, parainfluenza viruses type 1, 2, and 3, adenovirus, rhinovirus, enterovirus, human metapneumovirus, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

Later in the day, the scientists at Hong Kong University sent an e-mail indicating that they had isolated an agent from two patients with SARS. The agent, isolated in continuous rhesus monkey kidney cells, produced a cytopathogenic effect, indicating growth of a virus. In addition, in an immunofluorescence assay of virus-infected cells, done in a blinded trial, sera from SARS patients had rising antibody titres to the new virus isolate. By contrast, sera from blood donors taken long before the disease emerged in Hong Kong had no antibody to this virus. Furthermore, virus-like particles in the cytoplasm and at the cell membrane were seen in thin electron microscopic sections from infected cells. These findings proved to be the turning point in the search for the SARS causative agent.

On March 22, the laboratory in the USA isolated a virus that caused a cytopathogenic effect in Vero E6 cells from a patient from Thailand, and showed the presence of coronavirus-like particles on electron microscopy (size

70–100 nm). In samples from the same patient, the US laboratory found positive PCR signals with primers for picornavirus, which was later identified as rhinovirus. The Government Virus Unit in Hong Kong and the US laboratory sent electron microscopy pictures of the coronavirus-like particles to be posted on the website simoultaneously. Laboratories in Canada, Paris, and at the Chinese University detected paramyxovirus, human metapneumovirus, or both on electron microscopy or PCR in various samples. The Singapore laboratory detected human metapneumovirus with a test kit supplied by the Rotterdam scientists. The Government Virus Unit in Hong Kong provided the laboratory in the USA with convalescent sera. The laboratory in Canada found more particles of 20 nm size on electron microscopy and posted the phylogenetic tree of human metapneumovirus sequences on the secure website.

On March 23, the laboratory in the USA confirmed the classification as a coronavirus based on a coronavirus-like sequence of the PCR-amplified product, and posted initial primers for amplification on the website. The Government Virus Unit in Hong Kong tested in-house coronavirus primers and found coronavirus RNA in two of eight samples. The USA laboratory reported the presence of coronavirus in postmortem kidney samples from Hong Kong. It also developed an immuno-fluorescence assay for detection of seroconversion. Trials in non-human primates were started by intratracheal infection with nasopharyngeal swabs taken in Singapore and Hong Kong. The laboratories in Paris and Canada found a coronavirus in respiratory samples on electron microscopy and PCR, respectively. Suckling mice and hamsters inoculated 3 days previously at the Pasteur unit in Lyon with samples from Frankfurt and Hanoi were described as still healthy and have remained so. Laboratories in Germany, Japan, and Singapore isolated a cytopathogenic-effect-causing agent in Vero cells. The laboratories in the UK detected with specific PCR four pneumovirus sequences in respiratory samples from probable and suspected cases consistent with human metapneumovirus.

From March 24 to 26, a coronavirus was detected on PCR and electron microscopy in more laboratories. Laboratories in Germany and Hong Kong developed and shared refined primers that detected the new coronavirus. In a German laboratory, PCR products were sequenced, two of which matched, at the protein level, the polymerase gene of known coronaviruses. Several laboratories reported coronavirus particles on electron microscopy in respiratory samples and faeces. Sequencing of the new coronavirus began at laboratories in Germany, Rotterdam, and Hong Kong. A German laboratory and the Hong Kong University laboratory posted on the website the first phylogenetic trees of what the group collectively had discovered: a new coronavirus.[30]

From March 27 to 31, Hong Kong University made available their virus isolate to members of the network. Monkey trials continued and the first coronavirus isolates were obtained. Hong Kong University and the US laboratory reported negative results for antibodies to the new coronavirus in large numbers of blood-donor serum samples. Virus, antibodies, and RNA on PCR were, however, consistently detected in increasing numbers of SARS patients in many of the network laboratories. The laboratory in Japan received samples from Singapore and Hong Kong and identified the new coronavirus, which was also confirmed by seroconversions. They also developed PCR primers and an immunofluorescence assay system for IgM. Hong Kong University reported that 27 of 27 paired sera from patients with clinically typical SARS showed rising titres of antibody to the new coronavirus, and detected RNA in faeces in five of ten SARS patients. The Government Virus Unit in Hong Kong reported consistently positive PCR for the new coronavirus in faeces from SARS patients between days 6 and 16 after onset of clinical signs. A laboratory in Germany found RNA of the new coronavirus in conjunctival liquid of one patient on the day of onset of clinical symptoms. Human metapneumovirus continued to be detected in samples from SARS cases in various countries, which suggests that SARS might be caused by co-infection with two viruses. Coronavirus-primers were used in various laboratories, resulting in an increasing number of positive samples. In parallel, human metapneumovirus was isolated and found on PCR in various samples from patients in Canada

From April 1 to 9, in the Netherlands laboratory, monkeys were infected with the new coronavirus, the human metapneumovirus, or both—first with coronavirus followed by metapneumovirus. Animals infected with the coronavirus alone developed full-blown disease. Animals infected with the human metapneumovirus developed only mild rhinitis. The monkeys infected with coronavirus and metapneumovirus did not develop more serious disease than monkeys infected with metapneumovirus alone. On the basis of these findings, the network scientists collectively agreed that the coronavirus alone can cause the symptoms of SARS seen in human beings. However, co-infection with other agents, including chlamydia and human metapneumovirus, could result in a more severe clinical course.

ELISA tests developed by the laboratory in the USA detected antibodies from day 20 after onset of clinical signs. The Hong Kong University laboratory reported, on indirect fluorescence, detection of antibodies (IgM) from day 10. Additional mice and hamster infection trials were started at the Pasteur unit in Lyon. In-vitro ribavirin efficacy trials began in Rotterdam and Germany, and the laboratory in Japan began human interferon efficacy trials. The Chinese laboratory in Beijing continued to report chlamydia in postmortem samples from SARS patients. The Chinese laboratory in Guangdong reported positive coronavirus findings by PCR in two samples.

Many laboratories have now isolated the new coronavirus in Vero cells. Serological evidence is mounting on the possibility of dual infection by coronavirus and human metapneumovirus in SARS patients. Sequencing of the new coronavirus continues in Germany, Rotterdam, Hong Kong, and the USA. Chlamydia pathogens have been found in samples from Germany. Laboratories in Japan, France, and Rotterdam, and the Government Virus Unit in Hong Kong have extended studies on the comparative performance of PCR primers. The laboratory from Canada has shared, via the website, a comprehensive report on coronavirus and human metapneumovirus findings in Canadian SARS patients. Up-dated phylogenetic trees and more sequencing information on the new coronavirus from the laboratories in the USA and Rotterdam have been posted. First inactivation experiments in Germany have revealed that the infectivity of the virus in serum is destroyed by incubation at 56°C for 30 min.

Reaction to results

On April 16, 1 month after the network began to function, participating laboratories collectively announced conclusive identification of the new coronavirus as the causative agent of SARS. The announcement was made

based on the results from the monkey studies done in the Netherlands laboratory. This virus was found in many SARS patients from several countries. The virus causes a cytopathogenic effect in two cell lines (Vero cells and fetal rhesus kidney cells). Electron microscopy of cell culture and respiratory samples from SARS patients show coronavirus-like particles. Immunofluorescent assays with serum from convalescent patients detect cells infected with the virus in cell culture. Reactivity with this new coronavirus could not be detected in serum from several hundreds of non-SARS individuals in the USA, Canada and Hong Kong. Generic coronavirus primers can detect the new coronavirus RNA in cell culture and in samples from SARS patients. Specific primers have been developed in several laboratories and are currently being compared for sensitivity. Hyperimmune sera against transmissible gastroenteritis virus, feline infectious peritonitis virus, and 229E human coronavirus react with the virus antigen in cell culture. Partial sequencing of the new coronavirus in several laboratories has confirmed its affiliation to the genus *Coronavirus* but shown dissimilarities with known members belonging to each of the three existing groups of this genus.

Three diagnostic tests are now available, but all have limitations. Since the ELISA detects antibodies reliably only from about day 20 after the onset of clinical symptoms, it cannot be used to detect cases before they potentially spread the infection to others. The second test, an immunofluorescence assay, detects antibodies reliably after day 10 of infection. Various versions of real-time and block-based PCR tests are currently being developed to improve their low sensitivity and reduce the number of false-negative test results. All existing tests, used individually or in combination, can only confirm the disease in suspected or probable SARS cases. More work is needed before reliable, easy-to-use and sensitive tests become available in all countries. Work towards this objective is continuing and is proceeding at a rapid pace. Each laboratory has contributed substantially to the rapid identification and characterisation of the new coronavirus associated with SARS.[31–33]

This paper is published in memory of Carlo Urbani, a WHO staff member who died of SARS. The participating network laboratories are: Centers for Disease Control and Prevention, National Centres for Infectious Diseases, Atlanta, GA, USA; Erasmus Universiteit, National Influenza Centre, Rotterdam, Netherlands; Government Virus Unit, 9/F Public Health Laboratory Centre, Hong Kong SAR, China; Guangdong Centre for Disease Control and Prevention, Guangzhou, People's Republic of China; Institut für Medizinische Virologie im Klinikum der Johann Wolfgang Goethe-Universität Frankfurt am Main, Frankfurt, Germany (in collaboration with Institute for Tropical Medicine, Hamburg, Germany and Institute of Virology, Phillips-University, Marburg, Germany); Institut Pasteur, Unité de Génétique Moléculaire des Virus Respiratoires, National Influenza Centre (Northern-France), Paris, France; National Institute of Infectious Diseases, Department of Viral Diseases and Vaccine Control, Tokyo, Japan; National Microbiology Laboratory, Population Pubic Health Branch, Health Canada, Winnipeg, MB, Canada; Public Health Laboratory Service, Central Public Health Laboratory, London, UK; University of Hong Kong Faculty of Medicine, Queen Mary Hospital, Hong Kong SAR, China; Virological Institute, Chinese Centre for Disease Control and Prevention, Beijing, People's Republic of China; Virology laboratory, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China; and Virology Unit, Singapore General Hospital, Singapore

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