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What We Have Learned and What We Still Do Not Know about COVID-19

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On 1st January 2020, China formally notified the WHO of an outbreak of "mysterious" virus-based pneumonia in Wuhan. The outbreak of what is now called the COVID-19 epidemic was subsequently traced back to early October 2019 (Nsoesie et al., 2020). Since then, the virus has spread around the world, unleashing the worst public-health crisis in a century. Up to now more that 12 million people have been infected and 550,000 have died. The pandemic has prompted a scientific "race" (more than 30,000 scientific papers) to understand the biology of the causative agent of the COVID-19 flu-pneumonia, i.e. SARS-CoV-2, and to find reliable treatments for it.

Despite the huge effort deployed in this period, many questions and puzzles have not yet been satisfactorily answered. Here we outline some of them.

1. Although microbiologists and health officials had long warned of the pandemic potential of certain coronaviruses carried by bats (and other animals) in China, when the virus suddenly began to appear all over the world, it caught everyone unprepared. How did this happen? How (and why) was the lesson from previous pandemics forgotten (Kleinman and Watson, 2005)?

2. Computational models, cell studies and animal experiments are being used to pinpoint the viral host that kicked off the pandemic. According to Nature magazine, "There is strong evidence that the virus originated in bats. The biggest mystery remains how it got from bats to people. Researchers overwhelmingly think that it is a wild virus, which probably passed to people through an intermediate species. But no one has found the virus in the wild yet, so other explanations cannot be ruled out entirely" (Mallapaty, 2020a). This is a critical question. In the absence of evidence to explain the hypothetical spillover, other explanations, including accidental release of the virus from the Wuhan lab, must be considered. Indeed, a zoonotic spillover should not be given undue credit, because the epidemic curve is consistent with substantial human-to-human transmission (Nishiura et al., 2020). Obviously, this possibility raises a number of embarrassing concerns.

3. Furthermore, ambiguity surrounds Chinese activities in the field of transgenesis and engineering of microorganisms. We still do not know when the epidemic actually broke out, how many deaths it has caused and where the virus originated. Chinese research in transgenesis and molecular biology has long been the focus of attention for its ethical and safety implications. Over the years, Chinese researchers have shown a rather supercilious attitude to safety rules and ethical principles, sometimes incurring criticism and criminal convictions, as in the case of Dr He (Normile, 2019).

4. How deadly is COVID-19? Death rates vary for two main reasons: 1) differences in testing reliability between countries and the limited number of tests performed, which ultimately lead to underestimation of the true incidence (for instance, until recently Chinese official reports did not include numbers of asymptomatic patients); and 2) uncertainty regarding the true cause of death. Because autopsies have been limited or for-

bidden in many countries (as in Italy until May 2020), a positive COVID-19 test has been deemed "sufficient" to explain clinical outcome; other prominent comorbidities have been discarded as causes of death. It is likely that a reliable global death rate will not be established until the end of the pandemic. However, a reappraisal of true incidence rates and critical re-examination of concomitant pathologies has enabled scientists to estimate that the infection fatality rate may be significantly less than that usually reported by the media, probably averaging around 0.6 percent (de Jesus, 2020). Indeed, a recent commentary in Nature suggests that "a growing number of studies from different regions have estimated IFRs (infection fatality rates) in the range of 0.5–1%" (Mallapaty, 2020b).

5. Has management of the epidemic (political, non-pharmacological measures (i.e. quarantine), including mass-media communication) been adequate? Answers to this question will unleash a storm of controversy. Specifically, the utility of the lockdown has been questioned and is still debated (Melnick and Ioannidis, 2020), mostly because several countries (Japan, Sweden) in which such measures were not adopted (or adopted in a "mild" version, as in Denmark) did not show significant increases in incidence or fatality rates from COVID-19. Furthermore, besides generating political controversy, it is questionable whether citizens benefited from information delivered by "accredited experts", who often aired disparate and disputable opinions instead of making wise recommendations. The sad result was that people lost trust in science.

6. An intriguing feature of COVID-19 is the paucity of symptoms in the vast majority of patients (60-70%) with less than 30% requiring hospital admission. According to different reports, only 3.4 to 10% of infected patients develop severe acute respiratory distress syndrome (ARDS) and require intensive care (Grasselli et al., 2020). How can this data be explained? Attempts to correlate such findings with SARS-CoV-2 mutations or different genetic profiles of patients have failed (Parens 2020). A plausible explanation may be found by looking at COVID-19 from an "organism" viewpoint. At this level, the complex interactions taking place during the infection can be deciphered. Indeed, people dying of COVID-19 are mostly concentrated in the very elderly age group (>75 years), and already have other serious diseases (including cardiovascular diseases, hypertension, renal failure and cancer). In these patients, COVID-19 triggers an autoimmune-like response, involving a huge inflammatory reaction with venous and arterial thromboembolic complications, which ultimately unleash a cascade of events, including the so-called cytokine storm that leads to ARDS (Cecconi et al., 2020). In a nutshell, people admitted with severe COVID-19 lung complications die from a wrong/diminished/insufficient "organism" response.

These are the reasons why ORGANISMS is taking a special interest in the COVID-19 pandemic. As previously stressed by many contributors to this journal, disease cannot be "reduced" and "explained" by focusing solely on the "main causative factor". SARS-CoV-2 infection alone cannot provide a satisfactory comprehensive answer. Such an answer is provided by considering the organism as a whole with its different levels of interaction with the surrounding milieu. Here we are hosting a first special issue on COVID-19. A second one will be published in December 2020; submissions with alternative views of COVID-19 are welcomed. The Editorial Board hopes that this collective effort will contribute to a more inclusive appraisal of this challenging disease.

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