EDITORIAL

COVID-19: Perspectives on the Potential Novel Global Threat

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For long time human coronaviruses (HCoVs) have been deemed as nearly inconsequential pathogens, responsible for up to 30% of common cold cases worldwide each year [1] and causing more relevant respiratory syndromes only occasionally in fragile populations such as elderly subjects [2] and transplant patients [3]. The scenario has dramatically changed in the current century, wherein each decade has been characterized by the advent of a novel and more dangerous HCoV.

The first HCoV into the spotlight was the causative agent of the severe acute respiratory syndrome (SARS-CoV), an epidemic that originated in China in 2002 but was detected only at the end of February 2003 [4]. The epidemic involved more than 2 dozen Countries and its death toll reached 774 people out of 8098 affected individuals: the case-fatality risk (CFR) was equal to 9.6% [4]. The spread through international travel and nosocomial outbreaks were reason for serious concern, but luckily no cases of SARS have been reported since 2004 due to proper measures of infection control [4]. In 2012, a second highly pathogenetic HCoV was identified: the causative agent of the Middle East respiratory syndrome coronavirus (MERS-CoV) [4]. As of December 2019, MERS-CoV, almost exclusively circulating in Saudi Arabia or in other Arabian Peninsula countries, has brought about a total of 2499 cases and 861 deaths, being its CFR equal to 34.5% so far [5].

SARS-CoV and MERS-CoV have many commonalities: both are zoonotic viruses, whose reservoir is represented by bats, and both may cause severe atypical pneumonia [4]. Nevertheless, key differences stand out: I) intermediate hosts favouring the spillover to humans were diverse, namely civet palms and dromedaries, respectively; II) the first virus, though more contagious, was vanquished, whereas the second, more lethal, still today provokes sporadic infective episodes; III) the main receptor for entry target was angiotensin-converting enzyme 2 (ACE2) for SARS-CoV and dipeptidyl peptidase 4 (DPP4) for MERS-CoV, whose distribution accounts for different clinical phenotype (relevance of gastrointestinal symptoms and renal dysfunction in case of MERS besides respiratory involvement) [4].

Lessons from these two previous HCoVs are very precious nowadays, in order to counter the third harmful HCoV of this century, that has been defined as "*a public health emergency of international concern*" by the World Health Organization: SARS-CoV-2, the etiologic agent of the so-called coronavirus disease 2019 (COVID-19) [6]. COVID-19 was recognized as a novel clinical entity only in January 2020, but the first official report about a cluster of presumably viral pneumonia cases in Wuhan, a densely populated city in Central China, dated back to 31 December 2019 [7]. The inciting agent was a novel HCoV whose genome was unveiled on January 8th by Chinese researchers, showing a close relation (88% identity) with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, being more distant from SARS-CoV (about 79%) and especially from MERS-CoV (about 50%) [8]. Therefore, the animal origin of the virus was postulated and, reportedly, the epicentre of the outbreak was the local Seafood Market, in which a cross-species jump would have happened through a still not identified intermediate host [7]. The majority of the first laboratory-confirmed cases (27/41, 65.9%) reported direct exposure to the Wuhan Seafood Market [9]. Actually, the epidemic curve seems consistent with a relevant human-to-human transmission already in December 2019 in Wuhan, thereby the role of the Seafood Market should not be overemphasized [10].

As of February 25, a total of 80,239 confirmed cases of COVID-19 have been reported globally: 96.9% (77,780) of them were in China [11]. Outside China, 33 countries have been involved from all continents barring South America [11]. Overall, 2,700 deaths have been counted, being the CFR equal to 3.3% [11]. Of note, CFR values vary according to the geographical setting: 3.9% (2,563/64,786) in the Chinese province of Hubei (whose capital is Wuhan); 0.8% (103/12,994) in the other Chinese provinces; 1.4% (34/2,459) outside China [11]. Needless to say, many potential biases may affect CFR estimates during the early phases of an epidemic, and more consolidated data are necessary to establish the lethality of COVID-19 [12].

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To date, the following information have been acquired upon SARS-CoV-2: it can be transmitted from person to person through droplets, usually after close contact with an infective subject; the mean incubation period is about 5 days, but probably may last up to 2 weeks; the role of asymptomatic individuals in fuelling transmission is not clear, but they do not appear to be the major driver of viral spread; the ensuing clinical syndrome is not specific, including fever and dry cough in most cases and atypical pneumonia (with infiltrates and ground glass opacities) in patients needing hospital admission [13]. The main receptor of the virus should be ACE2 [13]. No proven effective drugs are available: the antiretroviral combination of protease inhibitors lopinavir and ritornavir, interferon beta and remdesivir (nucleotide analogue developed against Ebola virus) are being tested on the field [1].

Compared with the HCoVs responsible for SARS and MERS, the causative agent of COVID-19 is associated with a lower CFR, but with a greater infectivity: its attack rate is at least 10%, namely the same as the one of influenza viruses [14], as exemplified by what is happening on the Diamond Princess cruise ship quarantined in the Yokohama (Japan) port, wherein 355 people have been affected out of 3,711 among passengers and crew members as of 16 February [15]. The basic reproduction number (R_0), namely the number of secondary cases induced on average by a contagious person in a completely susceptible population, ranges from 2 to 3: at any rate, a conservative estimate of 2.3 means that infection control measures must block well >60% of transmission to be successful in interrupting the chain of transmission [16].

The largest case series so far is represented by the Chinese Center for Disease Control and Prevention about 72,314 case records from the whole country, of which 44,672 were classified as laboratory-confirmed, the remaining 16,186 as suspected cases [17]. Focusing on the cases confirmed by molecular testing on throat swab samples, the most were 30 to 79 years of age (87%), only 1% were aged 9 years or younger, and only 3% involved people aged 80 years or older. Most cases were defined mild (81%; no pneumonia or mild pneumonia, but 14% were severe (namely presenting at least one of the following criteria: dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (requiring admission in intensive care unit – ICU – because of respiratory failure, septic shock, and/or multiple organ dysfunction or failure) [17]. The overall case-fatality rate (CFR) was 2.3%: 1,023 deaths out 44,672 confirmed cases. No fatalities were observed in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and this value was even higher (14.8%) in patients aged 80 years and older [17].

Useful data could be inferred by a smaller and earlier report upon 138 hospitalized patients at Zhongnan Hospital in Wuhan in January (follow-up until 3 February) [18]. In this cohort, it was apparent that, compared with non-ICU subjects, patients in ICU were older (median age, 66 years versus 51 years), and were more likely to have underlying comorbidities (26/36 versus 38/102, namely 72.2% versus 37.3%) [18]. Interestingly, there was a time lag of 5 days from symptoms onset to shortness of breath and of 8 days to ARDS [18].

Interestingly, no vertical intrauterine transmission was demonstrated in a retrospective case series of 9 pregnant women, all having a caesarean section and not showing different clinical features from non-pregnant subjects [19].

As of February 25, South Korea, with 977 confirmed cases [11] and Italy, with 322 cases [19], were the country most affected by COVID-19 epidemic beyond China. Italy, due to two outbreaks in its Northern area, is the Western country showing the higher spread of the novel virus, and its response will be crucial to prevent further circulation of SARS-CoV-2 in Europe and not only.

The availability of genetic sequence and data on the epidemiology and clinical consequences are only the first step to better understand COVID-19 infection. However, many pivotal questions are actually open. In particular, its origin, the duration of transmission in humans, the ability to infect other animal hosts and the pathogenetic spectrum of human infections. The study of virus in successive generations of human infections will be the way to follow viral evolution and to improve diagnostic tools. Another challenge is manufacturing proteins from the virus, needed to develop fast a potential vaccine. However, the time to achieve this objective cannot be predicted. We can conclude that is mandatory to realize globally every effort to control COVID-19 infection, not only at scientific and medical levels, but also on the economic and politic plans.

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