

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 knowl-

edge 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 prophetic: “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 (R_0), 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, R_0 measures the potential transmissibility of an infectious disease: the higher the R_0 value, the greater the risk of spreading the epidemic. If the R_0 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 R_0 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

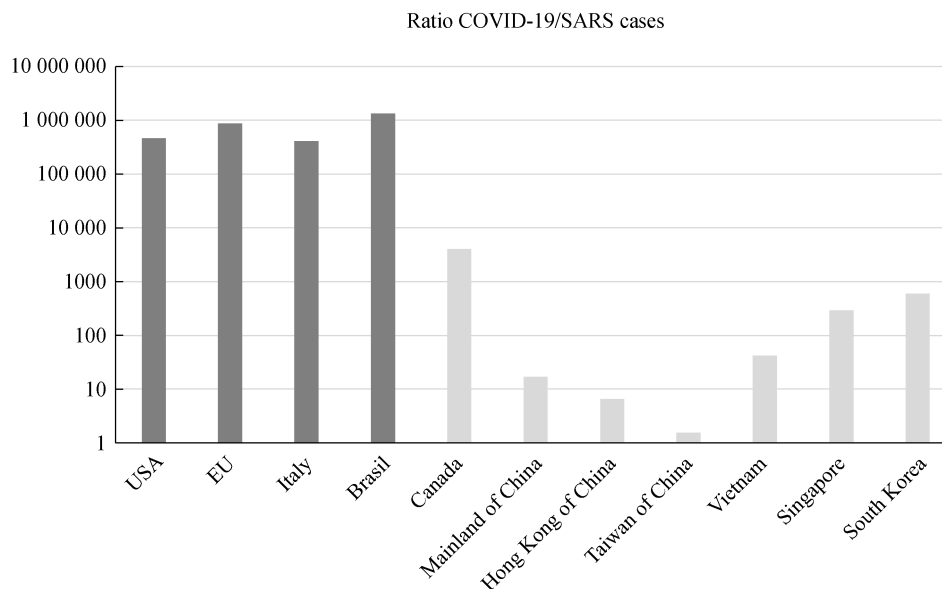


Fig. 1 Ratio between the reported cases of COVID-19 and those of the SARS, or MERS (for South Korea only) pandemic, resulting in the highest number of local cases. (Source: local governments and WHO.)

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 counter-measures 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.

Acknowledgements

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.

References

1. Apolone G, Montomoli E, Manenti A, Boeri M, Sabia F, Hyseni I, Mazzini L, Martinuzzi D, Cantone L, Milanese G, Sestini S, Suatoni P, Marchianò A, Bollati V, Sozzi G, Pastorino U. Unexpected detection of SARS-CoV-2 antibodies in the prepandemic period in Italy. *Tumori J* 2020; [Epub ahead of print] doi: 10.1177/0300891620974755
2. La Rosa G, Iaconelli M, Mancini P, Bonanno Ferraro G, Veneri C, Bonadonna L, Lucentini L, Suffredini E. First detection of SARS-CoV-2 in untreated wastewaters in Italy. *Sci Total Environ* 2020; 736: 139652
3. Zhong NS, Zheng BJ, Li YM, Poon LLM, Xie ZH, Chan KH, Li PH, Tan SY, Chang Q, Xie JP, Liu XQ, Xu J, Li DX, Yuen KY, Peiris JSM, Guan Y. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 2003; 362(9393): 1353–1358
4. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, Laman JD, de Jong T, van Doornum G, Lim W, Ling AE, Chan PK, Tam JS, Zambon MC, Gopal R, Drosten C, van der Werf S, Escriou N, Manuguerra JC, Stöhr K, Peiris JS, Osterhaus AD. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 2003; 362(9380): 263–270
5. Riski H, Hovi T. Coronavirus infections of man associated with diseases other than the common cold. *J Med Virol* 1980; 6(3): 259–265
6. Tannock GA, Reid AL, Gillett SM, Herd R, Gillett RS, Hensley MJ, Barry RD, Lawrance IP, Nichols J, Adams M, Henry RL, Saunders NA. A study of respiratory infections in a healthy adult population during the 1987 Australian winter. *Fam Pract* 1993; 10(4): 378–386
7. El-Sahly HM, Atmar RL, Glezen WP, Greenberg SB. Spectrum of clinical illness in hospitalized patients with "common cold" virus infections. *Clin Infect Dis* 2000; 31(1): 96–100
8. van Elden LJ, van Loon AM, van Alphen F, Hendriksen KA, Hoepelman AI, van Kraaij MG, Oosterheert JJ, Schipper P, Schuurman R, Nijhuis M. Frequent detection of human coronaviruses in clinical specimens from patients with respiratory tract infection by use of a novel real-time reverse-transcriptase polymerase chain reaction. *J Infect Dis* 2004; 189(4): 652–657
9. Falsey AR, McCann RM, Hall WJ, Tanner MA, Criddle MM, Formica MA, Irvine CS, Kolassa JE, Barker WH, Treanor JJ. Acute respiratory tract infection in daycare centers for older persons. *J Am*

- Geriatr Soc 1995; 43(1): 30–36
10. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997; 315(7115): 1060–1064
 11. Lina B, Valette M, Foray S, Luciani J, Stagnara J, See DM, Aymard M. Surveillance of community-acquired viral infections due to respiratory viruses in Rhone-Alpes (France) during winter 1994 to 1995. *J Clin Microbiol* 1996; 34(12): 3007–3011
 12. Folz RJ, Elkordy MA. Coronavirus pneumonia following autologous bone marrow transplantation for breast cancer. *Chest* 1999; 115(3): 901–905
 13. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med* 1997; 102(3A): 2–9
 14. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367(19): 1814–1820
 15. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet* 2015; 386(9997): 995–1007
 16. Lee JY, Kim YJ, Chung EH, Kim DW, Jeong I, Kim Y, Yun MR, Kim SS, Kim G, Joh JS. The clinical and virological features of the first imported case causing MERS-CoV outbreak in South Korea, 2015. *BMC Infect Dis* 2017; 17(1): 498
 17. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* 2018; 18(8): e217–e227
 18. Guamer J. Three emerging coronaviruses in two decades. *Am J Clin Pathol* 2020; 153(4): 420–421
 19. Schnitzler SU, Schnitzler P. An update on swine-origin influenza virus A/H1N1: a review. *Virus Genes* 2009; 39(3): 279–292
 20. Jacob ST, Crozier I, Fischer WA 2nd, Hewlett A, Kraft CS, Vega MA, Soka MJ, Wahl V, Griffiths A, Bollinger L, Kuhn JH. Ebola virus disease. *Nat Rev Dis Primers* 2020; 6(1): 13
 21. Agumadu VC, Ramphul K. Zika virus: a review of literature. *Cureus* 2018; 10(7): e3025
 22. Hawkins R. Preparing the biochemistry laboratory for the next outbreak: lessons from SARS in Singapore. *Clin Biochem Rev* 2005; 26(3): 59–64
 23. Fouchier RA, Hartwig NG, Bestebroer TM, Niemeyer B, de Jong JC, Simon JH, Osterhaus AD. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc Natl Acad Sci USA* 2004; 101(16): 6212–6216
 24. Poon LL, Guan Y, Nicholls JM, Yuen KY, Peiris JS. The aetiology, origins, and diagnosis of severe acute respiratory syndrome. *Lancet Infect Dis* 2004; 4(11): 663–671
 25. Oosterheert JJ, van Loon AM, Schuurman R, Hoepelman AI, Hak E, Thijsen S, Nossent G, Schneider MM, Hustinx WM, Bonten MJ. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. *Clin Infect Dis* 2005; 41(10): 1438–1444
 26. Ieven M. Currently used nucleic acid amplification tests for the detection of viruses and atypicals in acute respiratory infections. *J Clin Virol* 2007; 40(4): 259–276
 27. Cheng VC, Tang BS, Wu AK, Chu CM, Yuen KY. Medical treatment of viral pneumonia including SARS in immunocompetent adult. *J Infect* 2004; 49(4): 262–273
 28. Wang JT, Sheng WH, Fang CT, Chen YC, Wang JL, Yu CJ, Chang SC, Yang PC. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. *Emerg Infect Dis* 2004; 10(5): 818–824
 29. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Nguyen-Van-Tam JS, Beck CR; Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015; 211(1): 80–90
 30. Saez-de-Ocariz M, Gámez-González LB, Rivas-Larrauri F, Castaño-Jaramillo LM, Toledo-Salinas C, Garrido-García LM, Ulloa-Gutierrez R, Santamaría-Piedra M, Orozco-Covarrubias ML, Scheffler-Mendoza S, Yamazaki-Nakashimada MA. Kawasaki disease mimickers. *Pediatr Int* 2020; [Epub ahead of print] doi: 10.1111/ped.14561
 31. Woo PC, Lau SK, Tsoi HW, Chan KH, Wong BH, Che XY, Tam VK, Tam SC, Cheng VC, Hung IF, Wong SS, Zheng BJ, Guan Y, Yuen KY. Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. *Lancet* 2004; 363(9412): 841–845
 32. Woo PC, Lau SK, Tsoi HW, Huang Y, Poon RW, Chu CM, Lee RA, Luk WK, Wong GK, Wong BH, Cheng VC, Tang BS, Wu AK, Yung RW, Chen H, Guan Y, Chan KH, Yuen KY. Clinical and molecular epidemiological features of coronavirus HKU1-associated community-acquired pneumonia. *J Infect Dis* 2005; 192(11): 1898–1907
 33. Falsey AR, Walsh EE, Hayden FG. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. *J Infect Dis* 2002; 185(9): 1338–1341
 34. Forgie S, Marrie TJ. Healthcare-associated atypical pneumonia. *Semin Respir Crit Care Med* 2009; 30(1): 67–85
 35. Pedrosa PB, Cardoso TA. Viral infections in workers in hospital and research laboratory settings: a comparative review of infection modes and respective biosafety aspects. *Int J Infect Dis* 2011; 15(6): e366–e376
 36. Erdem H, Lucey DR. Healthcare worker infections and deaths due to COVID-19: a survey from 37 nations and a call for WHO to post national data on their website. *Int J Infect Dis* 2021; 102: 239–241
 37. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021; 19(3): 141–154
 38. Viceconte G, Petrosillo N. COVID-19 R0: magic number or conundrum? *Infect Dis Rep* 2020; 12(1): 8516
 39. Nickell LA, Crighton EJ, Tracy CS, Al-Enazy H, Bolaji Y, Hanjrah S, Hussain A, Makhoul S, Upshur RE. Psychosocial effects of SARS on hospital staff: survey of a large tertiary care institution. *CMAJ* 2004; 170(5): 793–798
 40. Maunder R. The experience of the 2003 SARS outbreak as a traumatic stress among frontline healthcare workers in Toronto: lessons learned. *Philos Trans R Soc Lond B Biol Sci* 2004; 359(1447): 1117–1125
 41. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. *Emerg Infect Dis* 2004; 10(7): 1206–1212
 42. Marra MA, Jones SJ, Astell CR, Holt RA, Brooks-Wilson A,

- Butterfield YS, Khattri J, Asano JK, Barber SA, Chan SY, Cloutier A, Coughlin SM, Freeman D, Girm N, Griffith OL, Leach SR, Mayo M, McDonald H, Montgomery SB, Pandoh PK, Petrescu AS, Robertson AG, Schein JE, Siddiqui A, Smailus DE, Stott JM, Yang GS, Plummer F, Andonov A, Artsob H, Bastien N, Bernard K, Booth TF, Bowness D, Czub M, Drebot M, Fernando L, Flick R, Garbutt M, Gray M, Grolla A, Jones S, Feldmann H, Meyers A, Kabani A, Li Y, Normand S, Stroher U, Tipples GA, Tyler S, Vogrig R, Ward D, Watson B, Brunham RC, Krajden M, Petric M, Skowronski DM, Upton C, Roper RL. The genome sequence of the SARS-associated coronavirus. *Science* 2003; 300(5624): 1399–1404
43. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephtimios IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM, Detsky AS. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; 289(21): 2801–2809
 44. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, Tellier R, Draker R, Adachi D, Ayers M, Chan AK, Skowronski DM, Salit I, Simor AE, Slutsky AS, Doyle PW, Krajden M, Petric M, Brunham RC, McGeer AJ; National Microbiology Laboratory, Canada; Canadian Severe Acute Respiratory Syndrome Study Team. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med* 2003; 348(20): 1995–2005
 45. Gumel AB, Ruan S, Day T, Watmough J, Brauer F, van den Driessche P, Gabrielson D, Bowman C, Alexander ME, Ardal S, Wu J, Sahai BM. Modelling strategies for controlling SARS outbreaks. *Proc Biol Sci* 2004; 271(1554): 2223–2232
 46. DiGiovanni C, Conley J, Chiu D, Zaborski J. Factors influencing compliance with quarantine in Toronto during the 2003 SARS outbreak. *Biosecure Bioterror* 2004; 2(4): 265–272
 47. Wallinga J, Teunis P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *Am J Epidemiol* 2004; 160(6): 509–516
 48. McDonald LC, Simor AE, Su IJ, Maloney S, Ofner M, Chen KT, Lando JF, McGeer A, Lee ML, Jernigan DB. SARS in healthcare facilities, Toronto and Taiwan. *Emerg Infect Dis* 2004; 10(5): 777–781
 49. Loutfy MR, Wallington T, Rutledge T, Mederski B, Rose K, Kwolek S, McRitchie D, Ali A, Wolff B, White D, Glassman E, Ofner M, Low DE, Berger L, McGeer A, Wong T, Baron D, Berall G. Hospital preparedness and SARS. *Emerg Infect Dis* 2004; 10(5): 771–776
 50. Webster RG. Wet markets—a continuing source of severe acute respiratory syndrome and influenza? *Lancet* 2004; 363(9404): 234–236
 51. SARS Investigation Team from DMERI, SGH. Strategies adopted and lessons learnt during the severe acute respiratory syndrome crisis in Singapore. *Rev Med Virol* 2005; 15(1): 57–70
 52. James L, Shindo N, Cutter J, Ma S, Chew SK. Public health measures implemented during the SARS outbreak in Singapore, 2003. *Public Health* 2006; 120(1): 20–26
 53. Goh KT, Cutter J, Heng BH, Ma S, Koh BK, Kwok C, Toh CM, Chew SK. Epidemiology and control of SARS in Singapore. *Ann Acad Med Singap* 2006; 35(5): 301–316
 54. Webster P. Canada strengthens pandemic plan in wake of SARS. *Lancet* 2004; 363(9409): 628
 55. Woo PC, Lau SK, Huang Y, Tsoi HW, Chan KH, Yuen KY. Phylogenetic and recombination analysis of coronavirus HKU1, a novel coronavirus from patients with pneumonia. *Arch Virol* 2005; 150(11): 2299–2311
 56. Lau SK, Lee P, Tsang AK, Yip CC, Tse H, Lee RA, So LY, Lau YL, Chan KH, Woo PC, Yuen KY. Molecular epidemiology of human coronavirus OC43 reveals evolution of different genotypes over time and recent emergence of a novel genotype due to natural recombination. *J Virol* 2011; 85(21): 11325–11337
 57. Awadasseid A, Wu Y, Tanaka Y, Zhang W. SARS-CoV-2 variants evolved during the early stage of the pandemic and effects of mutations on adaptation in Wuhan populations. *Int J Biol Sci* 2021; 17(1): 97–106
 58. Urhan A, Abeel T. Emergence of novel SARS-CoV-2 variants in the Netherlands. *Sci Rep* 2021; 11(1): 6625
 59. Bernasconi A, Canakoglu A, Masseroli M, Pinoli P, Ceri S. A review on viral data sources and search systems for perspective mitigation of COVID-19. *Brief Bioinform* 2021; 22(2): 664–675
 60. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JC, Muecksch F, Rutkowska M, Hoffmann HH, Michailidis E, Gaebler C, Agudelo M, Cho A, Wang Z, Gazumyan A, Cipolla M, Luchsinger L, Hillyer CD, Caskey M, Robbiani DF, Rice CM, Nussenzweig MC, Hatziioannou T, Bieniasz PD. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *Elife* 2020; 9: e61312
 61. Martin J, Klapsa D, Wilton T, Zambon M, Bentley E, Bujaki E, Fritzsche M, Mate R, Majumdar M. Tracking SARS-CoV-2 in sewage: evidence of changes in virus variant predominance during COVID-19 pandemic. *Viruses* 2020; 12(10): 1144
 62. Peccia J, Zulli A, Brackney DE, Grubaugh ND, Kaplan EH, Casanovas-Massana A, Ko AI, Malik AA, Wang D, Wang M, Warren JL, Weinberger DM, Arnold W, Omer SB. Measurement of SARS-CoV-2 RNA in wastewater tracks community infection dynamics. *Nat Biotechnol* 2020; 38(10): 1164–1167
 63. Bosch A, Guix S, Sano D, Pintó RM. New tools for the study and direct surveillance of viral pathogens in water. *Curr Opin Biotechnol* 2008; 19(3): 295–301