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COVID-19 update : what's going on?

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Abstract 109

The COVID-19 pandemic has surprised and profoundly changed the world conditions and life style. Months after the first reported cases, information about the virus's mechanisms of action remains sparse and, for many, uncertain. The causing agent isolated from the epithelial cells of the respiratory tract of these patients was a virus belonging to the coronavirus family. Like all viruses, the viral genome does not remain unchanged. Each new isolate is different from the others, there is a constant evolution of the viral genome. The present COVID-19 pandemic is similar in part to the occurrence of the SARS epidemic in southern China in 2002. Both occurred in winter, the first cases have been exposed to living animals sold on markets, and both were caused by formerly unknown coronaviruses. However, the spread of SARS-CoV-2 has been faster by far although the mortality rate is much lower than that of SARS. With regard to treatment, studies that remain to be verified are emerging with their share of new implications. In this review, these essential points are reviewed. The thorny questions which we face in order to initiate strategies to fight this unprecedented pandemic at several levels, among them the treatments but also the production of the vaccines, are discussed.

1. At the origins

In December 2019 a new epidemic had declared itself in the Chinese province of Wuhan. A number of individuals with pneumonia of unknown causes have been recorded in this locality. These patients all have frequented a market selling fish, seafood and other live animals in this city. The causing agent isolated from the epithelial cells of the respiratory tract of these patients was a virus belonging to the coronavirus family. It was a new virus member of the betacoronavirus family which forms a clade in the subgenus sarbecovirus, subfamily of Orthocoronavirinae [1]. This virus was first named 2019-nCoV and then renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). A SARS-CoV-2 genome sequence was first released on January 10th, 2020, and then five other genome sequences were published [2, 3].

Slightly different from MERS-CoV and SARS-CoV, SARS-CoV-2 is the seventh member of the coronavirus family that infects humans. Four of the six viruses: 229E, OC43, NL63 and HKU1 are widespread and usually cause common cold symptoms in immunocompetent individuals [4]. The other

two viruses, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) have a zoonotic origin and have been linked to life-threatening illnesses [5]. SARS-CoV caused an epidemic of acute respiratory syndrome in 2002 and 2003 in Guangdong Province, China. MERS-CoV caused epidemics of serious respiratory disease in 2012 in the Middle East [5].

The present COVID-19 pandemic is similar in part to the occurrence of the SARS epidemic in southern China in 2002. Both occurred in winter, the first cases have been exposed to living animals sold on markets, and both were caused by formerly unknown coronaviruses. However, the spread of SARS-CoV-2 has been faster by far (transmission power between humans is very potent) although the mortality rate is much lower than that of SARS (2.5 to 13% and a world average of 7.03% for 2019-nCov; 10% for SARS-CoV and 34% for MERS-CoV) [5]. Though, the SARS-CoV-2 has caused far more deaths than the other two viruses (3 267 184 confirmed cases and 229 971 deaths as of Mai 2, 2020 for 2019-nCov; 8,098 cases and 774 deaths for SARS-CoV and 2,494 cases and 858 deaths for MERS-CoV) [6, 7].

2. A changing virus

Coronaviruses are enveloped RNA viruses which are broadly distributed within humans, mammals and birds that cause respiratory, enteric, hepatic and neurological diseases [4]. The SARS-CoV-2 genome consists of a positive polarity RNA molecule with a size of 29,870 bp (not including the poly tail (A); GenBank accession number: MN908947) [8]. Five coding regions (typical ORF) on the same coding strand have been identified (figure 1), including the polyprotein ORF1ab (7096 aa), the spike glycoprotein (1273-aa), the envelope protein (75-aa), the membrane protein (222-aa) and the nucleocapsid protein (419-aa) [8].

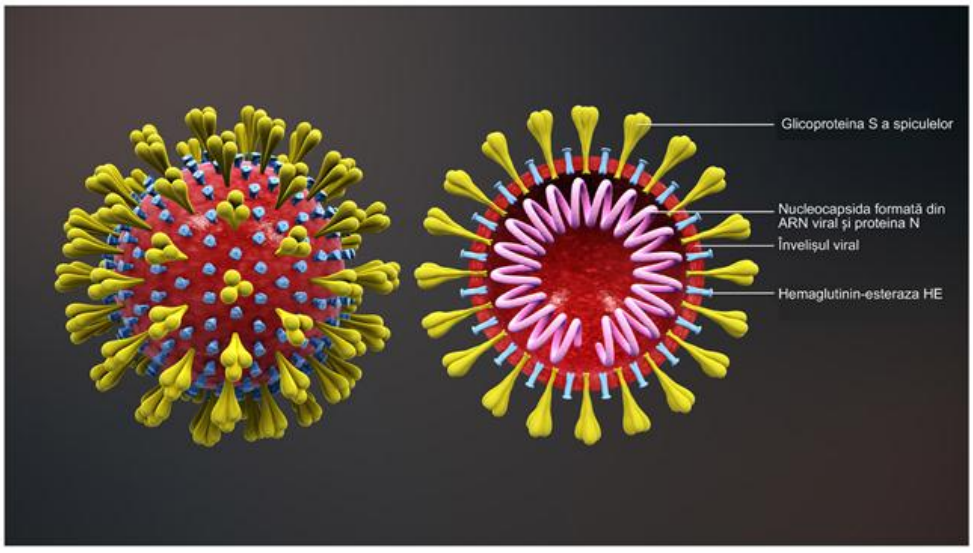

Figure 1. Schema of a Coronavirus. Source: https://www.scientificanimations.com/wiki-images

For many viruses, one of the crucial steps in the emergence process is the transition from animals to humans. However, to date the animal source of SARS-CoV-2 has not been identified with certainty. Bats are known to harbour more than 30 types of coronaviruses and whose complete genomic sequences are known [9]. Comparison of the genomic sequence of SARS-CoV-2 with that of the coronaviruses deposited in genetic databases showed that the SARS type of the bats coronavirus (BatCoV RaTG13) was

the closest compared to SARS-CoV-2 (percentage of nucleotide similarity is 96%) [10]. This suggests the role of bats as the main reservoir for 2019-nCoV, but there is no prove of it so far. Thus, the zoonotic potential of SARS-CoV-2 is currently under investigation.

The SARS-CoV-2 virus since its detection for the first time in the Chinese province of Wuhan, has spread almost globally. Like all viruses, the viral genome does not remain unchanged. Each new isolate is different from the others, there is a constant evolution of the viral genome. It has been suggested that nucleotide substitution is one of the most important mechanisms of viral evolution in nature. A recent study compared the viral genomes of eighty-six complete or nearly complete genomes of SARS-CoV-2 [11]. Numerous mutations and deletions on the coding and non-coding regions have been discovered [9]. Thus, genetic analysis has discovered three deletions in the SARS-CoV-2 genomes of isolates from Japan (Aichi), United States (Wisconsin) and Australia (Victoria) [11]. Alignment of nucleotide sequences also revealed ninety-three mutations across all viral genomes. An important finding from this study is the discovery of three mutations (D354, Y364 and F367) located in the binding domain of the surface glycoprotein receptor [11]. The surface glycoprotein plays an essential role in binding to receptors in the host cells and determines the tropism of the host [12]. It is also the main target of neutralizing antibodies [13]. Mutations in the surface glycoprotein (Figure 2) could induce conformational changes, which may well have led to the alteration of antigenicity. These information are crucial for the development of future vaccines and neutralizing antiviral antibodies to fight the virus. These observations also supplied evidence of the genetic diversity and rapid evolution of this new Coronavirus [11].

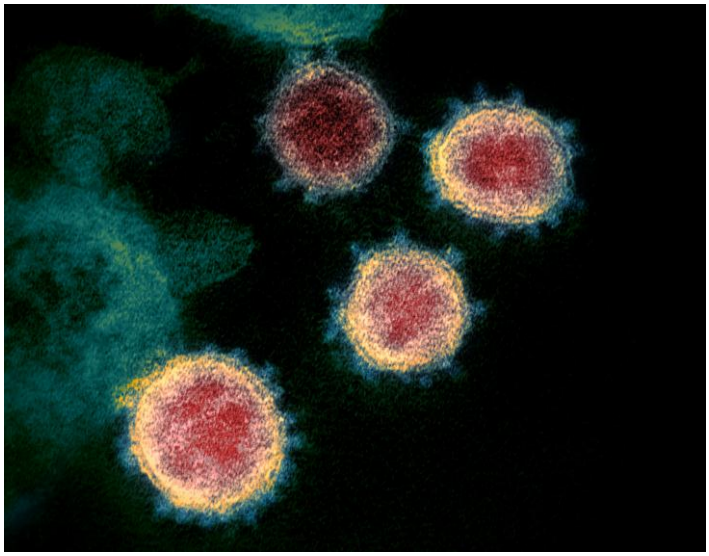

Figure 2. This transmission electron microscope image shows SARS-CoV-2 also known as 2019-nCoV, the virus that causes COVID-19 isolated from a patient in the U.S. Virus particles are shown emerging from the surface of cells cultured in the lab. The spikes on the outer edge of the virus particles give coronaviruses their name, crown-like. Source : https://commons.wikimedia.org/w/index.php?curid=87484997

3. Diversity of expression of the viral receptor in humans

The ACE2 gene codes for the Angiotensin-Converting Enzyme 2 protein, known to be the receptor for both SARS-coronavirus (SARS-CoV) and human respiratory coronavirus (NL63) [14]. Recent studies indicate that ACE2 is the host receptor for the new SARS-CoV-2 coronavirus. The virus is capable to penetrate the target cells through adsorption to the ACE2 receptors. The virus glycoprotein S which

forms the spikes is adsorbed to the ACE2 protein which allows the fusion of the viral membrane with the membrane of the host cell and therefore the internalization of the virus. A number of ACE2 variants may reduce the strength of the association between ACE2 and S protein in SARS-CoV or NL63. Consequently, the level and the mode of expression of human ACE2 in different tissues could be critical for the sensitivity, symptoms and outcome of the SARS-CoV-2 infection [14]. Cells expressing ACE2 are a very small part of lung tissue cells [13]. The distribution of ACE2 receptors in different populations is variable, indicating the diversity of the ACE2 expression pattern in populations [14].

The analysis of 1,700 variants in the ACE2 gene region in different populations has been carried out [14]. Variants in the coding sequence in ACE2 and differences in allelic frequency (AF) between populations were analysed [14]. The results did not reveal any direct genetic evidence supporting the existence of ACE2 mutants that resist to the coronavirus S protein binding in the different populations studied. Variation in ACE2 expression in tissues under similar conditions may suggest a different sensitivity or response to SARS-CoV-2 in different populations.

The study of diabetic retinopathy has shown the existence of a genetic variability in the expression of the ACE2 receptor which modulates the risk of this pathology [15]. It has been shown that overexpression of ACE2 in the retina cells decreases the risk of developing diabetic retinopathy [15]. Thus, we can extrapolate that difference in expression of ACE2 receptors within different human populations can make these populations to be differently sensitive to the virus infection.

4. Clinical characteristics: not everyone is in the same boat.

Transmission of the virus between humans is well established. The virus enters through the airways (nose, throat) and possibly the eyes as well. The source of contamination are the viral particles in the droplets from a cough and sneeze from an infected individual. Viral particles seem to remain on contaminated surfaces for a longer or shorter period depending on the nature of these surfaces. The persistence of viral particles still active in the air that can infect an individual without direct contact between him and the source person has not been corroborated so far. Protection against this type of transmission involves the use of face masks with eye protection, gloves, gowns and hand hygiene. Due to the high risk of transmission to laboratory personnel from patient samples, it has been recommended that laboratory personnel use a Class 2 biological safety cabinet (PII) and personal protective equipment when processing samples likely to generate fine particles. It is of the utmost importance to decontaminate work surfaces and equipment with an approved hospital disinfectant [5].

In humans, the coronaviruses have brief incubation periods, varying from days for SARS-CoV and weeks for MERS-CoV, the COVID-19 appears to fall in between the two: between 2 and 10 days [4, 16]. The diagnosis is founded on Polymerase Chain Reaction tests (RT-PCR). Rapid but less sensitive tests than rRT-PCR have been developed and will make it possible to widen the population testing and consequently it will allow to fight more efficiently the spread of the virus.

The clinical characteristics are also quite similar to the SARS-CoV and MERS-CoV viruses: fever, cough, tightness in the chest, dyspnea and difficulty breathing [5]. Not all individuals have the same degree of severity of these clinical manifestations. The intensity of clinical manifestations ranges from asymptomatic cases, to cases with symptoms of lower respiratory tract infection with radiological signs of pneumonia or Acute Respiratory Distress Syndrome (ARDS). The main reason for admission to the intensive care unit is the development of ARDS. Gastrointestinal symptoms have been reported in 10% of cases, a higher ratio than that seen with other coronaviruses. The new coronavirus is also associated with fewer symptoms of the upper respiratory tract and lower respiratory symptoms than other

coronaviruses [17]. Fever is a predominant symptom, present in 98.6% of cases [18]. Between 20% and 25% require admission to the intensive care unit [18]. Patients admitted to intensive care had a higher serum white blood cell count, lower serum albumin, impaired liver and clotting function (higher D-dimer) [17]. Risk factors associated with the development of ARDS and progression of ARDS to death included advanced age, neutrophilia and organ dysfunction, and bleeding disorders [19].

Considerably, severe cases appear to be more frequent amongst the elderly, whereas very few cases of serious illness amongst children and young adults have been declared. In one study [19], patients with SARS-CoV-2 pneumonia who had developed ARDS had a significantly higher number of neutrophils than those without ARDS, which may have led to activation of neutrophils to execute an immune response against the virus, but also contributing to cytokine storm (Cytokine release syndrome: CRS). This may partly explain the positive association of high fever and ARDS in the early stages of virus infection. Furthermore, given the fact that advanced age is associated with a declining immune competence, [20] the results of this study [19] demonstrated that the advanced age was associated with both the development of ARDS and the occurrence of death. Thus, age-related deaths may be due to less robust immune responses. The results of this study [19] show that a higher number of CD3 and CD4T cells may prevent patients from the development of ARDS. By extrapolation of this fact it can be presumed that any condition that generates a weakened immune system (individuals with hereditary, acquired or temporary immunodeficiency following immunosuppressive treatment following a transplant or following chemotherapy, etc.) could lead to the development of ARDS and death from contracting the virus.

5. Treatments

A new study published by two researchers from Sichuan University in China, sheds light on part of the pathogenicity mechanism of SARS-CoV-2 [21]. The premise of this study is that Coronavirus is not a virus that attacks the respiratory system as we thought so far, but that it attacks the blood system. The study results showed that ORF8 and the surface glycoprotein could bind to porphyrin, respectively. At the same time, the proteins orf1ab, ORF10 and ORF3a could coordinate the attack of heme on the 1-beta chain of haemoglobin to dissociate iron from porphyrin. The attack results in less and less hemoglobin which can carry oxygen and carbon dioxide. Lung cells experience extremely intense poisoning and inflammation due to their inability to frequently exchange carbon dioxide and oxygen, which ultimately results in ground-glass-like lung images. The mechanism also interferes with the normal anabolic pathway of the heme of the human body, and should lead to pathology. Thus, these results could validate the mechanism of action of chloroquine. Chloroquine could prevent orf1ab, ORF3a and ORF10 from attacking the heme allowing porphyrin to form. Chloroquine also inhibits the binding of ORF8 and surface glycoproteins to porphyrins to some extent. These combined effects of the action of chloroquine relieve efficiently symptoms of respiratory distress. If these results are proven right, the use of artificial respirators could be entirely fruitless, and make it necessary to equip the hospital's intensive care units with blood purification devices. As such, the FDA (United States) has just authorized a treatment using blood purification devices (announcement of April 10th, 2020 on the FDA website). That being said, since the ability of chloroquine to inhibit structural proteins is not particularly clear, the therapeutic effect may vary from one patient to another.

A fact that may consolidate the hypothesis of inflammatory pneumonia in cases of patients with ARDS, is the observation that the inflammatory reaction is so disproportionate that it blocks the alveolar system perpetuating respiratory failure, evermore intensely, until the ultimate failure occurs. Thus, it has been

observed in some hospitals, that an anti-inflammatory therapy with corticosteroids has made it possible, in a large number of cases, to achieve remarkable improvements by progressively reducing the inflammatory pneumonia effects until its disappearance and complete recovery. What is being discussed now, is the anticipation of the appearance of post-viral pneumonia by means of a strategy that would stop the extreme immuno-inflammatory reaction before it becomes an irreversible pneumonia.
Favipiravir is one amongst other molecules that have given promising results in the treatment of the virus and who could also find their effects explained by the results of this study [21]. Favipiravir is the latest anti-novel coronavirus drug with specific therapeutic effects. Favipiravir may inhibit the envelope protein and ORF7a protein from binding to porphyrin, by this means avoiding the virus from entering host cells and catching free porphyrins.

6. A long overdue vaccine

Over the past decade, the scientific community and the vaccine industry have been called upon to respond urgently to epidemics of H1N1, Ebola, Zika and now COVID-19. An H1N1 flu vaccine was developed somewhat quickly, mainly since the flu vaccine technology was already fairly developed and major regulators had formerly decided that egg platforms and cells made vaccines could be authorized under the rules used for strain change. The vaccines preventing from SARS, Ebola and Zika have not been effective. The SARS and Zika epidemics ended before the vaccine was developed, and as a consequence public funding has been reallocated to other projects. The development of an Ebola vaccine was pending at the start of the Ebola epidemic in 2013-2016. Development continued still after the epidemic took end and during recent epidemics in the Democratic Republic of the Congo, the vaccine received conditional marketing authorization [22].
Previous research endeavors to come up with a vaccine for the SARS-CoV in the years following the 2003 pandemic made it possible for researchers to develop vaccine concepts and approaches for the COVID-19 pandemic. SARS-CoV and SARS-CoV-2 both have a high degree of genetic similarity and bind to the same ACE2 receptor in the host cell. Based on past experience with SARS-CoV vaccines, it is expected that all COVID-19 vaccines will necessitate careful safety assessments for immunopotentiation which could lead to increased infectivity or eosinophilic infiltration. Amongst the vaccine technologies evaluated are whole (but attenuated) virus vaccines, vaccines with recombinant protein subunits and nucleic acid vaccines.
There are now at least half a dozen candidate vaccines in development at various stages (as of March 3th, 2020) [23]. Two teams have already launched clinical trials, one in the United States and the other in China. According to the World Health Organization, 54 other "candidates" for vaccines are being developed by researchers from academia, biotechnology, large pharmaceutical companies and the military [24]. These candidate vaccines are of several types: live (but attenuated) viruses, subunits of recombinant proteins and nucleic acids. These candidate vaccines may offer promising preventive vaccines against COVID-19. However, each of these vaccines require additional manufacturing steps and formal toxicology tests before obtaining marketing authorization from the health authorities of different countries.
Finally, even if a vaccine or vaccines arrive on the market, ethical questions will arise as to whom will be vaccinated first and which countries will be able to afford it (we have seen the behaviour during this crisis of some countries in order to acquire sanitary equipment). Pandemics will generate simultaneous demand for vaccines worldwide. Clinical and serological studies will be needed to confirm which populations remain most at risk once vaccines are available and could form the basis for establishing a

fair global vaccine allocation system. This vaccination effort must be guided by three imperatives: speed, manufacturing and large-scale deployment and global access. In February 2020, the World Bank and the "Coalition for Epidemic Preparedness Innovations (CEPI)", which funds the development of vaccines against epidemics, co-organized a global consultation on these objectives. This consultation led to the launch of a "COVID-19 Vaccine Development Taskforce" which is currently working on how to finance and manufacture vaccines for global access.

In the end, although the current pandemic is unlikely to end abruptly before the vaccines are ready, efforts must continue to develop the most promising candidate vaccines to the point where they can be stored and ready for testing and emergency authorization in the case of epidemic resurgence.

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