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Editorial Commentary

COVID-19 and globalization

1. Introduction

The world is experiencing a major pandemic caused by SARS-CoV-2, the Coronavirus causing COVID-19. This disease first entered the human population in Hubei province, China, in mid-November 2019 and manifested in Wuhan, the largest metropolitan area of Hubei, when a cluster of patients were admitted to hospital with a 'severe pneumonia of unknown cause' in early December. Although humanity has survived previous pandemics by infectious agents, the present one is unprecedented in its capacity to take advantage of modern globalization allowing for massive transborder spread at a surprising speed.

When writing these lines, the pandemic affects 181 countries and territories, with around 1,084,000 infected subjects, more than 58,000 deaths and 225,000 recovered patients, according to the Johns Hopkins University [1].

2. Crucial question marks

The SARS-CoV-2 virus is optimized to bind to Angiotensin-Converting Enzyme 2 (ACE2) using the viruses' spike protein. ACE2 is a membrane-associated and secreted enzyme expressed predominantly on endothelium [2], but also present in cells of the alveolus, enteric cells, and in epithelial cells of the oral mucosa [3]. The capacity of this virus to develop and replicate in the oral mucosa, and thus in the upper parts of the respiratory system, allows for easy transmission similar to flu viruses. This upper respiratory involvement and high viremia at the beginning of the infection allows for transmission to other subjects even before the appearance of symptoms, which additionally to subjects showing a very mild clinical picture, poses a great epidemiological problem, which also happens with influenza viruses [4], of asymptomatic/presymptomatic carriers. The difficulties in detecting asymptomatic carriers, who often do not know they are infected, undoubtedly facilitates the spread and appearance of unexpected disease foci whose traceability becomes impossible in several cases [5].

Moreover, SARS-CoV-2 shares characteristics well known in other animal coronaviruses. Among them, its capacity to survive for several days outside the host's body helps explain how SARS-CoV-2 spreads by contact [6]. Although of an undoubtedly lower epidemiological role, this capacity indicates a significant difference from flu viruses. This is important when considering the additional faecal shedding of this virus [7]. Although the impact of climate characteristics typical of the end of spring and summer, e.g. high temperatures, longer UV radiation in the longer days, and a lower environmental humidity, causes interruption of the transmission of flu viruses and underlie their seasonality, climatic changes are not likely to have a great impact on COVID-19 transmission dynamics as evident by its already logarithmic spread in countries with warmer climates. The very high temperatures experienced in many countries of the Northern Hemisphere linked to the climate change phenomenon in recent years, e.g. temperatures higher than 40 °C, could have a negative impact on the transmission capacity of the virus, although for the aforementioned reasons, those factors alone are unlikely to alter the level of transmission.

When considering that we are still without specific clinical treatments, useful antivirals and vaccines, and other technologies to fight the virus, and that the successful development and deployment of such advances are many months away, there is no other way to face the very fast spread of this disease than using the old methods of isolation of infected subjects and quarantines of populations, towns and cities, extending restrictions to whole countries [17]. Ideally, these measures are coupled with diagnostic detection, isolation and treatment of all clusters of infection. Contact tracing is as important as simple isolation. There is simply no time to waste at the present level of the epidemic.

Another question arises concerning the capacity to modulate the epidemic curve in western democratic countries and in Islamic countries. A priori, the relatively fast success of China in controlling the disease does not seem to be something we can extrapolate outside of China. Differences in the capacities of political regimes to impose restrictions, on the one hand, and personal ideologies, traditions, and ways of life, on the other hand, suggest that it is unlikely for countries to be able to reach China's success at such a speed. Anyway, the way in which South Korea succeeded, with its emphasis on testing, treating, and isolating all cases, coupled with testing and isolating all close contacts of COVID-19 persons, provides provides optimism.

Unfortunately, data on the numbers of infected people in several countries, including those with very numerous populations, do not appear credible. Differences in methodology and coverage in the implementation of diagnostic tests are undoubtedly furnishing biased pictures, which do not allow for significant country comparisons nor a present global analysis or for an optimal global strategy. In that sense, the recent call by WHO to increase diagnostic test application goes in the right direction, although the capacity of many of the countries seems to fall below this aspiration.

Viral genome analyses of SARS-CoV-2 reveal a very slow mutation rate along its spread. Although this would help facilitate the development of efficient vaccines, vaccine development for a virus that has antibody-mediated enhancement is tricky. Thus, a vaccine to impede SARS-CoV-2's ability to become seasonal or to reduce its seasonal impact is challenging. Recent work on the evolution of SARS-CoV-2 using computational analyses strongly indicate that natural selection within a human or human-like ACE2 receptor permitted alteration to the most variable part of the coronavirus genome, namely the receptor binding domain (RBD) of the SPIKE protein allowing optimal binding to the human ACE2 to arise [8]. This shift in RBD led to its current easy spread among and within humans. Mutation of the SARS-CoV-2 genome

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relating to pathogenicity are less variable, thus it does not seem likely for this virus to readily become less pathogenic to humans in the near future, as happened with other previously emerging viruses, e.g. swine influenza. This adds to the question of immunization: will recovered subjects keep an effective immune status? and if yes, for how long?

More seriously is the question of whether a previous infection with SARS-CoV-2 could expose the individual to more serious disease when confronted by an altered form of SARS-CoV-2 in the manner that Dengue virus does. Thus, underlining the question of how the characteristic of antibody-enhanced infection of SARS-CoV-2 and of other coronavirus challenges not only the notion of immunity from having been infected, but the development of a safe and effective vaccine. In China, and elsewhere in the world, most of the population is still susceptible because, to date, there is no proven previous contact with the virus. This raises many serious questions regarding the threat of subsequent waves of infection.

It is evident that everyone is learning from the present situation with this One Health disease [17,18], from clinicians to virologists, epidemiologists, veterinarians, scientists of all kinds, and even economists, psychologists, politicians, and a wide spectrum of other professionals. But the reaction of governments, decision makers, supranational institutions, and international agencies merits an extra analysis.

3. Lessons to learn from COVID-19

Evidence indicates a zoonotic origin which reminds us of the origin of the avian influenza or bird flu pandemic by H5N1, similarly first detected in Guangdong province in China in 1996 [9,17,18]. It is evident that after what has happened with COVID-19 and its social impact and future economic repercussions, China and other nations where citizens frequently have close contact with wild animals, will need to implement strict control measures to avoid a similar pandemic to appear in their territory again. China has an immense international commerce reflected in its exchange of people and products with almost all countries and therefore its public health measures or lack thereof can have great consequences for all nations.

In developed countries of the Northern Hemisphere, it is hard to understand why supranational agencies and expert institutions did not understand the magnitude of the risk posed by such a singular virus, nor of its capacity to take advantage of globalization with an astonishingly rapid worldwide spread. Indeed, the crucial characteristics of COVID-19 lie in its transmission pathways, existence of asymptomatic/pre-symptomatic carriers and survival potential in the external environment, which were already explained and transmitted to the world by the Chinese colleagues since mid-January. So many scientific publications during the last two decades about the capacity of globalization to facilitate the spread of infectious agents seem to have been ignored. Worldwide spread of viruses following different transmission ways, as HIV virus, Ebola virus, *Aedes* mosquito-borne viruses as those of Zika, Chikungunya and dengue, yearly vaccine problems posed by the quick mutating seasonal flu viruses, seem to have been useless models now in comparison to the very fast spreading new virus. How is it that, in early January, after the recognition that this virus was incubating in China, no leaders seriously considered high risk of an accelerated rate of disease spread posed when Chinese people returned to other countries from their visits to China for the celebration of Chinese New Year?

For COVID-19, we learned early on that there are marked differences in pathogenicity based on age groups, with a pronouncedly higher mortality from the age of 60. It is difficult to understand that no developed country prioritized control measures to be applied to aged people's residences. Many deaths could have been avoided. Was no one in these agencies analyzing age-dependent data?

Initial inaction, subsequent slow reaction [10], and lack of consensus agreements (memorandums of understanding) by neighbouring countries, despite repeated warnings by WHO, suggest that the role of agencies put in place in the past precisely to prevent situations such as the present one, will need to be re-analyzed. The deceptive presentation of countries within the European Union, each acting as if each were working alone, unavoidably poses the question about the usefulness of having a European Centre for Disease Prevention and Control (ECDC, Stockholm). It seems inevitable to conclude that this agency failed in passing the correct message and failed to make the needed timely efforts to convince the leaders of European countries. Surprisingly, the US suffered from similar mistakes as the European countries, including a pronounced delay in creating tests, and in its inexplicable descensions to produce testing criteria that obscured community spread, coupled with a heavy reluctance by the US CDC and US governmental officials to change the testing criteria significantly until mid-March, and the dearth of equipment including lack of needed personal protective equipment, including surgical masks, and facemasks [11] and insufficient quantities of mechanical ventilators for the patients and lack of surgical capacity for hospital beds and ICU space. Much of this reflected the reduction of the Strategic National Stockpile which had been built up throughout the USA in the beginning of this century and slowly degraded to only two locations (Maryland and California), plus the reduction of the Global Health and Security unit (a unit responsible for pandemic preparedness) in the White House National Security staff [12]. The loss of the once robust Strategic National Stockpile for a minimal Stockpile is particularly lamentable, in light of the reality that in the absence of specific treatments, non-pharmacologic approaches rely on supportive therapies with oxygen and ventilatory support, and other equipment coupled with needed PPE that once formed a large part of that Strategic National Stockpile were no longer readily available nationwide. Too often governments focus their defense primarily against other nations and other ideological human actors. World leaders forget that mother nature is the most potent bringer of doom from massive cyclones, destructive wildfires, to horrific pandemics.

Lessons from all this should be learned and appropriate corrections implemented in the near future once the present picture begins to clear.

4. Short-, mid- and long-term scenarios

The short-term scenarios of the present situation pose many questions. China is now suffering from the boomerang of the pandemic and is obliged to recreate barriers to avoid the re-entry of COVID-19 to its territory after they detected the reintroduction by travelers coming from outside of China. In a country with such a massive population, where the vast majority still has not experienced COVID-19, and thus has no previous immunological contact with this virus, the risk of a second wave is very high.

In Europe and North America, no country has yet reached the peak of the epidemiological curve. And there is a great disagreement in the mathematical models being used. One important aspect appears obvious: the successful experience of China in its rapid control of the outbreak cannot be easily extrapolated to occidental democracies where individual freedom is a largely internalized concept, nor do leaders outside of China have the capacity to impose these measures at the level of the Chinese regime [13]. What will happen in countries of the Indian sub-continent, the Middle-East and South America, where crowded living is traditional, mass gatherings are usual, and the national health systems are far from sufficient, also remains an open question. The possibility of the appearance of subsequent secondary peaks cannot not be underestimated.

We should also take great interest in analyzing the, thus far, incomprehensible and considerable differences in mortality rates between different countries (e.g., China-Italy) and between different areas inside the same country (Lombardia compared to its neighbouring areas inside Italy). None of the explanations so far proposed clarify this.

In the mid-term, the subsequent scenario in the Southern Hemisphere must be considered. Nearly all South American, Caribbean and African countries have limited national health systems with insufficient capacity to prevent spread of COVID-19 and to mitigate death

and disabilities. Several of these nations quickly decided to close frontiers, although generally too late, as they already had the disease inside. All indications reveal that the Southern Hemisphere will not escape from the massive problems of this disease. A worrying scenario for their immediate future. The problem is coupled to the question of the extent to which developed countries will manifest the will and the capacity to help Low and Middle Countries. The outbreak in the Southern Hemisphere is flaring now, and this is happening while the higher income nations are still struggling over their own issues in (i) implementing control measures, (ii) trying to recover from the immense social and economic impacts, and (iii) concentrating in impeding re-entry of the virus by foreigners. Nations everywhere must recognize that in this era of massive global exchange of persons and goods, leaving the outbreaks soring anywhere posses a risk everywhere.

The potential long-tern scenario of likely secondary waves of infection is also concerning. A second wave may be more devastating than the first one, as happened in other pandemics in history. Several factors must be considered: (i) once the peak of the epidemiological curve is reached, there will still be many people who are not exposed to the virus, and (ii) we still do not know whether COVID-19 infection furnishes a protective immunization status, or worsens the outcome of second infection, nor do we know anything about the length of such an immunological response.

The fast speed of this pandemic and the unavoidable time needed to discover and develop useful medications, antivirals and vaccines, advocates strongly for the urgency of quickly implemented public health measures of hygiene (respiratory, hand, and environmental), case detection with proper case management and isolation, coupled with social isolation and population quarantines of a duration which may differ according to the objectives such as buying time to (i) avoid the collapse of local health systems, (ii) for the discovery of useful treatments, antivirals and vaccines (dealing with a potential antibody enhanced infection as with SARS may pose difficulties in getting a vaccine), and (iii) have sufficient capacity in terms of ICU, beds, ventilators, and other equipment needed to save lives.

5. The role of scientists and experts

Besides health professionals on the frontline, we need psychologists to help people adapt to the confinement measures, economists to analyze economic consequences, as well as scientists research, develop, and analyze for safety and efficacy useful treatments, antivirals and vaccines, and epidemiologists to analyze the quickly changing epidemiological data, as well as other engineers and others to innovate solutions. All of this is not only crucial but urgent [14,17]. Regarding epidemiological data, it is evident that data on infected subjects from the different countries are only indicative but cannot be compared. Diagnostic test application, i.e. test availability and number of health personnel for sample taking and analysis, differs markedly between countries. This does not mean, however, that these data are not internally useful for a country to follow their epidemiological curve and evaluate the success of their control measures applied.

The recent preliminary results of the observational studies of infected and control patients treated with a combination of hydroxychloroquine sulfate and an antibiotic drug with previously demonstrated action against Zika and Ebola viruses (azithromycin) are promising. Despite the limitations of a small sample size, short-term outcome follow-up, and lack of positive response by 10% of the infected subjects, this appears to be one of the first antiviral drug combination to show serious promise as a cure to COVID-19 and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 worldwide [15]. Another combination with promise is hydroxychloroquine with Remdesivir. More recently, the mechanisms of antiviral effect, the risk-benefit ratio, and the thresholds of efficacy of hydroxychloroquine have been reviewed, and attention has been drawn to the need for high-quality evaluation protocols of the potential beneficial effect of hydroxychloroquine as a post-exposure drug for people exposed to SARS-CoV-2 infection, i.e. people with close contact with positive tested patients, including home and medical caregivers [19].

Additionally, scientists, public health experts, doctors, and experts in infectious diseases should advise governors and other decision makers and be ready to answer requests from the different media. Our expert role is crucial now in transmitting the appropriate information to the people.

We must be very careful in measuring the words we use to avoid misunderstandings. A good example was the initial insistence by governments to downplay the outbreak of the disease. Thus, when it became plain that the spread of the disease in their countries could be significant and could produce severe, even deadly disease, and that strict measures implying individual freedom restrictions should be implemented, a wave of criticism and disbelief immediately followed because people did not understand this change.

Another example has been the continuous reference to flu to help people understand the transmission and the clinical characteristics of the disease. The consequence has been that people immediately considering though that COVID-19 was not so serious, thus complicating subsequent efforts to help people and even decision makers understand that COVID-19 is not a flu.

The way of referring to age-group dependent pathogenicity and mortality also led the youth to think this disease was not relevant to them, which led to massive problems in convincing the youth of their responsibilities in following isolation measures and hygienic standards.

The next problem is to help people understand that reaching the descending arm of the epidemiological curve does not necessarily mean the end of the local epidemic, and that it does not exclude the possibility for further peaks to appear. The temporality concept is not easy to explain, though models exist, thus, no one knows how long it will take to reach the descending arm of the epidemic in each area and whether in neighbouring areas it will follow the same pattern.

Most branches of the media are not accustomed to interviewing scientists and, similarly, many scientists are not used to explaining their science in layman's terms. Scientists must adapt their messages so as to convey the information in a way that laymen can understand. We must recognize that most of the lay audience has virtually no serious background knowledge about health, infectious diseases, or epidemiology. The task may be very difficult, but it is also vital. We must be available and we must communicate, otherwise the media will call on non-expert people who are likely to provide misleading information. The risk from the dissemination of inappropriate information is obvious, even more at a time where people confined to their homes dedicate significant amounts of time to obtain information through the different media.

Economists are logically highly concerned about the economic impact of control measures and go on giving priority to the economic side of the crisis. Even though plenty of models existed that show the economic impacts of the disease, most economists are challenged by the social and economic depth of the COVID-19 pandemic. They are struggling to understand that better control soonest, though of apparent great in economic losses, can ultimately lead to much less total economic loss and to faster recovery. They have not yet grasped that prolonging the outbreak causes far more economic damage than that of taking drastic measures to end the pandemic globally as soon as possible. Similarly, many governmental leaders have difficulties in changing their political “chip” after decades of repeating respective party priorities.

There is an important role for the scientific societies in domains related to the present pandemic. National societies are a good tool to channel appropriate advise up to government decision makers.

We know that globalization and climate change are giving rise to new scenarios in which new infectious agents have more opportunities to originate and, similarly can facilitate spread of already existing agents, which take the advantage to enhance their geographical spread

and can perhaps lead to worse pandemics than the present one [16]. A message to the people is needed to help all persons understand that this changing world unavoidably implies higher probabilities for such situations and that wide research results suggest that other epidemics or pandemics may appear in the future, and to plan for and maintain trained persons with appropriate access to needed equipment and supplies and an easily expanded surg capacity. Understanding the lessons of this pandemic and incorporating those lessons at all levels should lead us towards improving our preparedness in all sectors to mitigate risks from the inevitable next pandemic.

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Santiago Mas-Coma[a,*], Malcolm K. Jones[b], Aileen M. Marty[c]

[a] *Departamento de Parasitologia, Facultad de Farmacia, Universidad de Valencia, Av. Vicent Andres Estelles s/n, 46100 Burjassot, Valencia, Spain*

[b] *School of Veterinary Sciences, Australian Centre for Infectious Diseases, University of Queensland, Brisbane, Queensland 4072, Australia*

[c] *Health Travel Medicine Program, Vaccine Clinic, Emergency Response Team Development, Florida International University, Miami, USA*

E-mail address: s.mas.coma@uv.es (S. Mas-Coma).

* Corresponding author.