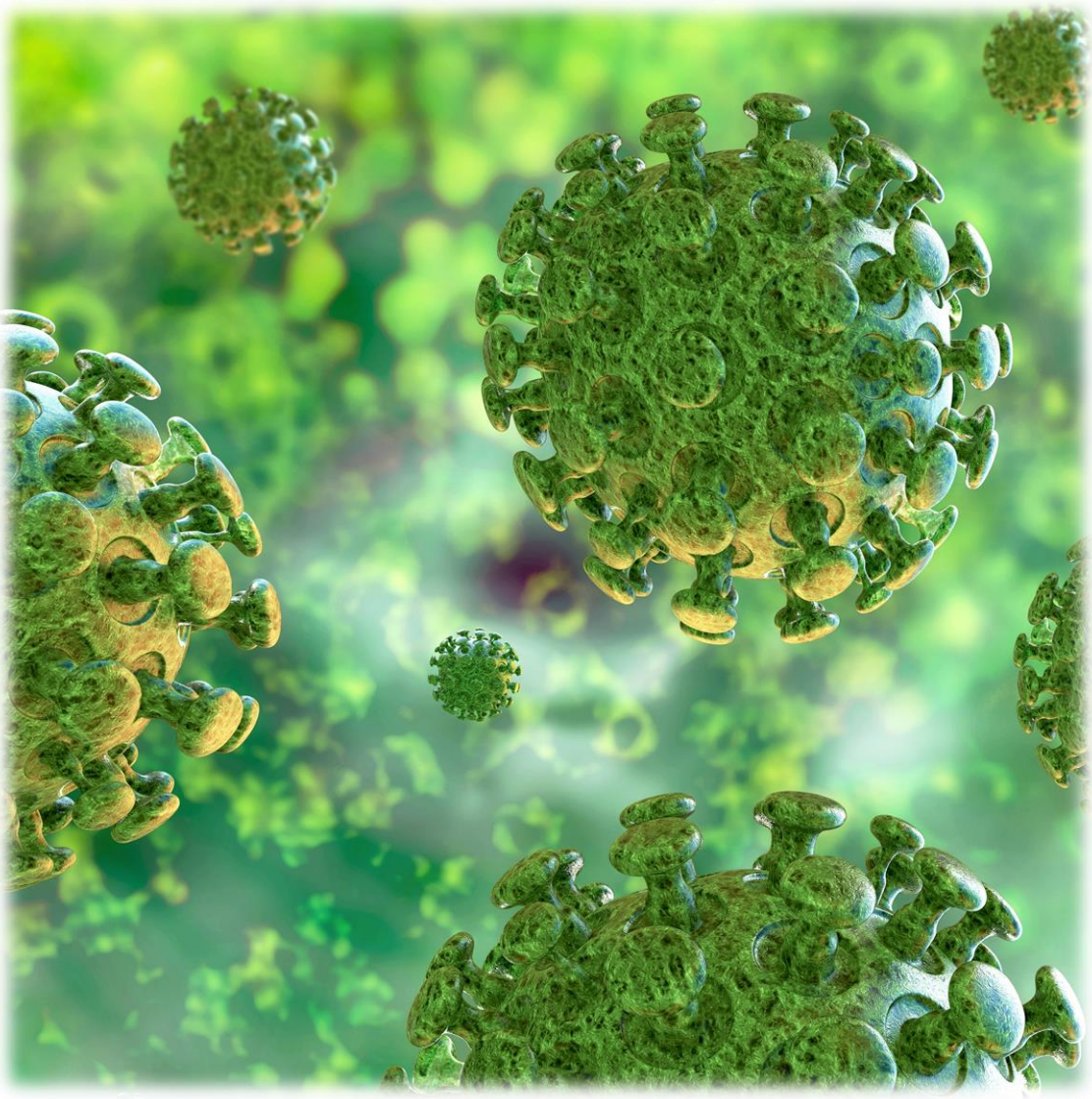
EMERGING VIRUSES. THE EXAMPLE OF COVID-19



Human coronaviruses (HCoVs) have not been considered of great importance in medicine since their discovery in the 1960s. According to the International Committee of Taxonomy of Viruses advised by the Coronaviridae Study Group [(1)], the virus causing the current pandemic crisis (2020) belongs to the Coronaviridae family and is closely related [genomic homology] with which it triggered the epidemic that arose in the province of Guangdong, People's Republic of China, in 2003.

Until the current century, coronaviruses were only responsible for between 10% and 30% of upper respiratory tract infections (common colds). They are RNA-viruses, classified into four genera: α, β, γ, δ; only α and β being

infectious to humans. All four strains that cause upper respiratory tract infections in humans (HCoV 229E, NL63, OC43, and HKU1) are endemic worldwide. The main animal reservoir for these coronaviruses is bats. These animals also act as a reservoir for numerous zoonosis-causing viruses, including the Marburg, Hendra, Nipah, and Menangle viruses, but also viruses better known as the rabies virus [(2)]. Some characteristics of the life cycle of these chiropterans make them optimal virus hosts: they live in large social groups and they are long-lived compared to animals of their size. In addition, they fly, have night-time habits and frequently change their communities. Other animals, both wild and domestic, act as intermediate hosts, contagious after the bite of these chiropterans.

Viruses undergo mutations or gene exchanges when they transfer between different species, including humans. New viruses arising from these gene mutations or transpositions can acquire infectious ability, and /or modify their virulence.

Until 2002, coronaviruses received some medical attention, as several cases of atypical pneumonia were described in the Chinese province of Guangdong, later acquiring epidemic entity, affecting more than twenty countries. The new disease was designated with the acronym SARS (Severe Acute Respiratory Syndrome) [(3)] and the causal germ β-HCoV, which was named SARS-CoV thereafter. The infections took place in street markets where live wild animals were sold, in this case civets and raccoons. However, it was soon known that these animals were in fact the second hosts of the virus, bats being their natural reservoirs. The symptoms of SARS were fever, cough, dyspnoea, and, more rarely, watery diarrhoea. Between 20 and 30% of those infected required support to breathe; and approximately 10% of all infected died, mostly elderly people with chronic comorbidity. Some direct infections between humans were reported, activating the risk of a pandemic. However, direct contagion between humans was limited to the hospital setting, where the most seriously ill patients were found, possibly with a higher "viral load". This nosocomial expansion was explained by the fact that the SARS-CoV' glycoprotein-S was linked to a more abundant enzyme ("angiotensin-

convertase-II") in the bronchial cells of the lower respiratory tract. The distribution of this enzyme (predominantly in the lower respiratory tract) explains why the most severe symptoms appear approximately ten days after contagion when most of the patients had already been hospitalized. Often the patients needed to be intubated, which indirectly contributed to the nosocomial expansion of the infection.

Hong Kong played a major role in the dissemination of the epidemic. In the Amoy Gardens housing complex direct human-to-human transmission was first seen in an outpatient setting, and it is believed that the virus' international spread started from clients of the Metropole Hotel. The factor (or factors) that induced or favoured the jump from zoonotic transmission to direct contagion between humans is still ignored. The improbability (not impossibility) of direct contagious between humans caused the epidemic to end as suddenly as it arose, without needing the use of the vaccine that was developed 20 months after the start of the epidemic. 8,098 people were infected, of whom 774 died (just under 10%).

In 2012, another β-Cov (β-coronavirus) was isolated from the sputum of a Saudi man who ended up dying of respiratory failure. It was the first case of another pneumonic syndrome, the so-called MERS (acronym for Middle East Respiratory Syndrome) [(4)]. The responsible coronavirus was designated MERS-CoV. Unlike SARS, this new virus did not spread worldwide, leaving it confined to Saudi Arabia and a few relatively distant countries, notably Iran and Algeria. In this case, the transmission was solely zoonotic, affecting camel keepers. The first cases were reported in the palm groves of the *Al Ahsa* oasis (Saudi Arabia), considered the largest in the world. Although MERS transmissions were mostly zoonotic, some nosocomial infections occurred among people with great contagiousness, the so-called super-transmitters. The incidence of the outbreak reached a peak coinciding with the time of the year when female camels calve. Apparently, bats (very abundant in desert oases) bit camel calves, from where the virus spread to keepers. 2,494 persons were infected by MERS-CoV. Between 50 and 89% required mechanical ventilation, the mortality rate being 36%.

The mortality rate gap between SARS and MERS, both severe atypical types of pneumonia, is due to the latter also producing gastrointestinal symptoms and acute kidney failure: β-MERS-Cov' glycoprotein appears to have an affinity for the human enzyme DPP4 ("Dipeptidyl-Peptidase-4"), abundant both in the kidney, and the lower respiratory and gastrointestinal tracts.

Although the MERS outbreak did not cause the global alarm of SARS, despite being much more deadly (36% MERS *vs*. ~ 10% SARS), these outbreaks evidenced the risks associated with viral zoonotic. World Health Organization included these viruses in Priority Pathogen List [(5)]. The author of this paper wrote in an article published on his website on 6th June of 2013[(6)], regarding the MERS: *all this epidemic information might seem culturally and geographically distant. However, we must assume, knowingly but not fearfully, that an emerging virus, sooner rather than later, will cause a global pandemic. It may arise in China, in the Central African jungles, Bangladesh, or the Arabian Peninsula, but it will likely acquire global dimensions* (*sic*).

On 31st December of 2019, authorities in the People's Republic of China reported an unusual outbreak of pneumonia at a seafood market in Wuhan City, Hubei Province. An unidentified coronavirus was responsible for this new pneumonic outbreak. The number of infected began to increase following a geometric (exponential) progression. During the first ten days of January 2020 researchers at the Shanghai Public Health Clinical Centre in collaboration with the School of Public Health deciphered the entire genome of this new virus. The selfless delivery of this scientific achievement allowed a rapid global response to this emerging infection. This new coronavirus (Cov-19) has a homology [genomic] with the SARS of 2003: both interact with the enzyme «angiotensin-convertase-II». However, unlike SARS-Covid-1 (from 2003), this coronavirus (Covid-19) is directly transmitted between humans, both through respiratory droplets produced when coughing or sneezing, and by contaminated objects. The World Health Organization declared the pandemic situation on 11th March of 2020.

Some drugs have been tested to treat the most seriously infected:

- Remdesivir, patented by Gilead Sciences (which delivered a significant number of doses to the People's Republic of China). This medicine was already used during the Ebola haemorrhagic virus epidemic [(7)] in 2014.
- The anti-retroviral drugs Lopinavir and Ritonavir, and Interferon-γ, have been used, but the clinical outcome has not been published yet.
- Umifenovir (Arbidol®), an anti-influenza drug used exclusively in Russia and China, together with the anti-retroviral drug Darunavir, have been tested, but their efficacy has not been objectively determined. In addition, various anti-retroviral drugs are being tested in some hospitals.
- Although there is no evidence of its efficacy, some countries (Germany, United States) are using the anti-malarian agent Chloroquine (and Hydroxychloroquine) as a possible treatment. The argument is based on an observation considered hitherto almost marginal: Chloroquine (and Hydroxychloroquine) blocking of the cellular protein *sigma-1*; and the fact that Covid-19 interacts with this protein. The World Health Organization has announced the start of a clinical trial using Chloroquine and the macrolide antibiotic Azithromycin. This clinical trial has been branded as Solidarity.
- At the moment of the writing of this paper, 22 drugs are been trialled *in vitro* in the Icahn School of Medicine Mount Sinai in New York and at the Pasteur Institute in Paris.

Another alternative is the development of a vaccine against Covid-19. Until a few years ago, the development of a new vaccine (either with inactivated or attenuated viruses) took usually from 15 to 20 years. However, the emergence of *new* viruses with pandemic potential has accelerated this *interim*. The 2003' SARS epidemic vaccine was developed in 20 months, the 2006 A / Indonesia H5N1 flu vaccine was completed in 11 months, the A / California H1N1 flu shot was achieved in 4 months, and the Zika' virus vaccine [(8)] took only 3.5 months. Therefore,

the development of the Covid-19 vaccine is not expected to take too long. However, the *Achilles heel* of these accelerated formulation and authorization procedures is the lack of long-term safety studies.

Addressing the uncertainty of the current situation under the sword of Damocles that hangs over each one of us is a complicated exercise, but a necessary one. The pandemic will pass, leaving a trail of suffering, death, and socioeconomic destruction, unpredictable when this text is been written (around March 28, 2020), and goes beyond the purpose of the article. At least, we must learn something from this sad scenario: new viruses with pandemic potential will emerge. There is an urgent need to streamline research on effective treatments for viral and multi-resistant bacterial infections [(9)].

Bibliography

1.- Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe Acute Respiratory Syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2 Nature Microbiology 2020; **5**: 536-44.

2.- López-Tricas, JM Rabia: anotaciones históricas (writting in spanish). In: http://www.info-farmacia.com/historia/rabia-anotaciones-historicas. In www.info-farmacia.com Consult: Mars 2020.

3.- López-Tricas, JM. Cuestiones básicas sobre el SARS. In: http://www.info-farmacia.com/actualidad/desarrollo-y-conciencia-social/cuestiones-sobre-el-sars-sindrome-respiratorio-agudo-grave. In: www.info-farmacia.com. Consult: Mars 2020.

4.- Middle East Respiratory Syndrome. Centers for Disease Control and Prevention (CDC). In: https://www.cdc.gov/coronavirus/mers/index.html. Consult: Mars 2020.

5.- 2018 Annual review of diseases prioritized under the Research and Development Blueprint. 6-7 February 2018. World Health Organization. In:

https://www.who.int/emergencies/diseases/2018prioritization-report.pdf?ua=1. Consult: Mars 2020.

6.- López-Tricas, JM. El enemigo silencioso (writting in spanish). In: http://www.info-farmacia.com/microbiologia/el-enemigo-silencioso. In www.info-farmacia.com. Consult: Mars 2020.

7.- López-Tricas, JM, Álvarez-de-Toledo-Bayarte, A. The Virus in the heart of darkness. European Journal of Clinical Pharmacy 2014; **16**(6):387-389.

8.- López-Tricas, JM. Zika: un bosque ugandés (writting in spanish). In: http://www.info-farmacia.com/historia/zika-un-bosque-ugandes. In: www.info-farmacia.com. Consul: Mars 2020.

9.- López-Tricas, JM. Drug Innonvation crisis. European Journal of Clinical Pharmacy 2015; **17**(2): 75-76.

Zaragoza (Spain) Mars, 27th 2020

López-Tricas, JM

Hospital Pharmacist