Severe Acute Respiratory Syndrome: Developing a Research Response

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When severe acute respiratory syndrome (SARS) first came to world attention in March 2003, it was immediately perceived to be a global threat with a pandemic potential. To help coordinate international research efforts, the National Institute of Allergy and Infectious Diseases convened a colloquium entitled SARS: Developing a Research Response on 30 May 2003. Breakout sessions intended to identify unmet research needs in 5 areas of SARS research—clinical research, epidemiology, diagnostics, therapeutics, and vaccines—are summarized here. Since this meeting, however, the identified research needs have been only partially met. Needs that have yet to be realized include reliable methods for early identification of individuals with SARS, a full description of SARS pathogenesis and immune response, and animal models that faithfully mimic SARS respiratory symptoms. It is also of the utmost importance that the global scientific community enhance mechanisms for international cooperation and planning for SARS research, as well as for other emerging infectious disease threats that are certain to arise in the future.

Severe acute respiratory syndrome (SARS) is the first severe and readily transmissible new disease to emerge in the 21st century. SARS cases were first observed in mid-November 2002 in Guangdong Province in Southern China. The disease spread along international air travel routes to Hanoi, Hong Kong, Singapore, and Toronto during February and March 2003 [1]. Chains of secondary community transmission subsequently occurred in hospital settings, affecting doctors, nurses, and other hospital staff who were initially unaware of the new disease and its mode of transmission. Although close contact was usually linked to viral transmission, cases were also observed after only incidental exposure [2].

SARS was immediately perceived to be a global threat with a pandemic potential. After the initial development of nonspecific symptoms, the disease often progressed to severe lower respiratory disease requiring hospitalization and intensive care, with a high case-fatality rate. Predictors of mortality were shown to be advancing age (>50% case-fatality in those ≥60 years of age), underlying chronic illness, and elevated lactate dehydrogenase concentration or white blood cell count at presentation [3–6]. Lung pathology specimens revealed hemophagocytosis and giant cells of macrophage origin, suggesting that the immune system plays an important role in pathogenesis [6, 7]. As a result, corticosteroids, in combination with ribavirin, were often administered as treatment, albeit with limited or no perceived benefit [8, 9].

On 12 March 2003, the World Health Organization (WHO) issued a global alert on SARS. With support from the WHO and other members of the international health community, authorities in affected regions implemented intense epidemiologic surveillance, rigorous adherence to infection-control procedures, strict practices of patient isolation, rigorous application of quarantine for asymptomatic contacts, and aggressive restrictions on travel. As a consequence of this international effort, SARS outbreaks were contained by mid-July. The cumulative impact was limited to 8098 probable SARS cases, with 774 fatalities [10].

Despite this success, continued vigilance is indicated.
Much like influenza and other respiratory pathogens, human coronaviruses that cause common colds follow a winter-seasonal pattern, with peaks in late fall and late winter/early spring [11]. It is possible that the SARS coronavirus (CoV) will follow a similar pattern. In addition, there is currently neither an effective treatment for SARS nor a vaccine to prevent infection.

To help coordinate the robust research response needed to address the multidimensional SARS threat, the National Institute of Allergy and Infectious Diseases (NIAID) convened a colloquium entitled SARS: Developing a Research Response on 30 May 2003 on the National Institutes of Health campus. Participants included >500 physicians, scientists, and policymakers from the United States, Canada, China, Europe, and elsewhere. The program was designed to facilitate interaction among participants in 5 areas of interest: SARS clinical research, epidemiology, diagnostics, therapeutics, and vaccines. The following 5 sections, with corresponding tables, represent the highlights of the discussions that took place on each of these topics. We conclude with a discussion of recent progress in SARS research and an assessment of what research needs remain to be addressed.

CLINICAL RESEARCH (TABLE 1)

**Clinical manifestations.** Careful description of the clinical manifestations of SARS, as well as correlation of the longitudinal course of disease with clinical, virologic, and immunologic parameters, is an important early goal for clinical research. These data would permit clinical investigators to develop a standard set of criteria to delineate progression and thus quantify the impact of different interventions on disease severity. Moreover, systematic correlation of symptoms with histologic, cytologic, virologic, and immunologic evaluations of early and late changes in patient samples would greatly aid the understanding of SARS pathogenesis.

It is also important to identify host and viral factors that are predictors of disease progression. Understanding the role of host genetics and laboratory surrogates would help to improve prognostic capabilities and allow identification of patients likely to benefit from aggressive interventions. Such information might also be of value in the development of entry criteria for interventional studies.

**Clinical virology.** Longitudinal evaluation of viral shedding by use of polymerase chain reaction (PCR) and viral culture from the lungs, gastrointestinal tract, and other sites would help in patient management and infection control; for example, routinely finding infectious virus in stool weeks after resolution of clinical illness would likely change recommendations with regard to isolation. Such data would also provide information about sites of virus replication and show whether these evolve over the course of illness.

Previous studies of animal coronavirus infections have shown that small changes in viral envelope proteins can have a dramatic effect on both tissue tropism and clinical manifestations. For example, a single amino acid change in the S, or “spike,” protein changes transmissible gastroenteritis virus from a predominantly respiratory pathogen into an intestinal pathogen [12]. For this reason, evaluation of viral quasi species obtained from different tissues, obtained from patients with different clinical manifestations of SARS, and obtained over time from single patients could be very rewarding. Error rates during transcription by coronavirus RNA–dependent RNA polymerases are typically on the order of 1 in 10⁴, which are similar to rates for HIV-1 reverse transcriptase. Such high rates will likely cause substantial variation in the viral genome to occur over time, which could permit drug-resistant isolates to emerge. Careful surveillance for the development of drug-resistant SARS strains should, therefore, be part of any antiviral research protocol.

**Clinical immunology.** It is important to thoroughly understand cellular and humoral immune responses to the SARS virus, including the impact of SARS on immune function and any immunopathologic responses the virus may engender. Study

| Area of study            | Specific targets of research                                      |
|--------------------------|------------------------------------------------------------------|
| Clinical manifestations   | Longitudinal evaluation and long-term follow-up                   |
|                          | Identification of Persistent symptoms and sequelae                |
|                          | Development of a SARS staging system                              |
|                          | Early events in pulmonary tissue                                  |
|                          | Predictors of disease progression                                 |
|                          | “Super-spreaders”                                                  |
| Clinical virology         | Viral shedding                                                     |
|                          | Viral quasi species                                                |
|                          | Clinical manifestations                                            |
|                          | Tissue tropism                                                    |
|                          | Development of resistance                                          |
| Clinical immunology       | Characterization of immune response                               |
|                          | Correlates of protective immunity                                 |
|                          | Possible immunopathologic phenomena                               |
| International            | Development of a coordinated network of clinical sites            |
| Collaboration            | Protocols for therapeutics and prophylaxis trials, to be initiated as agents become available |
|                          | Evaluation of antiviral and immunomodulatory strategies           |

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of the relationships between specific immune responses and subsequent clinical course would help to identify correlates of protective immunity, which would, in turn, be of great value in the development of vaccines and immune-based therapies.

Because an immunosuppressive element has been described in other coronavirus infections, examination of the effect of SARS on the ability of the host to generate an immune response to other antigens is indicated. Such research can be done through studies of immune response to recall antigens, such as tetanus toxoid, or to primary antigens, such as bacteriophage phi X 174. Interpretation of such studies must clearly distinguish effects that are specific to SARS virus infection from those that are generic to serious illness.

Better understanding of the role of the immune system in SARS pathogenesis is critical and would help in the development of new therapeutic strategies. These deleterious responses may be specific, as in the case of cross-reacting autoantibodies, or nonspecific, as with an overly robust inflammatory response. The severe lymphopenia described in patients with SARS remains a mystery, but it could be related to immune mechanisms. Detailed study of bone marrow function and lymphocyte kinetics in individuals with SARS may yield important clues to the cause of this anemia.

International collaboration. A global network of research centers should be formed to test therapeutic approaches as they are developed and to help conduct the basic clinical research described above. These SARS clinical centers must be located in countries where SARS occurs and must have the cooperation of local communities. They must also be appropriately equipped and must have access to the requisite scientific expertise, including clinical trial design, pharmacology, and data management. To the extent possible, protocols for trials of therapies should be developed in advance of need. Such trials must be designed to test new antiviral drugs, antibody therapies, and immunomodulatory approaches, such as the use of corticosteroids, and the trials must test the application of these therapies to both treatment of symptomatic patients and postexposure prophylaxis. (See Therapeutics for further discussion of therapeutic development.)

EPIDEMIOLOGY (TABLE 2)

Animal reservoirs. SARS CoV is almost certainly of zoonotic origin. Coronaviruses have a broad host range in avian and mammalian species. The initial SARS cases in Guangdong Province occurred among workers in food preparation and the restaurant industry, which suggests that practices associated with live-animal markets in this region were a source of human infections [13]. Moreover, some workers in live-animal markets in Shenzhen, China, showed serologic evidence of SARS CoV infection without a history of a SARS-like illness. Virologic surveillance in live-animal markets led to the isolation of coronavirus closely related to SARS CoV. Further study of the genetic diversity of related coronaviruses in a broad range of wild and domestic animals may help to identify potential animal reservoirs of SARS CoV, as well as virologic and environmental characteristics that favor zoonotic transmission.

Natural history. Little is known about the natural history of SARS CoV infection. It is also critical that the reproductive rate (R₀) be quantified in different subpopulations, settings, and climates. Initial estimates suggest that R₀ is ~3, considerably less than for highly transmissible viruses, such as influenza virus. R₀ may change seasonally, and a relatively small change may determine whether the virus becomes established in the human population. Moreover, the effect of host factors, especially age, on viral transmission remains to be clarified. Children infected with SARS CoV experience much less severe illness, whereas people >60 years of age suffer severe disease and high mortality; however, it is not yet clear how the probability of viral transmission varies among age groups. Similarly, the prevalence of asymptomatic infection, the possibility of transmission through an oral-fecal route or through blood transfusion, and the presence of host genetic factors that affect susceptibility have yet to be determined. Finally, the viral, host, and environmental factors that caused so-called “super-spreader” incidents, in which many people are infected by a single individual, should be elucidated as quickly as possible.

Table 2. Severe acute respiratory syndrome (SARS) epidemiology research priorities.

| Area of study                      | Specific targets of research                                      |
|------------------------------------|------------------------------------------------------------------|
| Animal reservoir                   | Surveillance in wild and domestic animals                        |
|                                    | Infectivity of SARS-like animal viruses                          |
|                                    | Mutations associated with interspecies transmission              |
| Natural history                    | Reproductive rate (R₀) and seasonal variability in transmission  |
|                                    | Risk factors for “super-spreaders”                               |
|                                    | Role of coinfections                                             |
|                                    | Role of enteric infection                                       |
|                                    | Potential for asymptomatic spread                               |
|                                    | Infectivity of human blood, plasma, and tissues                 |
| Infection control                  | Risk factors for transmission, including role of diarrhea, age, |
|                                    | pregnancy, chronic underlying illness                           |
|                                    | Isolation and quarantine                                        |
|                                    | Population screening techniques                                  |
|                                    | Use of masks and gowns and other standard precautions           |
| International                      | Collaborative surveillance and research networks                 |
| Collaboration                      | Pooling of epidemiologic data                                  |
Infection-control strategies. Currently, the only available strategy for the control of SARS is isolation and quarantine. Because these procedures will be needed to address SARS and other emerging infectious agents, the social and psychological consequences of isolation and quarantine should be studied, and incentives for people to adhere to implemented policies should be assessed. The efficacy of other infection-control techniques, such as screening for febrile passengers in airports, should also be examined.

International collaboration. The experience with SARS underscores the need to establish collaborative international disease surveillance and research networks, especially in Southeast Asia. In March, the WHO rapidly established a global network of SARS research centers, modeled on a network of influenza surveillance and research centers already in place, which helped to facilitate the isolation and identification of SARS CoV and the complete genomic sequencing of multiple isolates. Ultimately, internationally supported, on-site collaborative networks such as these will allow rapid exchange of information and reagents among skilled professionals and, therefore, enhance research for SARS and other emerging infectious disease threats.

Beyond the establishment of collaborative centers, it is of utmost importance that scientists worldwide share all available epidemiologic data with regard to SARS. Only analyses of pooled data from all affected countries can adequately clarify such complex issues as the role of “super spreaders,” diarrhea, and other factors affecting transmission; the identification of risk factors for severe disease outcome; and the benefits of various treatment strategies. Establishing a database linking epidemiologic, clinical, and laboratory data from individuals with SARS worldwide would therefore be of tremendous benefit.

DIAGNOSTICS (TABLE 3)

During the winter months, the diagnostic challenges of differentiating SARS from other infections is especially great. This means that it is essential to develop diagnostic assays that can differentiate SARS CoV from other respiratory pathogens rapidly, simply, and precisely. It is also important to develop diagnostic tests that are not disease specific but can rapidly recognize the presence of other known and novel pathogens.

Serologic assays. SARS CoV was initially identified using cell culture inoculation and passage, followed by electron microscopy and genome sequence analysis. Standard ELISAs, neutralization tests, and immunofluorescent antibody assays were developed immediately thereafter. Use of these tests demonstrated that individuals with SARS develop specific antibodies against the virus that do not cross-react with other human coronaviruses and that are not present widely in the population. These serologic tests are now widely available in countries where active SARS CoV transmission has occurred. IgG antibodies, however, do not appear for at least 10 days after infection. Because IgM antibodies typically appear earlier, IgM capture assays should be developed. Similarly, measurement of SARS CoV–specific IgA antibodies in rapid tests designed for use with oral fluids could prove useful.

PCR assays. The first complete genome sequence for SARS CoV was available within 8 weeks after the initial WHO global alert, and >40 distinct isolates have since been deposited in genomic databases [14]. The availability of the SARS nucleotide sequence allowed rapid development of standard and reverse-transcriptase PCR assays that can detect SARS CoV RNA in respiratory secretions, lung and kidney tissues, and stool and urine specimens. PCR assays are exquisitely sensitive, with a detection limit of ∼10–100 copies of the target RNA. However, the presence of viral RNA does not necessarily indicate the presence of infectious virus, and the method’s exceptional sensitivity may lead to false-positive results because of cross-contamination and other factors. Continued work to standardize the performance of PCR assays for SARS and to determine optimal protocols remains a high priority.

Reagent repositories. Reagents such as infectious virus, viral RNA, inactivated and recombinant antigens, and SARS CoV–specific polyclonal and monoclonal antibodies are essential tools for the development of diagnostic assays, as are well-validated clinical specimens from individuals with SARS. Global public health authorities should therefore continue to coordinate the collection, storage, and distribution of this material, perhaps through existing or new WHO collaborating research centers. Alternatively, the NIAID might consider including this material in the reagent repository now planned to support assay

Table 3. Severe acute respiratory syndrome (SARS) diagnostic research priorities.

| Area of study | Specific targets of research |
|--------------|----------------------------|
| Serologic assays | Validation of standard assays |
|               | Recombinant antigens         |
|               | IgM capture assays           |
|               | IgA in oral fluids           |
| PCR assays    | Validation of PCR assays using various primers/methods |
|               | Improvement of sensitivity/reliability |
|               | Expansion of availability of PCR kits |
| Reagent repositories | Repository for reagents and validated clinical specimens |
|               | Nonhuman pimate and small-animal models |
|               | Evaluation of oral fluid, stool, and respiratory aspirates as specimens |
|               | Optimization of procedures for early diagnosis |

NOTE. PCR, polymerase chain reaction.
development for bioterror threat agents. Moreover, because initial development of diagnostic assays and reagents can also be done using specimens from animal models, improvement of such models should continue.

**THERAPEUTICS (TABLE 4)**

*Antiviral drug screening.* Although antiviral chemotherapy and prophylaxis will be of great importance in the control of SARS, no clinically proven candidates currently exist. Working collaboratively, the United States Food and Drug Administration/Institute of Infectious Diseases, the NIAID, and the Centers for Disease Control and Prevention established a SARS antiviral drug-screening laboratory in March 2003. The assay used at that laboratory measured how much candidate compounds inhibit cytopathic effects of SARS CoV growing in cultured Vero cells. Initially, the antivirals drugs screened included those that are US Food and Drug Administration approved, those in clinical development, and those for which preclinical data suggested activity against a potential viral target protein. Some in vitro activity against SARS CoV was observed with certain preparations of interferon-α and -β, as well as with rimantadine at high concentrations and a cysteine protease inhibitor.

*Antiviral drug design.* Molecular virologic and genetic studies of SARS CoV and other coronaviruses suggest several possible molecular targets for antiviral drugs. These include viral binding, fusion, and other activities mediated by the glycoprotein spike on the coronavirus surface, as well as the viral RNA-dependent RNA polymerase, the papain-like cysteine protease, and the chymotrypsin–picornavirus 3C-like protease. Inhibitors of surface hemagglutinin-esterase or other activities involved in release of virus from cell surfaces may also represent a class of useful antiviral drugs. Molecular modeling and drug design strategies should continue to be pursued to develop compounds that modulate these viral activities.

*Immunomodulation and other therapies.* Available clinical and histopathologic data suggest that immune-mediated injury may be an important mechanism in SARS pathogenesis, particularly late in the course of illness. Thus, it would be useful to assess the use of immunomodulatory drugs, such as corticosteroids, either by themselves or in combination with antivirals. The effectiveness of administration of immunoglobulins with neutralizing activity against SARS CoV, for both therapy and prophylaxis, should also be examined.

*Preclinical studies.* Both nonhuman primate and small-animal models are needed for SARS antiviral drug development. Mouse hepatitis virus, a group II murine coronavirus, has been well characterized in mice and may prove to be useful in this regard, although it may differ significantly from SARS CoV. It may in the end prove necessary to develop several models to address different aspects of the pathogenesis of SARS, such as systemic versus respiratory tract infection. The NIAID should also strengthen its ability to produce sufficient supplies of promising experimental compounds to conduct preclinical toxicology studies and should continue to expand biocontainment laboratory facilities, a shortage of which has significantly inhibited antiviral development.

Collaboration between the US Food and Drug Administration and antiviral drug developers should occur at early stages of the development process, both to assess preclinical data and to plan clinical studies. Clinical trial networks, such as the NIAID’s Collaborative Anti-Viral Studies Group (CAGS), should be expanded and strengthened, particularly to include sites in countries where SARS has occurred. Collaborative clinical protocols should be prepared; CASG has developed a clinical protocol that could be used as a template for the establishment of such collaborative studies. These clinical protocols should look not only at disease progression but also at titer of excreted virus and duration of excretion, which are probably markers for the likelihood of transmission.

**VACCINES (TABLE 5)**

*Basic science.* Because SARS has just emerged, many important basic science issues have not yet been fully explored. These include the identity of the cellular receptor for the virus, the pathogenic mechanisms that cause disease, the initial routes of infection, and the role that enteric infection plays in pathogenesis or transmission. Immunologic issues that warrant intense
study include the relative roles of innate and adaptive immunity, a detailed description of the immunologic response throughout the course of disease, whether patients are immune from re-infection after recovery, and what immune system changes might confer immunity.

Experience to date indicates that the immune response might play a role in SARS pathogenesis, which has important implications for both treatment and vaccine development. It is encouraging that useful vaccines for some animal coronaviruses, such as mouse hepatitis virus, have been developed using various strategies, including live-attenuated, whole-killed, and subunit approaches. However, experimental vaccines based on these strategies directed against feline infectious peritonitis virus enhance disease in immunized animals. It is crucial, therefore, that any immune responses that contribute to disease be identified as soon as possible and that SARS vaccine candidates be evaluated for the possibility that they might potentiate disease. It is crucial, therefore, that any immune responses that contribute to disease be identified as soon as possible and that SARS vaccine candidates be evaluated for the possibility that they might potentiate disease.

**Vaccine development.** Given the need for quick development of a safe and effective SARS vaccine, multiple strategies for vaccine development should be pursued simultaneously. These include the development of live-attenuated and whole-killed vaccine candidates, in addition to other strategies that elicit strong T cell responses, such DNA-based vaccines and engineered adenovirus vectors, as well as those that elicit production of neutralizing antibodies. Adjuvants that confer longer-lived protective mucosal and systemic immune responses should also be pursued. Finally, subunit vaccines based on S protein fragments and peptides and epitope-based T cell vaccines, formulated with new adjuvants that target Toll-like receptors, should also be developed.

**Preclinical testing.** Animal models of SARS CoV infection are needed to test the safety and efficacy of candidate vaccines. A reagent repository from which researchers could obtain recombinant viral proteins, multiple spike proteins, monoclonal antibodies, plasmids, and immune and control patient sera would be extremely helpful, as would a molecular and immunology database containing descriptions of T and B cell epitopes and SARS CoV genomic data.

Moving candidate SARS vaccines rapidly through scientific and regulatory evaluation will require a coordinated effort of government, academic, and industrial organizations. These groups should work together to identify potential barriers to product licensing and should cooperatively develop plans for widespread testing and deployment of promising vaccine preparations in countries where SARS exists.

## DISCUSSION

The first wave of SARS was controlled by vigorous international application of the time-tested techniques of isolation and quarantine, and the international research response was both forceful and cooperative. In short order, the virus that causes SARS was identified and sequenced, first-generation diagnostic tests were developed and distributed, and development of both antiviral therapies and vaccines was initiated. Much of this progress was achieved through an international network of research sites that was built largely on a preexisting influenza network. It is a reflection of the astonishingly rapid pace of SARS research that the NIAID meeting summarized above, at which a great many fundamental insights into SARS were described, occurred only 10 weeks after the initial WHO global health alert.

Progress in SARS research has continued, even as the first wave of the disease has subsided, and several identified research needs have been at least partially met. For example, in vitro screening of antiviral candidates against SARS CoV is now moving at an accelerated pace as a result of the recent introduction of high-throughput assays that can screen up to 1000 compounds per week. In addition, many SARS vaccine candidates are in development around the world, and preliminary results from tests in mice and nonhuman primates indicate that neutralizing antibodies are protective; some vaccine candidates that elicit neutralizing antibodies may shortly enter human trials [15].

By the same token, however, several needs that cut across various fields of SARS research remain unfulfilled (table 6), although some progress has been reported in many of these areas as well. The most pressing of these needs are described below.

**Methods for early identification of individuals with SARS.** Many PCR and serologic diagnostic kits are available, and other diagnostic tools are under development [16].

### Table 5. Severe acute respiratory syndrome (SARS) vaccine research priorities.

| Area of study         | Specific targets of research                                                                 |
|-----------------------|---------------------------------------------------------------------------------------------|
| Basic science         | Cellular receptor(s) Pathogenic mechanisms Routes of infection Human immune response characteristics Innate vs. adaptive immunity Correlates of immunity |
| Vaccine development   | Multiple strategies simultaneously Possible antibody-dependent enhancement of disease Adjuvants |
| Other research needs  | Collaborative network for vaccine testing Government/academic/industrial coordination Nonhuman primate and small-animal models Repository for reagents and validated clinical specimens T and B cell epitope database Database for SARS genomic data |
A recent report describing changes in cytokine concentration patterns in peripheral blood mononuclear cells in individuals with SARS suggests that understanding of SARS pathogenesis, including any role of the immune response, has not yet been achieved. Understanding of SARS pathogenesis, together with a full picture of the human immune response, could detect SARS CoV before or shortly after the onset of symptoms in most patients, allowing early intervention and better clinical outcomes. However, a complete understanding of SARS pathogenesis, including any role of the immune response, is necessary to develop effective diagnostic procedures. For example, real-time PCR, coupled with an improved RNA extraction method, allows detection of viral RNA in nasopharyngeal aspirates with high specificity early in the course of infection in clinical specimens that are relatively easily obtained. Poon et al. [17] reported that real-time PCR, coupled with an improved RNA extraction method, allows detection of viral RNA in nasopharyngeal aspirates with 80% specificity, a considerable improvement over first-generation procedures. This research was made possible by the availability of a set of well-characterized clinical samples from individuals with confirmed SARS, coupled with matched controls. Rigorous testing of diagnostic procedures using standardized samples remains a challenge to the international community, however. In addition, a more complete understanding of where in the body the virus can be found at different stages of the disease might lead to new diagnostic strategies. For example, the report that SARS CoV can replicate in peripheral blood mononuclear cells in individuals with SARS shortly after the onset of symptoms indicates that both might be an appropriate clinical specimen for diagnosis [18,19]. Availability of a highly accurate and specific diagnostic assay that could detect SARS CoV before or shortly after the onset of symptoms would be a tremendously valuable public health tool in any future SARS outbreaks [20].

**SARS pathogenesis and immune response.** A complete understanding of SARS pathogenesis, together with a full picture of the human immune response, has not yet been achieved. In this regard, it is particularly important to understand what role, if any, the human immune response plays in severe disease outcomes. A recent report describing changes in cytokine concentrations in 61 patients seropositive for SARS CoV in Beijing at early, peak, and recovery stages of the disease indicates that the immune system responds abnormally to the virus [21]. This is the kind of study that can provide useful insights into both pathogenic mechanisms and the effectiveness of experimental therapies. Another report indicates that angiotensin-converting enzyme 2 is a functional receptor for SARS CoV [22]. Further work to systematically unravel all aspects of how SARS CoV interacts with its human host at the molecular and physiologic levels will help ensure rapid development of therapeutic techniques, diagnostic assays, and vaccines.

**SARS animal models.** It has been shown that the virus will replicate in several small animals, including masked palm civets, raccoon dogs, mice, domestic cats, and nonhuman primates; researchers have a variety of animal models from which to choose. The development of vaccines and therapeutic strategies will rely on several different models, because each will have advantages in different experimental settings. However, no animal model described to date can reliably mimic the respiratory symptoms seen in humans with SARS. A recent report indicates that SARS-infected ferrets become ill, although these animals show no evidence of pneumonia [23]. Follow-up work on these and other animals might lead to the discovery of an animal model that reproduces SARS symptoms in humans.

**Enhanced mechanisms for international cooperation.** Access to well-characterized specimens and reagents is still a limiting factor for many avenues of SARS research, although some progress has been made [13, 24, 25]. Moreover, increased compilation and analysis of existing epidemiologic, laboratory, and clinical data from multiple SARS-affected areas would speed research. For example, no single site has had a sufficient number of “super-spreading” events to provide enough data to completely explain them; however, data pooled from many sites in different countries would provide a much greater chance of explaining this important phenomenon. Similarly, data on the success or failure of the various treatment strategies already attempted should be rigorously compared and analyzed. Finally, although protocols for clinical testing of therapeutic and vaccine candidates have been prepared, common protocols should be implemented across multiple international sites, and data acquired during these trials should be made widely available as they are acquired.

To combat SARS, the international public health community must effectively harness the experience and creative talents of laboratory scientists, public health workers, physicians, and other health care workers all over the world. Although the intense effort exerted in the first months of 2003 controlled the initial outbreaks, we must not be lulled into a false sense of security. The pandemic potential of SARS, a novel agent transmitted via respiratory secretions, remains present today. It serves as a reminder that the emergence of pathogens, whether natural or intentional, can have devastating human and economic costs. For these reasons, planning efforts for future pandemics must be

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**Table 6. Keys to further progress in research on severe acute respiratory syndrome (SARS)**

| Category for further research | Specific targets of research |
|------------------------------|-----------------------------|
| Topics for further research  | Origin of SARS coronavirus and its ecological relationship to other animal coronaviruses |
|                              | SARS epidemiology, especially the role of so-called “super-spreaders” |
|                              | Human immune responses to SARS coronavirus, including correlates of immunity |
|                              | SARS pathogenesis, including any role of the immune response |
| Cross-cutting research needs | Nonhuman primate and small-animal models that mimic SARS symptoms |
|                              | Well-characterized specimen, reagent, and data repositories accessible to the scientific community |
|                              | Expanded international SARS research network |
|                              | Partnerships between researchers, government regulators, and the pharmaceutical industry to develop drugs, vaccines, and diagnostic tests |
sufficiently flexible to cope with any emerging respiratory virus. Performing the research needed to effectively counter SARS will require both a continued global investment of human and financial resources and an ongoing commitment to collaborative sharing of data and materials.

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