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REVIEW

SARS-CoV: Lessons learned; opportunities missed for SARS-CoV-2

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Summary

SARS-CoV-2 and Covid-19 have made a retrospective analysis of other coronavirus diseases important, so this article reviews the history of the SARS-CoV viral disease from 2003. Standard and clinical chemistry diagnostics were developed in response to the outbreak. The response to SARS is examined to determine if there were lessons learned before it disappeared in June and July 2003. Various diagnostic approaches were developed and implemented to assist in the rapid identification of patients and treatment of their illness, yet many of the approaches required days or weeks from the onset of fever to show statistical significance. Most of the therapeutic methods used during the outbreak relied on treating symptoms of the underlying illness, such as lower respiratory infections and systemic infection, rather than effectively suppressing or curtailing replication of the virus. Retrospective studies are examined to determine how the SARS outbreak was viewed 10 years on and what the authors hoped would be instructive patterns for possible future pandemics. Implementation of some of these recommendations might have helped ease the current pandemic but were overlooked for budgetary reasons that seem short-sighted at present.

KEYWORDS

COVID-19, diagnostics, pharmacotherapy, SARS, viral disease

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease 2019 (Covid-19) pandemic have catalyzed a global effort to diagnose, treat, and cure increasing numbers of patients.[1] As of July 24, 2020, infected patients passed 15 million, while deaths headed towards 700 000.[2] While these numbers are reported from one of several official global reporting resources, it is assumed by some epidemiologists that the numbers underestimate the actual extent of the disease. Possible explanations for underreporting include limited or inadequate testing, lack of diagnosis, or deaths due to other factors while Covid-19 is a comorbidity, thus allowing tabulation of an alternative cause of death.[3,4,5] It is impossible to know at present how many people will be infected, how many will die, and how many will recover. It is impossible to know for how long the pandemic will be active or how significant its global financial impact will be.

While there are many differences between the severe acute respiratory syndrome (SARS) outbreak of 2003 and the current Covid-19 pandemic caused by SARS-COV-2, it is worthwhile to examine the past SARS epidemic to understand what was learned and what might have been done better in the intervening years. Both, for instance, are

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome-associated coronavirus-2; Covid-19, Coronavirus disease 2019; SARS-CoV, Severe acute respiratory syndrome; ARDS, Acute respiratory distress syndrome; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; RNA, Ribonucleic acid; RT-PCR, Reverse-transcription polymerase chain reaction; IFA, Immunofluorescence assay; IL-6, Interleukin 6; INF-γ, Interferon gamma; IL-8, Interleukin 8; TGF-β, Transforming growth factor beta; IL-13, Interleukin 13; IL-16, Interleukin 16; TNF-α, Tissue necrosis factor alpha; IL-10, Interleukin 10; PPE, Personal protective equipment; IL-1, Interleukin 1; NAI, Neuraminidase inhibitor; M2, matrix-2 protein; HIV-1, Human immunodeficiency virus type 1; EUA, Emergency use authorization; CEPI, Coalition for epidemic preparedness innovations.

coronaviruses. Both fit the definition of zoonotic diseases. Both present with an initial fever, followed by other symptoms resulting in lower respiratory infection or acute respiratory distress syndrome (ARDS). Both have required a massive global effort to define, treat, and cure those who have become ill.

Among the purposes of history should be counted its capacity to inform us of how events have transpired and guide us through similar events in our present and future. This purpose is applicable in the histories of disease, diagnosis, treatment, and recovery, as well as the histories of scientific research and application of findings. A condensed history of the brief and deadly SARS pandemic follows, along with some possible lessons to be learned for current and future viral pandemics.

1.1 | A new disease starts to spread

As the SARS coronavirus appeared and started spreading in humans in February 2003, global, governmental, and local health organizations around the world started to come to terms with this new viral threat. It soon was thought that a case of atypical pneumonia that presented in November 2002 might have been the first harbinger of the virus, but it was not until February 10, 2003 that the World Health Organization (WHO) was alerted to a disease that had "already left more than 100 people dead."[6] The Chinese Ministry of Health reported on 11 February that there were 305 cases in Guangdong, with five fatal cases.[7] It would take until 12 March for the WHO to issue a global alert. Two days later, the Centers for Disease Control and Prevention (CDC) activated its emergency operations center to support the WHO.

1.2 | Defining a diagnosis

Examination of the report issued by Morbidity and Mortality Weekly on March 21, 2003, shows that evidence was accumulating for a more dire outbreak than had previously been assessed. The WHO had reported 246 cases in 11 countries, with the preponderance of the cases in Hong Kong, Singapore, Vietnam, the U.S., and Canada.[8] The illness was characterized by "rapid onset of high fever, myalgia, chills, rigor, and sore throat, followed by shortness of breath, cough, and radiographic evidence of pneumonia," along with low platelets, natural killer (NK), T, and B cells and leukocytes. The WHO reported that the cell counts initially might present as typical and take 3–4 days from fever onset to show a significant decrease.[9] An additional criterion is that a suspected patient must have been in "close contact within ten days of onset of symptoms," which is "defined as having cared for, having lived with, or having had direct contact with respiratory secretions or bodily fluids of a person suspected of having SARS" within 10 days of symptom onset.[10]

Diagnostic problems frustrated identification of the infection. Initial diagnosis relied substantially on self-reported symptoms (eg, fever, myalgia, chills, sore throat, shortness of breath). Consultation with a medical professional and return of hematology laboratory results and chest radiography were compatible with a range of causes. Reporting of proximity to an infected person also required prompt, honest self-reporting and may have been complicated by a newly exposed person not knowing whether they were in the presence of a SARS-affected patient within the previous 10 days. However, even with this battery of possible symptoms, only fever presented in 100% of the cases identified later as being SARS-positive. Other symptoms occurred in between 10% and 74% of patients, further confusing diagnosis.[11]

1.3 | Determining the cause

CDC reported that some initial data indicating that "paramyxovirus-like particles" were being reported, a misleading clue.[7] The CDC report was remedied in the 28 March issue, which attributed blame to a "previously unrecognized coronavirus."[11] A new coronavirus—SARS-CoV—was identified as one of a family of RNA viruses that cause respiratory illnesses, including a coronavirus that causes some cases of the common cold.[12] Identification of the virus led to its isolation and genome sequencing on April 14, 2003, through a collaboration involving laboratories in the U.S., Canada, The Netherlands, and Germany.[13,14] Genome sequencing allowed the identification of sequences required for the development of diagnostic tests, particularly reverse-transcription polymerase chain reaction (RT-PCR) assays,[14] but also identified structural and nonstructural proteins as possible immune targets.

By 28 March, the Weekly Epidemiological Record reported that the number of probable cases had reached 1323 with 49 deaths.[15] The 4th April issue dedicated over half of its 24 pages to issues surrounding the spread of SARS, travel precautions, and reporting protocols.[16]

1.4 | Searching for biomarkers

Starting in March 2003, a group at the Chinese University of Hong Kong started using an indirect immunofluorescence (IFA) method to detect antibodies to SARS-CoV. Their work involved a control group of 635 naïve subjects and 103 SARS patients who screened positive for the virus by RT-PCR, as well as meeting the WHO criteria for SARS. The test was useful in identifying all SARS-positive patients and differentiating them from the control group. It also showed that the earliest seroconversion was seen 6 days after fever onset, although samples collected 5–10, 11–15, and 16–20 days after fever onset were increasingly likely to test as antibody-positive (34.3%, 78.3%, and 97.7%, respectively).[17] The paper went on to state that the method was labor-intensive and required experienced technicians. Given the delay in obtaining confirmatory results from between 6- and 20-days post-fever onset and the increasing likelihood of confirmation during the later period, it could have been of little help in determining patient treatment protocols. In the first

1–10 days following fever onset, up to 66% of samples would have tested negative. While their method may have been shared between clinical sites, the paper was not published until March 2004. Whether their work was formally cross-validated with other laboratories remains a question.

In the April 19, 2003 issue of The Lancet, Peiris, et al. published results from their work with 50 patients who met criteria for SARS infection. Peiris screened nasopharyngeal aspirates using IFA antigen detection for "…influenza A and B, parainfluenza types 1, 2, and 3, respiratory syncytial virus and adenovirus," along with cell culture-based assays for "conventional respiratory pathogens" including human-metapneumovirus.[10] None of the IFA results were positive for these well-characterized viral agents. A year later, Bermingham et al. wrote that eliminating SARS-CoV from consideration should incorporate screening for *Mycoplasma pneumoniae*, *Legionella pneumophila*, and human metapneumovirus, "particularly in returning travelers from countries where SARS is considered likely to re-emerge from an animal reservoir."[18] The Peiris group also reported mixed signals for hematology and enzyme biomarkers:

> …lymphopenia was present in 68%, leucopenia in 26%, thrombocytopenia in 40%, and anaemia in 18%. Alanine aminotransferase (45–350 U/L) and creatinine kinase (141–1379 U/L) were raised in 34% and 26%, respectively.[10]

Some investigators found potentially significant changes in some cytokines. Samples were collected within 3–7 days of onset of symptoms. Increases in IL-6 and INF-γ and decreases in IL-8 and TGF-β seemed to hold some promise for diagnostic purposes, although other investigators found that IL-13, IL-16, TGF-β, and TNF-α were found at high levels during initial phases (3–7 days) of the illness.[19,20] A study published by Huang et al. showed that "…IL-10 and TGF-β were continuously overproduced for the entire course of SARS infection," in direct conflict with Zhang et al.[21]

1.5 | Attempting treatment

While the definition of biomarkers was being pursued, pharmacotherapy was being tested in a scattershot approach[10] using antibiotics (levofloxacin, amoxicillin, clarithromycin, ceftriaxone, and azithromycin) and anti-viral drugs (oseltamivir, ribavirin, and amantadine). The antibiotics were given to address the incidence of bacterial lung sequelae to the initial viral infection and immunocompromised state caused by SARS-CoV. The glucocorticoids hydrocortisone and methylprednisolone were given intravenously for 2–3 weeks in gradually decreasing doses and showed mixed results. Peiris concluded that early use of anti-virals and steroids might be helpful, but the approach lacked consistency or large numbers of patients at the time of publication.[10] It was shown that early, accurate detection is the mainstay of determining the underlying illness and prescribing an appropriate therapeutic response.

1.6 | An unexpected end

After a substantial rise in global cases of SARS in late March and April, the illness tapered off in July 22, 2003.[22] As of June 11, 2003, the WHO reported a cumulative total in 29 countries of 8435 probable cases with 789 deaths.[23] On August 29, 2003, the WHO issued a tabular report summarizing all cases of SARS known. Out of 8422 cases, 64 patients were still hospitalized, 7442 patients had recovered, 916 patients had died, and the case fatality rate was 11%. The overall patient count included 1726 health care workers—about 20% of affected patients.[8] While the healthcare workers probably understood the use of personal protective equipment (PPE) better than their patients, a significant number of them still contracted the virus. Was the appropriate PPE used? Did they use PPE properly in every instance? Was enough PPE available to all healthcare workers? Was PPE reuse necessary? Addressing these questions at the time could have helped inform responses to the current pandemic.

Aside from an afflicted group of virology researchers in early 2004, SARS infections seemed to disappear from the global population, so SARS and the coronavirus that caused the outbreak resolved as quickly as it had occurred through the application of time-honored isolation techniques.

2 | SUMMARIZING SARS

The single, highly predictive diagnostic for SARS seemed to be the onset of fever, caused by the induction of endogenous pyrogens, such as IL-1, TNF-α, IL-6, or other cytokines.[24] SARS showed mixed results for common cytokine biomarkers even when measured several days after onset of fever.

All clinical tests, however simple or complicated, either 1) required several days or weeks for a biomarker to show a statistically significant difference from the control group, 2) were present in varying percentages of patients tested, 3) were ambiguous when examined across studies, or 4) all of the above. In 2004, Oxford et al. published a study on recommendations for the use of neuraminidase inhibitors (NAIs) in the treatment of SARS and other viral respiratory illnesses. The paper covered matrix-2 (M2) protein blockers (amantadine, rimantadine), broad-spectrum anti-virals (ribavirin, cidofovir), and the NAIs oseltamivir and zanamivir. It suggested that, while it is crucial to avoid wasting anti-virals in non-influenza respiratory disease, it could be essential to develop strategies to use available anti-virals that hold the promise of efficacy within of fever onset when an outbreak of viral respiratory disease is present in a community or region.[25] While medical costs present barriers to the early and widespread use of anti-virals, preventing hospitalizations, lower respiratory tract infections, and effects resulting from cytokine storm should take priority over the cost of pharmacotherapy.[26]

In a review article, Cinatl et al. provided a list of anti-virals studied for SAR-CoV that have demonstrated mixed efficacy, usually in combination pharmacotherapy. Classes of anti-virals studied include ribavirin and analogs, interferons, HIV-1 protease inhibitors, nitric oxide

and donor molecules, calpain inhibitors, glycyrrhizin and derivatives, SARS-CoV main proteinase inhibitors, SARS-CoV entry inhibitors, anti-viral antibodies, and others. The paper states that research was inconclusive, leading to mixed results between laboratories, and calls for "predictive correlation between *in vitro* activity and anti-viral effects in relevant animal models that reflect the situation of SARS-CoV-infected humans."[27] In short, the conclusion was drawn that, if SARS returns or if a similar viral disease occurs, much work remained to be done for an effective response.

Effective early anti-viral therapies are vital, as are ultra-sensitive immunoassay, RT-PCR, cell counting (eg, flow cytometry) methods that can determine cell type and cytokine levels, blood cell (platelet, leukocyte, lymphocyte) trends, along with any other biomarkers indicative of the onset of viral disease. These may reduce the number of patients who become immunocompromised or have accelerating lower respiratory infections. It is insufficient to have these techniques and technologies available at a few sites. The techniques must be implemented globally within weeks of an outbreak if they are not already in place, with best-in-class methods validated and cross-validated to equivalency so that all investigators and healthcare workers are evaluating their patients in as identical a manner as possible. Collaborative international best practices committees entirely focused on achieving consensus on international excellence in testing should be formed and maintained on an ongoing basis. Much work that went into defining the structure and genetics of the SARS-CoV virus was intended for use in vaccine development and pharmacotherapy to mount a response to that specific coronavirus. Given the brevity of the outbreak, some of the work might have been less useful than efforts focused on diagnostic technologies and biomarker definition—although greater knowledge of any virus helps with diagnostics as well.

Importantly, SARS-CoV and the illnesses and deaths it caused allowed scientists around the world to access new information about the nature of viral disease, genetics, protein chemistry, diagnosis, treatment, recovery, and mortality for coronaviruses. The rapid global response to SARS-CoV resulted in 28 vaccine candidates entering preclinical testing, two entering phase 1 clinical trials and two entering phase 3 trials[28]. The coronavirus research effort then faded between 2003 and the present.

In their 2013 paper, Cheng et al. cited a series of improvements that were realized since the SARS outbreak. They state the need to implement "proactive infection control measures," particularly as "pathogens may emerge from wild animals as a result of their close interaction with humans in markets and restaurants." They allude to "the advancement of laboratory techniques," indicating they should be implemented into "proactive infection control measures against various bacteria and viruses," adding that "sophisticated molecular and sequencing techniques… also facilitated our investigation of outbreaks and pseudo-outbreaks." Several measures that should assist healthcare workers are also proposed, due to the "large number of healthcare workers with fatalities affected by SARS." Lastly, they state that "the concept of extensive contact tracing … has been harnessed for the control of multiple drug-resistant organisms."[29] In the same issue of Antiviral Research, published on the 10th anniversary of the SARS outbreak, Hilgenfeld and Peiris go on to cite huge progress in "the elucidation of structures and functions of SARS-CoV" and vaccine development. They also write:

> … after 2005-2006, it became difficult to obtain funding for research on SARS-CoV in many countries, especially for efforts to find new anti-viral therapies. Similarly, there was no incentive to further develop SARS-CoV vaccines in the absence of an overt threat to human health. Funding agencies and peer reviewers were probably short-sighted in this respect, but many virologists also failed to take seriously the threat of the re-emergence of SARS or of a SARS-like virus.[30]

3 | CONCLUSIONS

We may have learned much from the SARS outbreak, but we did not implement the massive local and global controls that were suggested. Fast forward to 2020. Healthcare systems the world over have been overwhelmed. Healthcare workers again are exposed, are suffering and dying due to the lack of available PPE. It is, of course, not the fault of these investigators that they did not explicitly foresee the disastrous scope of Covid-19. It is fair to say that some virologists and epidemiologists knew it was a possibility but were incapable of convincing governments and institutions around the world to take the exhaustive, pervasive, and persistent measures necessary to control a massive global pandemic adequately. Humanity remained ill-prepared.

SARS-CoV-2 is wreaking devastation around the world, but some lessons that might have been learned during SARS-CoV are not making the broad and deep impact necessary to truncate the pandemic. At present, there are scores of drug therapy candidates, and over 160 vaccines progressing through clinical trials. It will take months, if not years, to bring these therapies to global patients. The novel antiviral remdesivir has been approved through an emergency use authorization (EUA) that allows the unapproved drug to be used "in adults and children hospitalized with severe disease."[31] Dexamethasone and interferon-beta have demonstrated efficacy in randomized clinical trials.[32,33] Some monoclonal antibody therapies known to serve as interleukin-6 inhibitors have shown efficacy in some trials.[34] We are told that any vaccine is, variously, a few months away to as much as 5 years away.[35] As of July 21, 2020, the WHO lists 24 vaccines being tested in 40 phase 1, 2, or 3 clinical trials, as well as 142 vaccines in preclinical evaluation.[36] Patient testing for the SARS-COV-2 or Covid-19 is a patchwork across the globe and generally is seen as incapable of meeting the testing needs in various populations. Any therapies and ultrasensitive methods must be available to all healthcare workers and patients within 1–3 days of fever onset, rather than later. Identification of crucial eicosanoid biomarkers, implicated in fever and inflammation onset, might aid in the rapid identification of an underlying illness.[37] The more time that elapses from fever onset, the less likely the outcome will favor patient recovery.

The humanitarian and economic impact of a global pandemic is mind-boggling. It is unknown what the eventual cost of the outbreak will be—in lives lost and diminished, emergency budgets allocated, businesses closed, supply chains interrupted, depressed gross domestic product, and other health and economic metrics. Those costs might have been lessened considerably if a less parsimonious approach had been taken to preparing a broad range of anti-virals and related drug therapies, researching shared weaknesses amongst viruses and bacteria, driving testing technologies to new sensitivities and early disease biomarkers, developing flexible capacity in hospital beds capable of responding to pandemics, and warehousing ready-to-use PPE to prepare for a worst-case scenario. Research into finding universally applicable, genuinely effective anti-viral therapies is not an easy or inexpensive task, but it is one that should be joined by research groups across the globe. It is a task being modeled by the work done by the Coalition for Epidemic Preparedness Innovations (CEPI).[38] If remedies are found, they should be made available to any affected person in any country at virtually no cost to the patient. Therapies that benefit the economically gifted while leaving most patients to suffer provides little benefit to the population at large and may result in pandemic flare-ups.

Most fundamentally, a dire need exists for discovery and development of an anti-viral that arrests viral respiratory diseases without causing any significant side effects in a broadly defined target population, that is, everyone, regardless of comorbidities. Such an anti-viral could be dosed in response to illnesses ranging from the common cold to influenza, viral pneumonia, ARDS, and SARS-like illnesses. Development of a safe and effective anti-viral for use in a wide range of viral diseases is not an easy target to achieve and might be impossible; identification of drugs that are efficacious and safe is one of the more challenging enterprises engaged by humankind. The benefits of achieving the target, however, are overwhelmingly positive. The common cold might be a matter of a day's inconvenience rather than days out of work with their concomitant economic losses. The global population could live with a sense of calm when other viral outbreaks occur, knowing that securing the well-studied, safe, and efficacious anti-viral remedy is as close as a trip to the local pharmacy or physician's office. Achieving this kind of drug development goal is critical; it simply needs the funding and commitment of the global healthcare community.

Covid-19 proves that we must take the lessons of medical history as prescriptive for the future. If this lesson is not attended, it is possible that humanity will suffer similar tragedies. We must learn from what has happened and prepare for the possible.

CONFLICT OF INTEREST

The author has no competing interest.

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