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COMMENT

COVID-19: why not learn from the past?

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The numbers of the COVID-19 pandemic

With 194 million cases worldwide and 4.16 million deaths (as of July 2021), the ongoing global pandemic of coronavirus disease 2019 (COVID-19) is second only to the 1918–1920 flu pandemic in the number of (estimated) cases and deaths. However, while scientific knowledge on the H1N1 virus was non-existent in 1918, the same cannot be stated regarding the dramatic potential of novel coronaviruses, like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to cause harm to human health.

The following is a brief summary of the past 17 years of knowledge about coronavirus that the scientific community had already gathered regarding the potential threat to humanity of this type of emergent virus and, therefore, the evidence that the Centers for Disease Control and Prevention (CDCs) and the World Health Organization (WHO) seem to have ignored or at the very least underestimated.

A recent study has revealed that SARS-CoV-2 had been present in Italy at least since September 2019, as demonstrated by presence of neutralizing antibodies in the serum from patients enrolled in an oncological study [1]. The virus itself has been recently isolated in wastewater sampled in December 2019, in different Italian regions simultaneously [2]. By March 9, 2020 Italy was in lockdown. The WHO declared the COVID-19 outbreak a global pandemic on March 11, 2020. These facts alone highlight the total lack of appreciation of a looming local (Italian) and global threat, that has caused 128 000 deaths in Italy alone as of July 2021 (source: Italian Ministry of Health).

The striking chasm between available scientific knowledge and capacity to put it into practice by government-sponsored and publicly-financed institutions for disease "control and prevention" needs to be urgently addressed, if we are not to succumb to the new challenges that lie ahead.

Early warnings

In 2003, a spread of coronavirus infection associated with severe acute respiratory syndrome (SARS) resulted in approximately 8500 cases and 800 deaths worldwide. The virus responsible for the disease was rapidly identified as a "new" coronavirus [3,4]. The term "new" highlighted that it was an addition to other coronaviruses, since these viruses had been known for decades as one of the etiological factors of "atypical" pneumonia [5–8], particularly in the elderly [9–11] and in immunocompromised subjects [12,13]. Following the SARS outbreak, it is of note that attention has been drawn to the possibly underestimated frequency of the etiology of coronavirus pneumonia [8]. In late 2003, the US Institute of Medicine's (IOM's) Forum on Microbial Threats convened the workshop *Learning from SARS: Preparing for the Next Disease Outbreak*; its final recommendation now sounds prophetical: "Analyses of this epidemic could lead to improvements in the global community's preparedness for and response to future global outbreaks of infectious disease."

After SARS in 2003, the world experienced the Middle East respiratory syndrome (MERS), an acute epidemic infectious disease caused by the zoonotic coronavirus MERS-CoV (probably transmitted by dromedaries to humans) which spread for the first time in Jordan and Saudi Arabia in 2012 [14]. Some cases of MERS were also recorded in non-Middle Eastern countries, including France, Germany, Italy, Tunisia, South Korea and the UK, in people who had traveled to the Middle East [15–17]. Therefore, before COVID-19, the global community had already suffered two emerging coronavirus outbreaks in two decades [18]. The world scientific community had

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already warned of the risk of new pandemics, right after SARS and MERS, as well as of the spread of other viruses such as H1N1, Ebola, and Zika [19–21]. In 2019, there were undoubtedly already elements of medical and epidemiological knowledge on how to deal with pandemics.

What information was available about SARS in the scientific literature before the COVID-19 pandemic?

Laboratory practices and medical treatment guidelines were published during and shortly after the 2003 SARS outbreak, regarding coronavirus identification by RT-PCR, epidemiology, and containment strategies. Clinical chemistry guidelines [22], diagnosis based on RT-PCR [23–26] and indications for therapeutic treatment were readily available from the experience with SARS. Although this knowledge was available well before the COVID-19 pandemic, much of it was "rediscovered" in the latter. For example, the prescription of steroids to counteract hyper-inflammation in SARS [26–28] was initially rejected by opinion leaders in microbiology as an unacceptable therapeutic risk, to be subsequently approved by the guidelines of the general practitioners at the height of the COVID-19 pandemic. Similarly, the use of hyper-immune serum from recovered patients was indicated among the successful therapeutic interventions during the SARS outbreak [29] and was apparently rediscovered, as a new and innovative strategy, during the COVID-19 pandemic. Also the increased incidence of Kawasaki-like disease (or rather "syndrome" as this clinical presentation of the SARS-CoV-2 infection in children is now called), had been described during the SARS outbreak, and has occurred again during the COVID-19 pandemic [30], as should have been expected, given the much larger prevalence of the infection.

The existence of subclinical or non-pneumonic SARS-CoV infections was also described during the SARS pandemic [31] and should have risen concerns regarding the possible spread of SARS-CoV-2 by asymptomatic or pauci-symptomatic subjects, as indeed occurred. The higher sensitivity of the elderly to SARS-CoV infection was also described [32], with clinical features indistinguishable from other community-acquired pneumonias, thus requiring RT-PCR to attribute the disease to coronavirus infection [33].

Moreover, data on the high risk of infection among health care professionals and on the need for more protective measures and strategies to increase biosecurity were published after SARS [34,35], but such evidence has not been sufficiently disseminated among health care workers (HCW) in hospitals and nursing homes. The exact number of SARS-CoV-2-infected HCW worldwide is not even available and the WHO reports that deaths could be in the "several thousand," calling for a greater transparency about this silent slaughter [36]. In Italy, as of February 2021, the deaths reported among HCW were 430, a number that undoubtedly reveals the absence of containment in public health care facilities.

Finally, a crucial warning available to the entire scientific community on the viral spread of SARS-CoV and of SARS-CoV-2 has been the "base reproduction number" parameter (R0), which represents the average number of secondary infections produced by each infected individual in a population that can potentially be susceptible to a new emerging pathogen [37]. Thus, R0 measures the potential transmissibility of an infectious disease: the higher the R0 value, the greater the risk of spreading the epidemic. If the R0 value is less than 1, it means that the epidemic can be contained, while values greater than 1 indicate that the infection can rapidly spread to the population. In this sense, WHO has always reported estimates of R0 greater than 1 in the SARS-CoV and SARS-CoV-2 epidemic and, specifically in 2019, the estimates were at least between 1.4 and 2.5 in the affected areas in this first phase of viral diffusion [38]. Therefore, this epidemiological parameter alone would have allowed to predict that the coronavirus infection would rapidly become pandemic.

Who did better?

Apparently, countries/regions that suffered significant numbers of SARS cases in 2003 were better prepared to counter (or more aware of) the threat of the new pandemic. As shown in Fig. 1, Canada, the mainland of China, Hong Kong of China, Taiwan of China, Vietnam, and Singapore (light gray bars in Fig. 1) had a significantly lower ratio of COVID-19 vs. SARS or MERS cases than other countries/regions, which had few cases in the SARS or MERS pandemics and apparently underestimated the threat of a new coronavirus infection outbreak, and did not care to prepare in advance for what was actually a tragedy foretold.

Among Western countries, generally less hit in the 2003 and 2012 outbreaks, Canada fared significantly better than others, particularly as compared with its close continental neighbor, the US.

Scientists in Singapore and Canada published several studies during and after the SARS-03 pandemic, dealing with important aspects pertaining to the disease, including the psychological repercussions of the viral outbreak on HCW and on quarantined people [39–41] that most countries are now facing.

Canadian-based studies carefully analyzed all major aspects of the pandemic, including the genome of the isolated virus [42], the clinical features and diagnostic

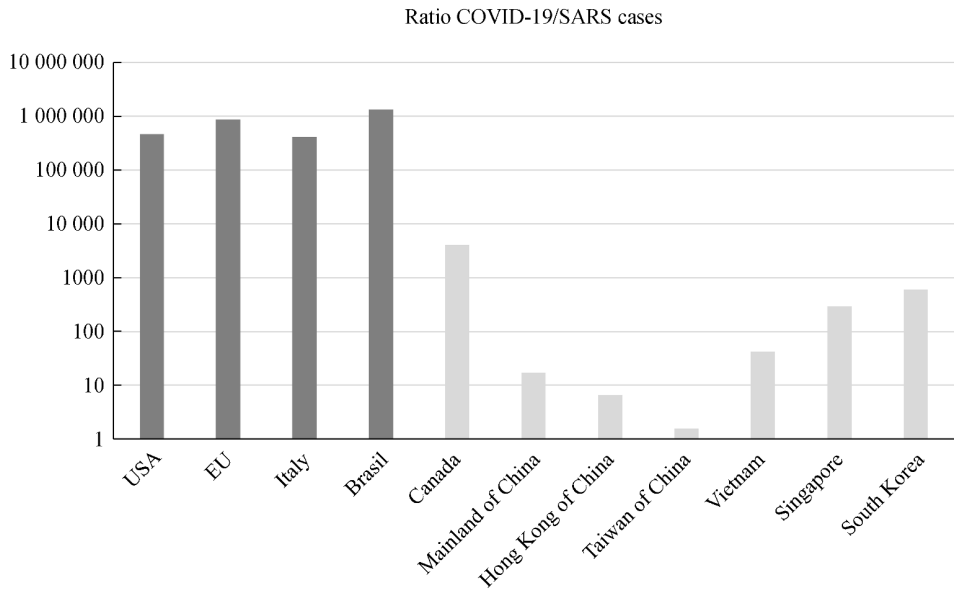

Fig. 1 Ratio between the reported cases of COVID-19 and those of the SARS, or MERS (for South Korea only) pandemic, resulting in the highest number of local cases. (Source: local governments and WHO.)

findings of the disease [43,44], strategies for disease containment in a pre-vaccine condition [45–47], particularly among HCW [48], and guidelines and scientific updates for hospital operators [49].

These publications also highlighted the continuing threat represented by wet markets as viral breeding grounds, which would have required a constant monitoring of these potential incubators for (new) coronavirus isolates in the Eastern countries from where the SARS pandemic originated [50].

Singapore also capitalized on the SARS experience by analyzing the critical issues that emerged from the crisis [51–53] and implementing the lessons learned in the subsequent COVID-19 outbreak.

As a result of their encounter with the SARS coronavirus, Canada [54] and Singapore [51] adopted new public health measures aimed at reducing the impact of a new SARS-CoV epidemic.

SARS-CoV-2 variants, the future challenge

New variants of SARS-CoV-2 keep being described [55–58] and deposited in old, as well as new, dedicated sequence databases (reviewed in [59]). As a measure of the staggering numbers of sequences, GenBank, which is continuously updated from laboratories around the world, had about 300 SARS-CoV-2 nucleotide sequences by the end of March 2020, and 27 660 by October 8, 2020, an almost 100-fold increase in just 6 months. Another widely available data-sharing platform, GISAID, currently (July 2021) contains $>$ 450 000 viral sequences. Ominously, several of these variants are already classified as Variant of Concern, or of High Consequence, as they display higher transmissibility than the original virus and/or have the capacity to escape neutralizing antibodies raised by current immunization protocols [60]. Variants are expected to increase in number with the spread of the virus and will require new vaccines, a scenario similar to what we observe with the yearly vaccination campaign against the latest influenza virus isolate.

Lessons for the future: are we ready for the next battle?

Already, there are ominous signs that the current one will not be the last outbreak of a coronavirus epidemic/pandemic. First, there exist spontaneous mutations that steadily improve the virus' capacity to infect and propagate among its human hosts, in a word, to evolve. Secondly, vaccines alone cannot guarantee safety against the outbreak of new variants in the future and may convey a false sense of protection in the population. This means that constant monitoring and alertness to this threat should go hand-in-hand with the enforcement of new measures to increase preparedness for timely interventions, in order to avert another pandemic. Furthermore, a slow vaccination campaign over time could also cause selective pressure for the SARS-CoV-2 mutation and allow its spread in the world population that has not achieved herd immunity, as well as difficulties in vaccinating populations in emerging and poor countries could make the immunization of the human species only hypothetical.

There are some critical issues that evidently need improvement, notwithstanding the development of new vaccines and anti-viral drugs: (1) continuous monitoring to allow the timely identification of new coronavirus variants; (2) international cooperation to spread this information globally; (3) timely adoption of local lockdown measures; (4) public awareness to the ongoing battle and preparedness to comply with government dispositions.

A deeper problem probably lies at the heart of the matter: why did those who should have been on the alert, i.e., the CDCs, particularly from those countries that suffered most (Fig. 1), NOT learn from the past, despite warnings from the scientific community? Why did the information made available by scientists worldwide NOT result in the acquisition of new measures by all those CDCs which should have been at the forefront of prevention? Monitoring of SARS-CoV-2 in wastewater is emerging as an effective means to measure the spread of the virus and its possible variants [61,62]. Nothing new, as it has previously been used to monitor other viruses spreading in the community [63]: why was it not implemented after the SARS-outbreak?

The answers to these questions are not related to science. It would be advisable in the future to learn from past mistakes, to overcome a politically-motivated reluctance to acknowledge that globalization poses risks to public health and to close the apparent gap between the global scientific community's understanding of the threat and the belated and ineffectual implementation of the necessary countermeasures by national and international CDCs, who inform governments' decisions. At the border where science merges with politics, some information is apparently "lost in translation."

Science-led, not policy-driven decision-making on public health issues is essential. It is time to examine the process by which Western National and International Centers for Disease Control enroll and train their staff and how they use the information coming from the "field" to implement national and international response plans. The stakes are too high not to demand excellence from the official organisms that shape the decisions that will affect our lives in the near future.

The negligence and tardiness of the Western CDCs in applying effective preventive measures to a pandemic foretold must be confronted and overcome, in order not to repeat the same mistakes in the future. Putting the blame on foreign countries for what should be in the first place the responsibility of each national public health protection body does not go in the right direction to address this issue.

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Many more references could be cited regarding any one of the issues addressed in this comment. The authors privileged those published in influential, high-impact scientific journals to highlight the visibility of this information and apologize for not citing more studies pertinent to each topic.

Compliance with ethics guidelines

Elena Zocchi and Giuseppe Terrazzano declare that they have no conflict of interest. This comment summarizes data available to the general public either on scientific journals authored by scientists or on websites publishing information from national and international agencies for disease control. Thus, no personal data are being disclosed. In all these publications the principles outlined in the *Declaration of Helsinki* have been followed.

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