

What we have learned for the future about COVID-19 and healthcare management of it?

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Abstract *Background and aim of the work:* COVID-19 is a current global pandemic. However, comprehensive global data analyses for its healthcare management are lacking. *Methods:* In this study we have researched through published scientific articles and international health care guidelines to find out actually about our knowledge for this new pandemic from SARS-CoV-2 and related COVID-19 disease that emerged from December 2019 in China in order to better manage this health emergency. *Results:* The pathogens represented by microorganisms (bacteria, mycetes or viruses) show their effect after days and are responsible for epidemics/pandemics as dangerous as the greater their possibility of transmission, especially by inhalation, and therefore their infectivity. *Conclusions:* The appearance of new pathogenic viruses for humans such as the COVID-19, which previously were found only in the animal world occurs through the spillover (is the third documented of an animal coronavirus to humans), it is thought that it could also be the same also for the origin of this virus. Furthermore, the trend of this pandemic in one of the countries most affected by Italy after China was also considered.

Keywords: Zoonosis, spillover, coronavirus, pandemics, SARS-CoV-2, COVID-19

Introduction

The new coronavirus, known to scientists as Covid-19, has already claimed the lives of thousands of people in China (in December 2019) and other countries. The new virus is believed to have originated at a seafood market in China's Uhan, where illegal animal trade took. The strain of Coronavirus (nCoV) and this positive stranded RNA viruses with a crown-like appearance called SARS-CoV-2 (previously 2019-

nCoV), has never been identified before being reported in China.[1,2] The target are the epithelial cells of the respiratory and gastrointestinal tract and can cause diseases with various clinical manifestations. The World Health Organization (W.H.O.) has declared that the epidemic is "a public health emergency of international interest", thus the pandemic wide world infection still until today. The international situation according to the latest WHO data (Health Emergency Dashboard) July 14, 2020 are 12,880,565 cases

confirmed worldwide since the beginning of the epidemic and 568,573 deaths and in particular in Europe 2,935,159 confirmed cases and 203,681 deaths [1,2,3].

The Coronaviruses

Coronaviruses were identified in the mid-1960s and are known to infect humans and certain animals. In fact, until today there are 7 Coronaviruses that can infect humans; the commonest human are the 2 Beta-coronaviruses (HCoV-OC43 and HCoV-HKU1) and the 2 Alpha-coronaviruses (HCoV-229E and HCoV-NL63) which can cause common flu syndromes, but also the 3 Beta-coronaviruses (SARS-CoV, MERS-CoV and 2019-nCoV- today called SARS-CoV-2) that can mainly cause middle or severe diseases of the lower respiratory tract [1,2,3].

The scientific community is currently trying to identify the source of the infection which is still uncertain. According to the recent evidences, in late 2019 someone at the Wuhan seafood market in Wuhan was infected with SARS-CoV-2, but specific animal associations have not been confirmed, and then the viral infectious disease spread from that first cluster in the capital of China's Hubei province to a pandemic. An initial study hypothesized that coronavirus was transmitted to humans by two species of poisonous snakes, the *Naja atra* (Chinese cobra) and the *Bungarus multicinctus* (Taiwanese or Chinese krait), which are sold in the open air market in Wuhan, China. Snakes hunt bats and report that the two snakes increase the chances of the 2019-nCoV spillover from species to species (i.e. bats) and from there to humans at the beginning. However, this study sparked heated debate in China, with many scientists questioning the possibility that COVID-19 was transmitted to humans by snakes, since in the past all known carriers of similar viruses were found in mammals.[4,5]

The most prevalent scenario, however, is that the COVID -19 was transmitted by bats. At least that's what scientists at the Wuhan Institute of Biology, which is at the center of the epidemic that is hitting China, have revealed. In a recent study a match of 96.2% was found through a large database examined all viruses, with a known coronavirus that sur-

vives in bats. Thus, according to the above results, the first patients who entered the Wuhan public market, consumed probably bats. However, not only does COVID-19 come from bats, but also other viruses such as rabies, Ebola, pandemics SARS (emerged in 2003) and MERS (emerged in 2012). In fact, various studies on their presence and ability to infect humans arrive after the appearance of SARS (closely related coronavirus), identifying the rich genetic heritage of this virus. The virus Sars-CoV-2, as in the SARS-CoV, shares the same spike key protein and through its adaptation to an ACE2 receptor it enters the cell more effectively than curved sores. So it has been noticed that bats host a high percentage of zoonotic viruses compared to other mammals and for this reason they are important hosts of Coronaviruses reservoirs in the world and therefore also in China (Tab1) [5,6,7].

The Evolution of COVID-19 Management

China has taken all necessary measures today, barring the Chinese from consuming any wild animals and meanwhile, has announced a temporary ban on wildlife trafficking as part of measures taken to stem the spread of the new corona, which was launched from a market where such animals were sold. According to the CDC, SARS-Cov-2 mainly spreads through close contact with affected individuals or through respiratory droplets after an infected individual coughs or sneezes. The virus can survive for relatively long periods on surfaces. The COVID-19 has been shown to spread to humans after close contact A recent study found that it was detectable in aerosol drops (*Flügge's drops*) for up to three hours, up to four hours on copper, up to 24 hours on cardboard and up to 2-3 days on plastic and stainless steel [2,3,8]. The CDC recommends hand wash with standard soap and water or a hand disinfectant that contains at least 60% alcohol and cleaning surfaces with detergents or common disinfectants (a solution of bleach or also the use of alcoholic solution 70%). The social distancing thus, close contact is still the main way in which this disease spreads. Avoid being six feet closer to others, stay home if you are sick, work from home if possible. the contact that exists between the patient and the people who care for him or the stay

Tab 1. Coronaviruses presence in animal species reported in China [5]

Coronavirus Species in Chinese animals				
	Bats	Birds	Pigs	Rats
α -CoV	BtCoV-HKU10		PEDV	LRNV
	BtRfCoV-HuB13		BtRhCoV-HKU2	
	BtMiCoV-1		TGEV	
	BtMiCoV-HKU8			
	BtMy-Sax11			
	BtNy-Sc13			
	BtScCoV-512			
	BtRhCoV-HKU2			
β -CoV	HCoV-HKU1			RtCoV-HKU24
	MERSr-CoV			
	SARSr-CoV			
δ -CoV		WiCoV-HKU20	PoCoV-HKU15	
		BuCoV-HKU11		
		MuCoV-HKU13		
		WECov-HKU13		
		NHCov-HKU19		
		CMCoV-HKU21		
γ -CoV		IBV (Avian infectious bronchitis virus)		

in the same place with the patient during the infection phase. Cases of virus transmission from patients to nursing staff have been reported, and human-to-human transmission cases are still being investigated in several endemic countries [1,3]. The WHO underlines that all people (healthy or otherwise) must protect themselves from COVID-19 infection in order to protect the whole population through the rules of the “*Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)*”. Indeed, International Health Agencies, Regional politics and media recommend maximum precautions and stress the importance for all communities to protect themselves and others by the use of personal protective equipment (gloves and medical masks) as a prevention measures to limit the spread and avoiding people aggregations and crowded

spaces, maintaining distance of at least one meter from any person. There were severe social isolation measures and the blocking of mandatory public traffic all over the world to avoid human contact is therefore the spread of the virus [1,9].

China and Italy have been the first countries with the earlier and most large number of patients and deaths. Italy, after three months from the arise of the current COVID-19 pandemics and after the lockdown are changing with some positive effects. To date, the total cases in Italy are 243,344 with current positives 12,919, discharged/healed 195,441 and 34,984 deceased. On 14/7/ 2020 the new healed cases were 374 and 27 new cases deceased (Graphics 1 and 2). From May 4, 2020, Italian Government allowed the so called “Phase two”, a period of greater freedom but always

with strong recommendations of respecting constant hygiene's measures, on alert for eventual rise in new cases. Now, it is recommended that people conduct hand hygiene frequently, if possible using hot water and soap, or rubbing them using an alcohol-based solution in public places or at home, cover the nose and mouth with the surgical mask in closed public places (but if you cough or sneeze without mask use your arm to cover your face and refraining from touching your mouth and nose in public places) and finally no clumping. Also, on the hospitals at the entrance there is the detection of body temperature [3,9-12].

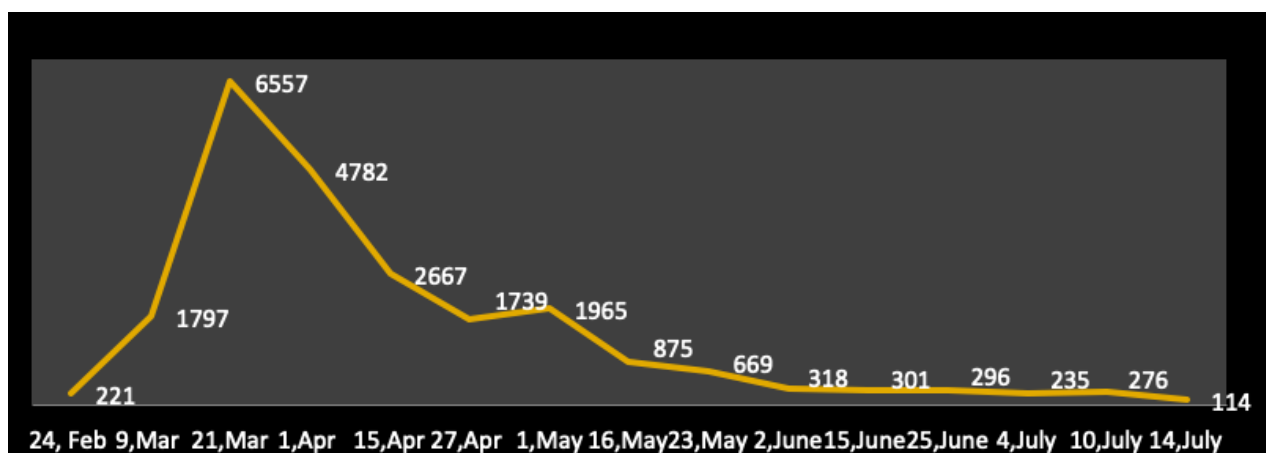
Currently, the American Veterinary Medical Association (AVMA) points out that there is no evidence that pets are infected with SARS-Cov-2 or that they spread it to humans. Their current recommendations are to practice normal hand washing before and after interaction with pets if you are not sick. If you are sick or know that you have been infected with SARS-Cov-2, AVMA advises you not to have contact with your pets and to ensure that someone else takes care of them very carefully [13].

Clinical Scenarios of COVID-19

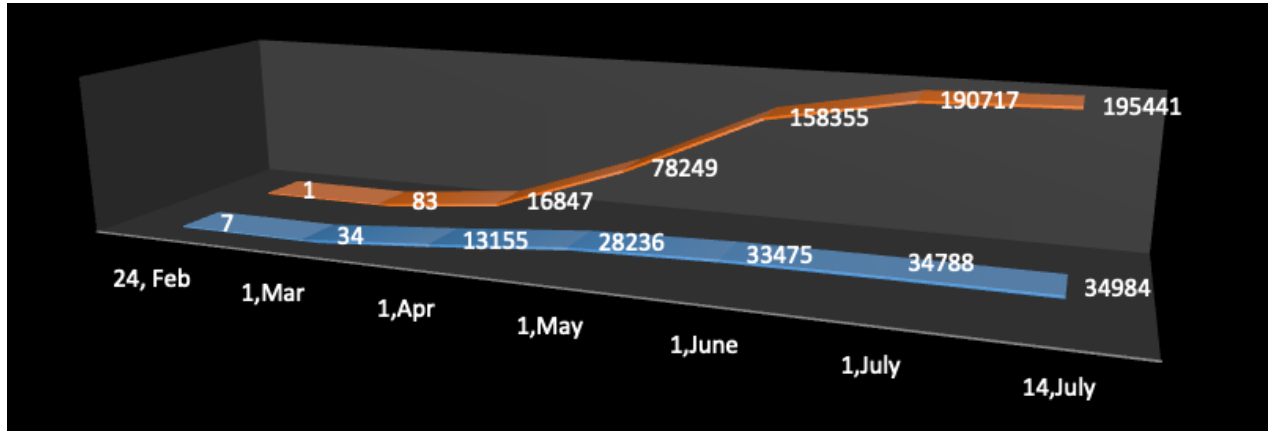
Evidence to date suggests that COVID-19 infects people of all age and the incubation period for is thought to extend to 14 days. Hospitalization rates it

is very frequent for people over 60 years of age. The appearance of the clinical manifestation forms is mainly two: asymptomatic or pauci-symptomatic. Generally, the symptoms are average not nonspecific, especially in children and young adults, and have a slow evolution in the beginning. In some patients the infection can be evolved in pneumonia, severe acute respiratory syndrome, multiple organ dysfunction (MOF), and even death and differential diagnosis should include the possibility of infection as a flaw [1,3,14-16]. So, we can have weakness, nasal congestion, runny nose, dry cough, fever, sore throat, muscle soreness or pain. In some cases, various neurological symptoms have occurred which may have their cause either by the direct effect of the virus on the nervous system or as a para-infectious or post-infectious immune-mediated response. Alongside this, they can occur in some cases, hyposmia, anosmia, ageusia, altered mental status (encephalopathy and encephalitis), cerebrovascular events (ischaemic strokes, intracerebral haemorrhages and other) and neuropsychiatric symptoms (psychosis, neurocognitive (dementia-like) syndrome, affective disorders) Graphic 3 [17,18].

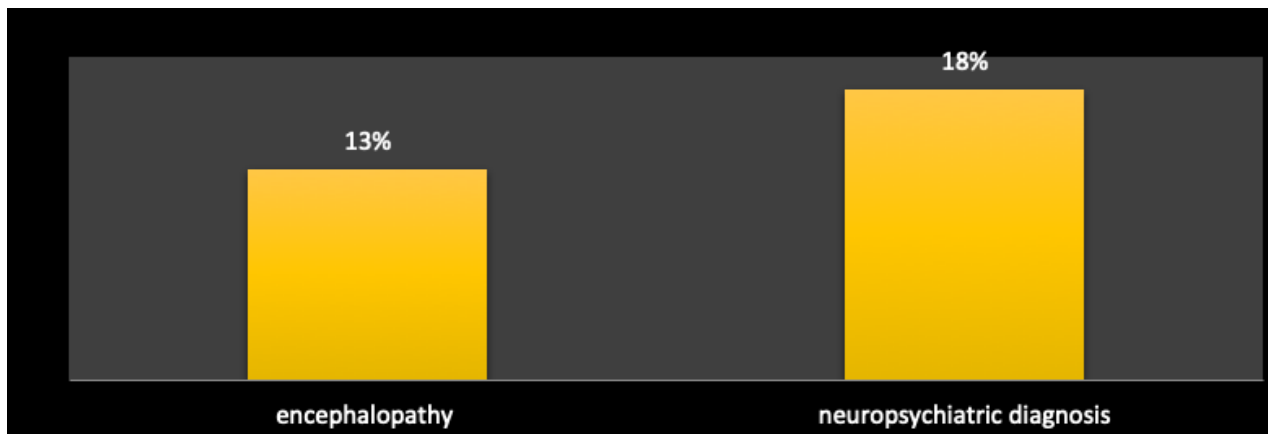
Furthermore, dermatological manifestation are usually skin sings such as urticaria, pityriasis rosea and other. Some patients may have gastrointestinal symptoms such as abdominal pain, nausea, emesis and diarrhea and later kidney failure. In addition, a toxic shock syndrome and atypical Kawasaki disease



Graphic 1. The number of new cases by month registered for Covid-19 of a total of 243,344. Notice that have only 114 new confirmed cases in 14, July 2020 after lockdown and with the individual protect people guidelines on *fase 2* (Data from the Department of Civil Protection COVID-19 case update, Italy)



Graphic 2. The total of healed cases (orange) and deaths (blue) by month to date (Data from the Department of Civil Protection COVID-19 update, Italy)



Graphic 3. Neurological or psychiatric symptoms in one report of 125 patients with Covid-19 [17]

symptoms have been frequently observed in children with precursor symptoms such as gastrointestinal, abdominal pain, and heart problems on inflammatory basis [14,16,19].

More likely can negatively influence the prognosis the patients or people with pre-existing diseases, such as high blood pressure, ischemic heart disease, atrial fibrillation, type 2 diabetes mellitus, heart failure, obstructive pulmonary conditions (COPD), history of cerebrovascular disorders (as stroke), chronic kidney failure, cancer history in the past 5 years, dementia, chronic liver diseases and immunosuppression or immunodepression [3].

From blood chemistry tests we can observe in some patients lymphopenia (that has been associated with increased disease severity and poor prognosis),

leucocytosis with agranulocytosis, increase of C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), myoglobin and sometimes troponin and cytokines (IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1a and TNF- α) and liver's enzymes (alanine aminotransferase-ALT and aspartate aminotransferase-AST) with average increased serum bilirubin. Finally, association of high C-reactive protein, D-dimer, and ferritin indicates the manifestation of pulmonary or cerebrovascular coagulopathy with has been shown to be associated with a high mortality [3,15-18]. It is a laboratory feature very similar to that of bacterial sepsis [20].

The virus can be detected by PCR in whole blood and in stool samples and the American Disease, Centers for Disease Control and Prevention

(CDC) recommends some criteria priorities for testing patients with suspected COVID-19 infection. Indeed, test patients and the people it should be performed through nasopharyngeal swab (for real-time reverse transcriptase-polymerase chain reaction: RT-PCR and serum blood exam (looks for antibodies created by the immune system). The Human body takes at least five to ten days after the infection to develop antibodies against virus even in patients with symptoms. Serological tests will provide a more accurate diagnosis of how many people have been infected and cured, but also the actual mortality rate and also provide information about whether people become immune to this virus once they are cured and, if so, how long that immunity lasts [1,3,21,22].

In general, the criteria for laboratory tests to date are limited in a) patients with severe acute respiratory disease in case of need or necessity b) Healthcare workers or guests in units of the elderly or chronically ill who develop acute respiratory infection with fever and cough or shortness of breath c) Healthcare worker developing acute respiratory infection with fever c) elderly (>70 years old) or people with severe underlying chronic conditions (e.g. chronic lung disease, chronic cardiovascular disease, diabetes, severe immunosuppression) who develop an acute respiratory infection with an acute respiratory infection with fever and cough or shortness of breath or shortness of breath [1,3,20].

The current issues about therapy

There is currently no specific treatment. It has been noted that most people who get SARS-CoV-2 will be able to recover at home. The therapies are still mainly under investigation. Antiviral drugs developed for other viruses still currently there is no specific treatment. [1,3] The National Institutes of Health and Centres of Disease Control and Prevention (CDC) issued some new recommendations regarding the information for clinicians on investigational therapeutics for patients with COVID-19. Thus, the antiviral agent remdesivir must use in hospitalized patients with severe infection ($SpO_2 \leq 94\%$ on ambient air at

sea level or those who require supplemental oxygen and in patients who are on mechanical ventilation or extracorporeal membrane oxygenation: ECMO) and for not intubated receive for five days. Anyway, that there are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy some experts extend the total remdesivir treatment duration to up to 10 days [23]. For the treatment of patients with mild or moderate infection there are insufficient data to recommend for or against remdesivir [23]. In patients on mechanical ventilation or who require supplemental oxygen it is recommended to use dexamethasone 6 mg daily for up to 10 days. It is allowed to continue therapy with for patients already treated previously for diseases other than COVID-19 (primary or secondary adrenal insufficiency, rheumatological diseases, asthma and chronic obstructive pulmonary disease ect) and come anche per HMG-CoA Reductase Inhibitors (Statins), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs) [23]

For the use of chloroquine or hydroxychloroquine the US National Institutes of Health and Centers for Disease Control and prevention (CDC) recommend to avoid their use for therapeutic proposes, except in clinical trials. Furthermore, they recommend against using the following therapies (but only for a clinical trials) hydroxychloroquine plus azithromycin (because of the potential for toxicities), lopinavir/ritonavir or other HIV protease inhibitors (because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit), lopinavir/ritonavir or other HIV protease inhibitors. For the prevention of venous thromboembolism (TEV) or arterial thrombosis unless there are other indications, patients not hospitalized anticoagulants and antiplatelet therapy should not be initiated, instead, hospitalized adults must receive VTE prophylaxis according to the standard of care for other hospitalized patients [23].

Recently some studies are pointing out the potential role of gut microbiota in determining a better immune and respiratory function in such patients and some authors, express the idea of a possible positive

modulation of respiratory function by probiotics/synbiotics supplementation and may be an aid for the prognosis of the patients with COVID-19 infection [24–29].

Currently our knowledge about symptoms and diagnosis and treatment has reached a remarkable goal. The same also for the individual protection of the population. In fact, social distancing and the subsequent protection of people with surgical masks and hand washing, and all other precautions have been successful as evidenced by the state of Italy. Patient therapy remains mostly empirical and experimental, as is the lack of a vaccine.

Conclusion

The COVID-19 pandemic is still a global emergency with confirmed growing cases and deaths such as in America (7 165 639) and Asia (3 075 573) [30]. The main characteristics to be addressed of a high biohazard event are: a) pharmacological treatment resistance, b) insensitivity to normal immunological factors and traditional vaccines, c) the possibility of persistence in the natural environment and the action of the anti-infection remediation substances, and d) the possibility of biotoxins production. So these microorganisms can pose a high National health and security risk because: a) they can be easily disseminated and transmitted from person to person, b) cause high morbidity and mortality, with potential for a serious impact on public health c) that can cause social disturbance (mainly economic and psychological) and d) require special actions for the public health response, e.g. ambulances for the transport of highly contagious patients each equipped with a specific stretcher transit isolator (STI).

Conflict of Interest Statement

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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