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Competing interests statement
The authors declare competing financial interests: see Web version for details.

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SCIENCE AND SOCIETY

Rapid response research to emerging infectious diseases: lessons from SARS

B. Brett Finlay, Raymond H. See and Robert C. Brunham

New and emerging infectious diseases continue to plague the world, and there is significant concern that recombinant infectious agents can be used as bioterrorism threats. Microbiologists are increasingly being asked to apply their scientific knowledge to respond to these threats. The recent pandemic caused by the severe acute respiratory syndrome (SARS) coronavirus illustrated not only how a newly evolved pathogen can rapidly spread throughout the world but also how the global community can unite to identify the causative agent and control its spread. Rapid response research mechanisms, such as those used by the SARS Accelerated Vaccine Initiative (SAVI), have shown that the application of emergency management techniques, together with rapid response research, can be highly effective when applied appropriately to new infectious diseases.

Throughout human history, infectious diseases have had an important role in shaping and evolving our world. Pandemics and epidemics have been commonplace as the density of the world's population and international travel and trade have increased to support the global spread of pathogens. Microbial pathogens are constantly evolving, and new pathogens are continually emerging from nature. The recent emergence of many new pathogens, including HIV, enterohaemorrhagic *Escherichia coli*, West Nile virus, *Legionella pneumophila*, *Cryptococcus neoformans* subspecies *gattii* and various influenza A strains, is actually biology taking its normal course, as microorganisms evolve to exploit new or altered ecological niches[1,2]. Therefore, it is no surprise that the first pandemic of the twenty-first century appeared quickly, late in 2002, with the severe acute respiratory syndrome coronavirus (SARS-CoV) causing significant morbidity (approximately 8,500 cases) and mortality (774 deaths), and had an estimated economic impact of US $90 billion worldwide[3].

The SARS outbreak provided an excellent opportunity to attempt to harness the power of modern science to provide rapid solutions to a public health emergency and placed pressure on many microbiologists worldwide to identify and sequence the virus, characterize the disease, apply modern epidemiological techniques to track and trace the virus and its origins, and develop strategies to treat and control the pathogen. Worldwide, scientists responded to these challenges with extreme vigour, and many achievements were made (FIG. 1), including identifying the causative agent, sequencing its genome, developing animal models of infection and determining where the pathogen originated in nature and how it was globally spread in human communities. However, despite the acquisition of this large body of scientific information, as SARS was spreading around the world a method of controlling the virus was required in case it escaped containment measures. This meant that alternative therapeutic and preventative methods were urgently needed.

The development of vaccines and other therapeutic agents usually takes at least a decade and costs hundreds of millions of dollars, yet a practical solution for SARS was needed before the beginning of the next respiratory virus season. In addition, other new microbial threats are likely to emerge, and scientists will again be asked to provide rapid solutions. So, a fast and successful response to SARS could provide an example of how science can be effectively applied in response to other new and emerging diseases.

Unfortunately, the usual scientific process is not designed to be focused on quickly solving a practical problem. Grant applications, peer review and funding mechanisms are traditionally not rapid processes. Responding to emerging infectious diseases of pressing public health importance requires a scientific process that is significantly different from traditional procedures. Such a response must focus the science directly on a practical solution to the problem, and solve several scientific problems in parallel instead of in sequence. The SARS pandemic provided the perfect opportunity to attempt to develop such a system.

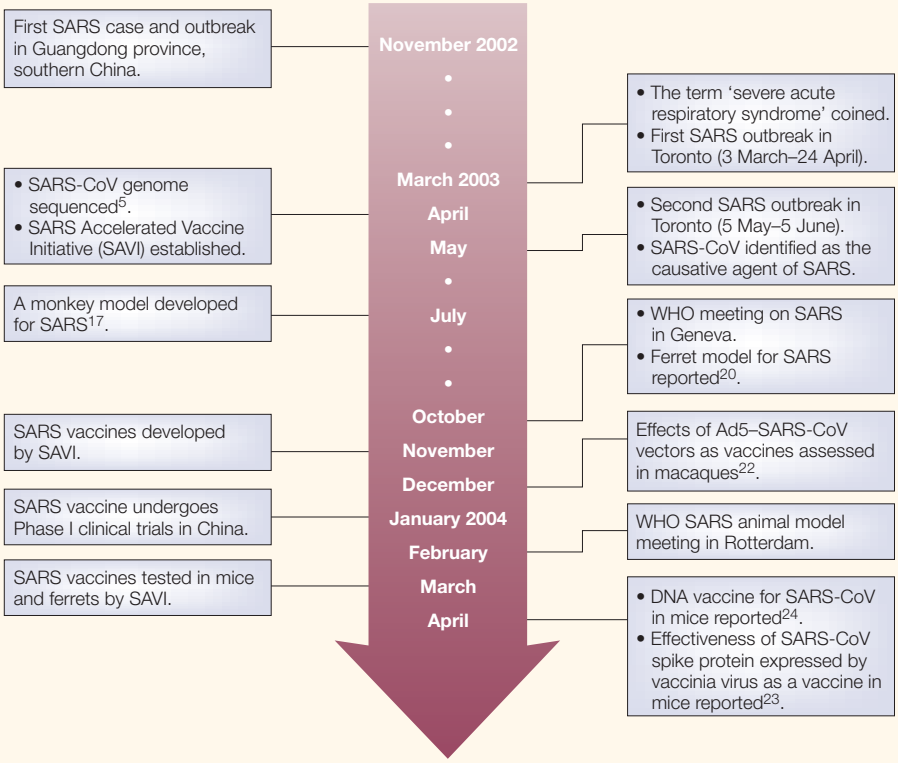

Figure 1 | **The severe acute respiratory syndrome (SARS) pandemic and important findings.** As Canada was badly affected by SARS, SAVI was set up with the explicit aim of developing a human vaccine for this disease.

A SAVI solution to SARS

With the emergence of SARS, many scientific groups worldwide began to study the disease. Canada was particularly affected by SARS — there were 438 cases, 44 deaths and a World Health Organization (WHO) Travel Health Advisory was issued — and therefore had a strong interest in the pandemic[3,4]. The Michael Smith Genome Sciences Centre in Vancouver had an emergency management plan in place that allowed the entire facility to be dedicated to the rapid sequencing of an infectious agent. In collaboration with the British Columbia Centre for Disease Control and Health, which supplied the SARS clinical virus strain (known as Toronto 2 or Tor-2), this centre generated the first genome sequence of the SARS-CoV within six days of receiving the viral nucleic acid[5]. Several other groups followed with other genome sequences shortly thereafter[6,7].

The key to sequencing the genome so quickly was having a rapid response emergency management plan already in place. This entailed a top-down management approach to be taken, with team members in parallel projects able to dedicate their time and expertise to their assigned tasks. This success, coupled with the concern that, in Canada, quarantine would not contain the SARS-CoV, led to the provincial British Columbia government providing Cdn $2.6 million in April 2003 to establish the SARS Accelerated Vaccine Initiative (SAVI) that was dedicated to developing a human SARS vaccine as rapidly as possible. A vaccine approach was chosen for several reasons, including previous success with animal coronavirus vaccines, the ease of product development and the use of vaccines to prevent infection in cases of defined risk exposure (such as healthcare workers in hospitals).

SAVI was established to apply rapid response research to a public health issue. It was designed with only one goal — to develop a safe and effective human SARS vaccine as rapidly as possible. All SAVI-funded vaccine-development initiatives were evaluated with this goal in mind. A senior management committee was established that had significant expertise in animal coronavirus vaccines and epidemiology, clinical trials and grant-funding mechanisms. An emergency management strategy was adopted, with weekly teleconferences between all members, as well as regular management committee discussions. Parallel research strategies were designed, with vaccine development as the ultimate goal. So, in addition to identifying vaccine candidates, immunological assays, clinical trials, regulatory affairs and international collaborations were all developed in parallel instead of sequentially. As soon as the genome became available, a bioinformatics web site was created, which was used by SAVI scientists as well as many other SARS researchers around the world (see SARS Bioinformatics Suite in the online links box). In addition, there was a large demand worldwide for full-length sequenced clones of the various SARS coronavirus genes. Several programmes were put in place to clone and express viral proteins that could be used both as reagents and in vaccine studies. Methods were developed for growing the virus in tissue culture (using Vero cells), and a neutralization assay was developed, both of which were necessary for vaccine development.

An important factor in producing a vaccine quickly is the early availability of information about the basis for immunological protection against disease. Although the immune correlates for protection against SARS-CoV are not yet completely defined, individuals convalescing from SARS are known to develop high titres of neutralizing antibodies[8]. The appearance of these neutralizing antibodies coincided with the onset of resolution of SARS pneumonia[9,10] and, as with other coronaviruses[11], there is an inverse relationship between disease severity and the levels of pre-existing serum antibodies. So, neutralizing antibodies are likely to be important in protection against SARS. T-cell immunity is also likely to be necessary for protection from SARS, as it is for many other viruses. For instance, low concentrations of $CD4^+$ and $CD8^+$ T cells during a SARS infection are correlated with increased disease severity and mortality[12], and specific human leukocyte antigen (HLA) class I alleles have been correlated with SARS susceptibility[13]. Taken together, the data indicated that a vaccine for SARS would need to induce neutralizing antibodies and, possibly, $CD4^+$ and $CD8^+$ T-cell responses. This knowledge proved helpful in selecting vaccine candidates and immunization approaches.

There are many potential vaccine strategies that can be considered for the SARS-CoV, including a whole killed viral vaccine, an attenuated virus, such as adenovirus or vaccinia virus, expressing SARS proteins, recombinant SARS proteins or DNA vaccines. Successful vaccines have been developed for animal coronaviruses, indicating that one or more of these strategies might work. Information about which SARS proteins could be used as candidate vaccine antigens was also obtained from the development of other animal coronavirus vaccines[14]. These

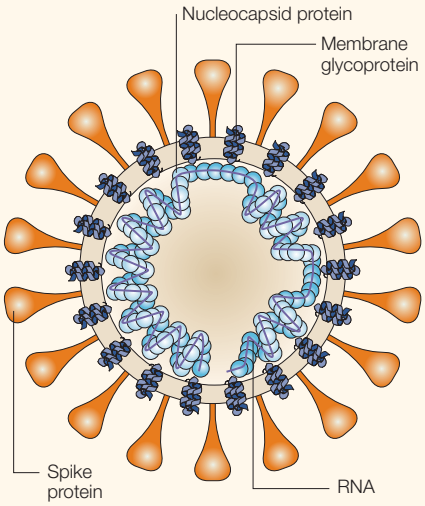

Figure 2 | **Schematic representation of the severe acute respiratory syndrome coronavirus (SARS-CoV) particle.** The positions of the spike (S) and nucleocapsid (N) proteins are indicated. The SARS Accelerated Vaccine Initiative (SAVI) is developing three vaccine candidates in parallel based on: inactivated whole virus; the S protein, which has been implicated in viral entry into cells; and the N protein that surrounds the positive-stranded genomic RNA[31].

include the spike (S) surface glycoprotein that is found on the viral surface (giving the viral particle a 'crown' and therefore its name) and the nucleocapsid (N) protein that is found inside the viral particle and which packages the RNA viral genome (FIG. 2). Deciding on which antigens and which vaccine approach to use posed significant challenges, as each has both advantages and disadvantages.

Most research groups chose a particular vaccine method that they were familiar with. By contrast, SAVI chose to develop three vaccine approaches in parallel, only making the final decision on which candidate should progress to human clinical trials after a direct comparison of the three vaccines in relevant animal infection models. This strategy also provided the opportunity to use more than one vaccine in a prime-boost strategy if necessary. Although this approach initially required more work, it was thought that it would significantly increase the likelihood of a successful vaccine being developed. So, work began on the three strategies: developing whole killed inactivated virus; developing a recombinant S protein; and modifying adenovirus and vaccinia virus to express the SARS-CoV S and N proteins. Both whole killed virus and recombinant S protein were targeted at inducing neutralizing antibodies, whereas the adenovirus and vaccinia virus vectors were targeted at inducing both cellular immunity and neutralizing antibodies. As the main goal of SAVI was to expedite vaccine development, only approaches and adjuvants that were already approved for use in humans were used in the studies, despite the potential advantages of many newer adjuvants[15] and technologies such as DNA vaccines[16] that were not approved by the US Food and Drug Administration (FDA). Using this rapid response model, SAVI scientists were able to develop three vaccine candidates within six months. These candidates are now being tested in ferret and mice models of SARS, with results of vaccine efficacy expected by mid-July 2004.

Another important consideration in vaccine testing is the availability of a relevant animal infection and challenge model. When the vaccine studies were initiated, there were no animal models available, but it was assumed that they would be developed quickly. As rapid vaccine development was the ultimate goal, it was decided, assuming they became available, to initially test the vaccine candidates in the most relevant animal infection model possible — non-human primates. Small-animal vaccine models can be misleading and time consuming. Soon after, a macaque infection model was published[17,18], and significant efforts were made to secure primates for these studies. However, recently there have been significant concerns that primate models are not the best infection models, and tests in many laboratories indicate that they only exhibit mild respiratory infections[19]. At present, ferrets seem to be the most relevant disease model[20], and relevant murine models have been developed that allow viral replication[21]. Owing to the high costs of doing primate experiments in biosafety level III containment facilities and the concerns about the relevance of a primate challenge model, at present SAVI vaccines are first tested in ferrets and mice, and then in non-human primates or other small animals for safety and immunogenicity. Similarly, other groups are testing adenoviruses[22], modified vaccinia viruses[23] and a DNA vaccine[24] in both murine and macaque models. Although this additional step adds time to the project, it is necessary and imperative to show protection in an animal infection model that closely mimics human disease. It was anticipated that testing in multiple animal models would also help eliminate concerns regarding vaccine-induced immune enhancement or immunopathology[14].

Rapid response: issues raised

In addition to the fundamental scientific questions associated with vaccine development, there are several related issues that impacted directly on the success of the project (FIG. 3).

Intellectual property. To successfully commercialize a vaccine, a strong intellectual property position is needed[25]. SAVI was fortunate in that it is partnered with the group that sequenced the SARS-CoV, and they protected the genome sequence[5]. However, additional intellectual property issues will arise as the project progresses, and there will also be pre-existing intellectual property in place that must be incorporated, such as the use of live attenuated vectors or protein expression systems. SAVI decided to not make itself a legal entity, but to leave the ownership of intellectual property with the inventors and their home universities. This saved significant time, as intellectual property mechanisms are already established at the various partner universities, and issues such as royalty rates are already settled. An appropriate way to deal with intellectual property remains a significant challenge worldwide for the development and commercialization of SARS vaccines.

Regulatory issues. Regulatory issues are another consideration when rapidly developing a vaccine. Vaccines often take many years to develop, yet the need for a SARS vaccine was urgent. So, at the beginning of the initiative, discussions were held with the appropriate regulatory bodies (Health Canada and the US FDA) to gain their support and obtain documents describing regulatory guidelines for biological agents. In addition, SAVI worked with regulatory authorities and consultants to define the steps that were needed for vaccine development, including the use of clinically approved cell lines for vaccine generation, avoidance of animal products for vaccine production, identification of plasmids and vectors suitable for human vaccines, understanding the vaccine manufacturing process under good manufacturing practice (GMP), and an understanding of what was needed to file a pre-investigational new drug application for vaccines. It was important to establish exactly what was needed, and to begin to solve these issues quickly. Difficult questions arise when one attempts to obtain rapid approval for a vaccine. For example, can clinical trials take place in a country such as China where SARS is prevalent and still be approved for use in North America? Can the trials be expedited? Who should the vaccine be tested on — healthcare workers who are at risk in a hospital setting or an at-risk community population? What happens if the number of SARS cases decreases such that there is not a population that is at risk from SARS on which the vaccine can be tested, as is currently the case? The regulatory agencies

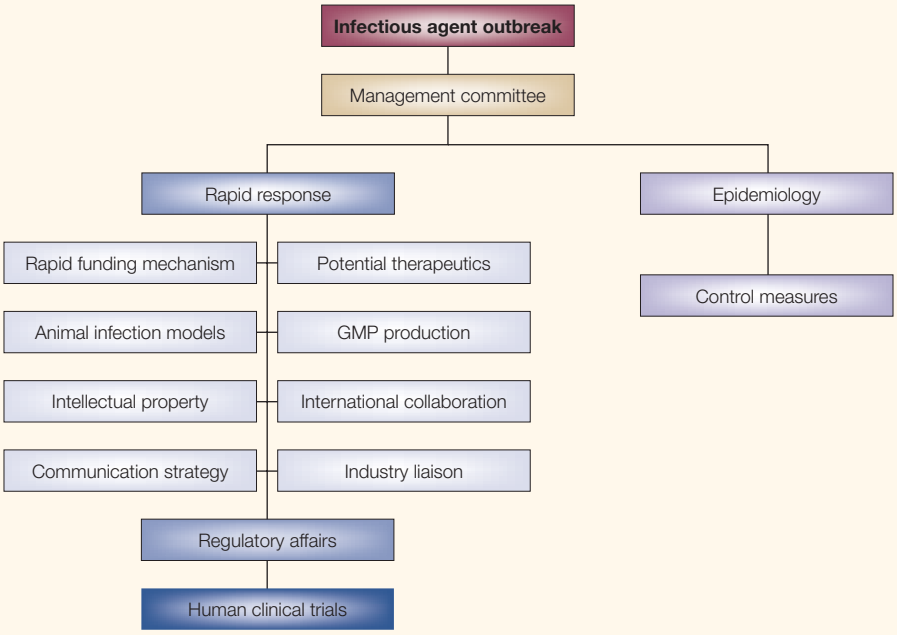

Figure 3 | **Generic model of the organization of a rapid research response to an emerging infectious disease.** An outbreak of an infectious disease (for example, severe acute respiratory syndrome (SARS)) requires the formation of a management committee to coordinate epidemiological studies for disease surveillance and implementation of control measures and policies, and a coordinated, parallel rapid research response involving collaborations between academic, government and industrial organizations to develop and license therapeutics or prophylactics to counter against the infectious pathogen. GMP, good manufacturing practice.

in Canada and the United States were extremely supportive and willing to work according to a 'risk–benefit' platform and if SARS had developed into the next major pandemic, they would have done everything possible to expedite the approval process to counter the risk of disease. Now that SARS is currently not a major threat, most agree that normal regulatory approval mechanisms should apply, and expediting vaccine approval might be unnecessary.

Handling the media. Any major disease outbreak receives significant media attention, and there is a continual demand for updates about research progress into potential therapeutics and preventatives such as vaccines. Therefore, mechanisms need to be in place to deal responsibly with media requests as these projects progress. Consequently, a system was established that enabled effective communication with the media as needed and provided a consistent message that handled (but did not expand) expectations and provided important messages about the progress of the project. Media briefings were also provided every six months. Scientific symposia were held every six months to keep the entire SAVI group of collaborators abreast of progress being made in different areas of the project.

Funding mechanisms. An important hurdle in rapid response research is distributing funds to researchers in a timely manner. The timeframe from starting to write a peer-reviewed grant application to when funds are received in the laboratory is usually more than one year, which is unsuitable for rapid response research. So rapid funding mechanisms must be established to ensure that appropriate research is carried out in a timely manner. When SAVI was established, the Michael Smith Foundation for Health Research, the provincial health research funding agency in British Columbia, was used to control and dispense the research funds. Using a five-member senior management committee consisting of senior scientists, a rapid review mechanism was established. Short (2-page), focused research proposals, together with a proposed research budget, which dealt directly with aspects of vaccine development, were solicited and accepted from the research community. The committee reviewed and evaluated the projects on the basis of scientific merit and the direct need for the project, and funds were dispersed to successful applicants immediately — usually 24 hours after the application was submitted. While ensuring that applications were peer-reviewed, this rapid review process significantly enhanced the speed of the project, and proved important in bringing together disparate research communities into a common effort. Researchers who obtained funding are still held accountable to standard grant regulations and research guidelines, including adequate accounting and reporting on completion of the project. A project director periodically reviews progress with each of the funded collaborators to ensure adequate progress and relevance, as well as coordinating diverse research groups.

International collaboration and vaccine development. As SARS was a pandemic, international coordination and collaboration was essential. The WHO had an important role in coordinating responses during and following the epidemic. In addition, in October 2003, the WHO hosted a meeting in Geneva that was attended by nearly all of the main research groups working on the SARS-CoV and SARS vaccines. This meeting was useful in many respects, including allowing the various groups to discuss strategies and progress, resolving intellectual property and regulatory issues, and selecting and developing animal models. Several additional collaborations were formed at this meeting, as well as a better understanding of where the world stood with regard to vaccines. More recently, in February 2004, the WHO held a meeting in Rotterdam to reach a consensus regarding which animal models represent the best infection models to test SARS vaccine candidates. Although a macaque model has been described for SARS[17], there were still questions regarding its suitability for vaccine testing. At least three North American laboratories have had little success in observing lung pathology and severe clinical signs in macaques after live SARS-CoV challenge[19]. Factors such as the dose or strain of SARS-CoV, the route of administration and the day of autopsy might account for the variability between the laboratories.

The consensus at the WHO meeting in Rotterdam was that standardization of conditions for SARS-CoV challenge was needed in the different laboratories before non-human primates could be used for vaccine testing. Some strains of mice, such as BALB/c and C57, have been shown to support SARS-CoV replication, but do not demonstrate significant pathology or clinical disease[21]. Other small-animal models for SARS such as ferrets[20] and hamsters (unpublished observations at the WHO meeting in Rotterdam, 2004; REF. 19) also support viral replication and demonstrate some level of pathology that is similar to humans. These animals offer

an alternative inexpensive disease model compared with non-human primates, although reports on the use of these small animals for SARS-CoV vaccine testing is scarce. However, despite these different animal models, no single animal species has been shown to reproduce all of the clinical signs and lethality that is observed in humans that are infected with SARS-CoV.

Anticipating that a re-emergence of SARS would be most likely to occur close to its original site of origin, SAVI initiated a collaboration with Chinese scientists in Guangdong province in southern China. This resulted in a bilateral agreement to work together on SARS vaccine trials. This collaboration was greatly facilitated by strong political support from both China and Canada, two countries that were significantly affected by SARS. The most obvious question is how SARS vaccines will be evaluated for human efficacy given the lack of human SARS cases globally this year. Ordinarily, Phase I to Phase III human clinical trials are designed to provide an understanding of the safety and immunogenicity of the vaccine in humans as well as identification of correlates of immunity. Without an outbreak of SARS that could be used to test the efficacy of the vaccines in humans, licensure of the vaccine under emergency conditions might have to take place under the FDA's 'animal efficacy rule', which states that vaccines or other biological agents can be licensed if they meet two criteria: human safety and the demonstration of adequate protection against a deliberate infection challenge in two species of animals (see vaccine policy in the online links). For the SARS vaccines to go directly from animals to humans under these conditions, vaccine efficacy and safety must be evaluated in animals followed by Phase I safety evaluation and immunogenicity testing in healthy human volunteers. Such a Phase I study is currently ongoing in China with an inactivated SARS virus[19]. At present, there are not enough SARS cases to test the vaccine further in Phase II and III trials. Despite the lack of an ongoing SARS threat, rapid response initiatives such as SAVI will continue to be necessary as it is important to have a vaccine available should SARS return. Furthermore, such initiatives are strongly supported by internationally recognized scientists, each with a strong expertise in a particular area of research and development. This is in contrast to pharmaceutical companies where product focus is more diffuse and the expertise is suitable for GMP vaccine manufacturing and organizing clinical trials in humans.

"the concept of working together in rapid response research towards a SARS vaccine was rapidly accepted by all researchers who were approached. All scientists were willing to … work towards a common goal"

Rapid response: lessons learned

The ability to do rapid research in response to an emerging infectious disease has significant appeal. As SARS was seen as a major public health threat in Canada and several countries in Asia, these countries in particular felt compelled to act.

Collaboration and cooperation. Experiences in Canada indicated that the concept of working together in rapid response research towards a SARS vaccine was rapidly accepted by all researchers who were approached. In fact, other scholars from the non-life-science areas of academia also freely offered their time and skills to deal with related problems. All scientists were willing to contribute their relevant expertise and a portion of their laboratory's resources to work towards a common goal, with no particular individual gain immediately obvious. Although this willingness is probably accentuated when one perceives a significant threat to one's country, it is also a powerful motivating factor when seeking to obtain particular expertise during rapid response research. Similarly, international cooperation and coordination are needed to avoid significant duplication and redundancy of efforts, as well as to share progress. In an ideal situation, expertise around the world would be coordinated, but this poses major logistical and political challenges. The WHO had a pivotal role throughout the SARS pandemic, not only in tracking the disease, but also by convening meetings of researchers working on potential vaccine therapeutics and diagnostics. In the face of future pandemics, a coordinated international rapid response research approach will be essential to develop new ways of controlling these scourges. A main difficulty with SARS research was the limited availability of clinical samples to researchers and the standardization of such samples. Some countries had national Centres for Disease Control that collected and coordinated clinical samples, whereas in others it was left to the individual hospitals. An important problem with studying emerging infectious diseases that was exemplified by SARS is patient consent. When clinical samples are taken, especially early during the outbreak, the potential research uses of such samples are not known, and it is difficult to specify exactly what they will be used for. However, having a large collection of clinical samples is crucial to understanding an infectious disease, and mechanisms for collecting and sharing such samples must be in place before an outbreak occurs.

Manufacturing considerations. For any vaccine or therapeutic product to be used in human clinical trials, it has to be made under stringent GMP[26]. Ideally, all rapid response research would be done under such conditions from the start, but this is nearly impossible, especially with infectious agents. Instead, once a candidate vaccine or therapeutic is identified, the work has to be reproduced under such conditions, which significantly lengthens the production time. At the outset, if standardized cell lines (such as Vero cells), attenuated viral vectors (such as adenovirus) and adjuvant (alum) are chosen that are already approved for human use, significant time can be saved in product development[15,26]. SARS is particularly challenging as it requires biosafety level III containment. All animal studies must be done in stringent containment facilities, of which there are only a few in the world. Similarly, if a whole killed viral vaccine is to be manufactured, highly specialized biosafety level III GMP facilities are needed, again few of which exist worldwide[27]. Owing to the perceived threat of biological agents, several Biosafety level III containment facilities have recently been approved for construction. However, performing rapid response research on highly infectious agents that are new to the world places a major burden on such specialized facilities, especially biosafety level III large animal (primate) and GMP facilities. Efficient use of such space requires global cooperation and judicial prioritization.

Commercialization. Commercialization of a SARS vaccine raises several complex issues. As it seems that SARS is not a worldwide threat at present, there is not a significant commercial market. So vaccine companies are unwilling to spend the hundreds of millions of dollars that are needed to commercialize a vaccine, as they are unlikely to recover their expenses[28]. There are several reasons why industry is unwilling to commit to developing specific vaccines. First, the huge cost of vaccine development (up to US $500 million) and the small and uncertain revenue from traditional vaccines have made vaccine manufacturers

wary of investing in development and production scale-up. Second, the lack of understanding of some diseases and the complexity of the science involved in producing the appropriate immune response for vaccines are also a deterrent. Finally, consumers are more willing to pay for treatment than prevention; this is one reason why vaccines represent less than 2% of the world pharmaceutical market[28,29]. The solution to this problem is the establishment of public health–biotechnology industry partnerships. Public and private sectors need to work together to ensure a 'win–win' system for vaccine development. Governments can help support vaccine development in several ways: set up public-sector laboratories and research facilities to help reduce research and development costs; sponsor human clinical trials to reduce costs and help acceleration of the product to market; set up tax credits to stimulate research and development in selected areas; set up public sector advocacy to stimulate demand; and purchase large volumes or stockpiles of vaccines, which would help reduce market uncertainty[28,29]. Companies provide valuable expertise in areas such as GMP production facilities and clinical trials and are therefore poised to take products further down the commercialization route. Successful contracts have been established between the US National Institutes of Health (NIH) and two vaccine companies to produce GMP-grade whole-killed vaccine that the NIH can test in Phase I human clinical trials. This should be ready for use in about one year. Although often difficult to structure, partnerships between corporate entities and research agencies are crucial to move findings from rapid response research forward into clinical practice.

Concluding remarks

Many valuable lessons were learned from the SARS pandemic. Research methodologies are significantly improved, and the application of rapid response research to SARS demonstrated that it is possible to rapidly identify a new pathogen, sequence its genome and develop preventative, therapeutic and diagnostic approaches within a very short time frame (FIG. 1). Although it required a slight redirection of researchers and resources, the response to SARS has shown that there are ample mechanisms available to use emergency management procedures and apply them to rapid response research with a direct goal in mind[27,30]. Although one cannot predict where or what the next pandemic will be, we know with certainty that there will be more. We need to learn from our research experiences with SARS and put the mechanisms and models in place to allow us to effectively respond rapidly to such threats. By so doing, we will be in a much better position than just relying on quarantine, isolation and infection-control precautions, which may or may not contain the outbreak. These approaches will provide the world with new and better ways to control emerging infectious diseases in a 'just-in-time' fashion.

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Competing interests statement

The authors declare that they have no competing financial interests.

Online links

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