



COVID-19. Unanswered issues

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Just three days before Austria accepted the conditions for the armistice and a full military German withdrawal from the Scheldt to the Aisne rivers to end World War I took effect, a Mexican newspaper dated Sunday November 3rd 1918, within different important published news reflecting the great havoc that influenza caused with entire towns that had fallen to the weight of the epidemic, the inhabitants that were saved being counted, while in the capital city with the exception of the poor neighborhoods it was still benign and in full growth, published the photograph of the Japanese doctor Takabatake with a mask of his invention, with the legend that this represented the best way to prevent the Spanish influenza.

Since then, different protective devices have been used by health professionals to protect themselves from the spread of different infectious diseases, especially the respiratory ones. Respiratory protection devices are used to protect the wearers from inhaling particles suspended in the air. Filtering face piece respirators are usually tested utilizing nonbiologic particles, whereas their use often aims at reducing exposure to biologic aerosols, including infectious agents such as viruses and bacteria.

We know that the net effect of coughing is the production of a brief but violent burst of air, which leaves the trachea at speeds very close to 800 km / hr (approximately 65% of the speed of sound), loosening mucus and foreign bodies if they exist and displacing them upwards, can you imagine the explosive exit of small particles of less than 100 nanometers from the airway? Although the mask usefulness has been demonstrated in certain clinical contexts, mainly in-hospital, through its correct use with different materials and filtration capacities depending on the specific medical activity to be carried out, we now see its indiscriminate use on the streets in times of shortage of personal protective equipment, mainly due to political decisions even against the WHO recommendations. We know that wearing a mask outside hospital facilities offers little, if any, protection from infection and that a person who wears a mask touches his face more frequently compared to what he would do regularly, and that eye protection is essential.

Then is it just a social talisman psychological effect?, a reminder of the importance of social distancing and other infection-control measures?, is it just pretending that something is being done to protect people, a reaction to anxiety?, or simply a decision to make visible the invisible danger that the virus represent?

Like this, there are a number of unanswered questions with this new disease that afflicts all humanity and carries one of the most horrible names in medicine: COVID-19, at least influenza (due to the influence of the stars) has an euphonic one.

One of them is how and when reopen the economy, maybe we should turn again our eyes to history; in 2003 a Canadian woman on a visit to Honk Kong became exposed there to SARS-CoV and incubated the virus as she traveled back home in Toronto. She developed fever, respiratory distress and died. Her son that cared her at home soon felt sick, with breathing difficulty and in a fully crowded emergency room, infected two more people which in turn spread to others including patients, visitors and health care workers. This resulted in 375 SARS-CoV cases, 45% or 169 of them were health workers, two nurses and one doctor died, the infection spread to eleven of Toronto's acute care hospitals. The WHO authorities advised a quarantine that, within 3 months after the first incident case, was discontinued when local authorities declared the crisis over. Nevertheless a second and larger wave followed, likely due to the political and business pressures to lift the WHO advisory warning, the removal of local emergency restrictions, and a decrease in the surveillance mechanisms. Many lessons have to be learned from this first pandemic of the twenty-first century, which is not the first in the history of humanity with exactly this error, but an important one is that local and national politics as well as government control to protect any nation's image, business, trade or economy must be secondary to international health concerns. There is currently pressure from the American government for Mexico to reopen different manufacturing activities with the idea of not interrupting production chains, with unknown future results. The different regions of the planet are experiencing different times of the pandemic and large nations, territorially and populationally like ours, must dynamically regionalize their action plans, being crucial factors to have accurate and reliable situational data and to be able to carry out a sufficiently large

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number of diagnostic tests that timely translate the dynamics of the epidemic in the different regions of the country. This figure has been calculated in the order of 900,000 daily tests in the USA in order to safely reopen the economy, well above the current testing capacity of that nation, so it is prevented from tracing the contacts of infected people; everyone can draw their conclusions for Mexico. That is why there are prevailing doubts: are we going in the right direction? Has the epidemic been contained? Is there a real risk of uncontrollable outbreaks? Are we out of danger? Should we extend the quarantine for longer? Only time will give us the answer, hoping that history does not point to this generation for not having learned the lesson and having made the same mistakes of the past; even though epidemics are of short memory in society.

On the other hand, we know from reliable scientific sources that COVID-19 does not have a specific treatment and that multiple and accelerated efforts are being made around the world in search of a desired cure for the disease, with almost 1,500 different trials registered in Clinicaltrials.gov mostly with therapeutic interventions. Recently remdesivir, an existing antiviral prodrug with negative results in the past for Ebola and hepatitis and whose active compound is an adenosine analog, and that has shown in vitro to be able to inhibit some of the previous and similar SARS-CoV-2 coronaviruses such as SARS-CoV and MERS-Cov and in subsequent studies in animals has shown utility in the treatment of MERS in mice and a prophylactic role in rhesus monkeys, has obtained an emergency authorization from the FDA in the USA (and later in other countries) to be used in cases of COVID-19 in its severe pneumonic form. This comes from an international unpublished controlled clinical trial organized by the NIH in the USA in which it was compared against placebo in a group of 1,063 patients with COVID-19 and in which the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran participated as a Mexican center. The final outcome was the time to achieve clinical improvement; preliminarily, it was observed that this experimental drug offered the advantage of requiring 31% less time to recover compared to placebo, which represents an average of 4 days less hospitalization in an average case (11 days). Mortality did not reach statistical significance between the two arms (8% with remdesivir vs. 11.6% with placebo, $p = 0.06$), similar to what was reported by Chinese researchers in another trial. We will have to wait for this work to undergo peer review and be published. Meanwhile, how long will it take for its mass production and distribution outside the first world? And at what cost? And above all, will it be really cost-effective? Continuing with the same line of thought about clinical research, one more aspect to consider in this pandemic is what has happened to medicine and daily clinical

management. It seems that years of effort in building the search for the best scientific evidence has been lost in a few weeks. We know that biological plausibility is insufficient justification to administer a medication to a critically ill patient outside of a clinical trial, however this is being done with worrying frequency in this pandemic, despite the fact that human clinical research is often highly regulated everywhere. Many drugs including hydroxychloroquine, azithromycin, doxycycline, remdesivir, lopinavir-ritonavir, heparin, low-molecular-weight heparin, tissue plasminogen activator, glucocorticoids in different doses, tocilizumab, eculizumab, interferons beta and gamma, IL-1 inhibitors, mesenchymal stem cells, convalescent plasma, inhaled nitric oxide, vitamin C, between others are being dangerously administered on a discretionary basis to many critically ill patients due to the desire to do something for them, even in the absence of compassionate use legislation and scientific evidence, the existence of negative clinical trials for both viral pneumonia and ARDS and may even constitute in some instances a qualified crime or at least an ethical misconduct, all under the silence of the administrative authorities. How many complications and how many deaths could be related to this inappropriate off-label and off-trial practice?, what message are we giving to the new generations of young physicians?, with these actions to what extent are the costs of care impacted during the pandemic?, the results of the management of these anecdotal cases, no matter if good or bad and in the absence of randomization and control groups, contribute to the advancement of science?, when will we have enough good quality research results to build robust evidence in the management of this disease?

Otherwise there have been signs of appreciation and recognition from society towards the medical community worldwide, although unfortunately and paradoxically also of aggression against health personnel, mainly in places with poverty, injustice and lack of culture where the sanitary infrastructure is usually insufficient, we can ask ourselves what is driving these pathological behaviors? Is it just ignorance? excessive fear in a society used to living in violence?, chronic injustice and lack of accountability?. Perhaps more if we pay attention to the fact that such assaults are directed more towards the female sex, particularly nurses, making it obvious a background of gender violence and extreme abuse of the weakest, an inadmissible behavior that must be quickly stopped and punished.

Moreover many other unanswered questions come to the mind, what will be the final number of asymptomatic patients and its effect on the final control of the pandemic in 2020-2021?, what will be the final number of mechanical ventilators in Mexico and will it be really feasible to move them in a timely manner based on geographic demand?, do mechanical ventilation strategies optimized

in ARDS trials still apply to this new disease?, how many total cases we will arrive in Mexico and in the world?, when will the peak of cases reach the different regions and what will be the final behavior of the pandemic?, what about the final number of testing and confirmed cases?, the global and national mortality rates?, how will the rest of the year be?, and to what extent this pandemic will change the future investment in medical infrastructure and training of health personnel adjusting it in the proportion required for population and economy size?

And on the other hand who will win the race for obtaining an approved COVID-19 vaccine: England, Germany, the USA, China or another nation?, and what ethical, political and economic pressures will drive its initial distribution and when?

And beyond medicine, the social and economic consequences of the pandemic are in sight, but what will happen to them in the medium and long term, and what will our future lives be like in terms of a new order and novel lifestyle?, how will education evolve in the new times to come?, and how will this different educational process impact knowledge, politics, humanism, society and all the activity and future of humanity?

Finally there are clear signals of change in the world, can we realize them?, for now, staying healthy is an essential job especially us intensivists.

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