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EDITORS

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COVID-19 Pandemic : A current review of animal and public health situations

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Introduction

Coronavirus disease 19 (COVID-19) is an emerging zoonotic disease caused by a novel member of human Coronaviruses (CoVs) that has recently emerged in Wuhan, Hubei Province in China, in December 2019. It is the third documented spillover of an animal coronavirus to humans in only two decades, resulting in a major epidemic. The virus was named by the International Committee on Taxonomy of Viruses as "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2)[1, 2] and announced by the World Health Organization (WHO), on January 30, 2020, as a Public Health Emergency of International Concern and a pandemic disease on March, 2020 [3]. SARS-CoV2 has emerged after the previously identified Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 [4, 5], leading to pulmonary failure and potentially fatal respiratory tract infections and causing outbreaks, mainly in China and Saudi Arabia, respectively [6].

As of the 3rd of June 2020, about 6.3 millions of cases have been reported worldwide, causing more than 370 000 deaths [7]. At the same date, 1 087 Covid-19 confirmed cases were registered in Tunisia [8].

This review summarizes the relevant scientific data concerning SARS-CoV-2 effects on animal and public healths with a focus on the Tunisian context.

1-Why coronaviruses are so particulars?

Coronaviruses infect humans and many species of animals and have been described for more than 50 years [9].

They were classified into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The first two genera include only mammalian CoVs, while all avian CoVs are members of the other two genera [10]. CoVs are characterized by an exceptional genetic plasticity. These viruses are well recognized for their ability to change their tissue tropism, hurdle the interspecies barriers and get adapted to the ecological variations [10]. Indeed, viral replicase (an RNA dependent-RNA polymerase) does not possess a good proof reading activity; therefore, the incorporation of wrong nucleotides at each replication cycle and the consequent accumulation of mutations in the viral genome lead to progressive differentiation of the viral progeny from the parental strain. In addition, the particular replicating machinery of CoVs facilitates recombination events not only with genomic sequences of other CoVs (homologous recombination), but also with RNAs of different viruses and other organisms (heterologous recombination). Consequently, genetic diversity is responsible for continuous emergence of viral strains with increased virulence, different tissue tropism and/or expanded host range [11, 12].
According to Global Initiative on Sharing Avian Influenza Data (GisAid), from December 2019 to June 2020, 4641 genomes were sampled and genetic analyses, using Wuhan-Hu-1/2019 as a reference strain, have shown big diversity in genomic structure and distinct viral clades (G, GR, GH, O, S, L and V). The map below shows the geographic distribution of various viral clades (Figure 1) [13].

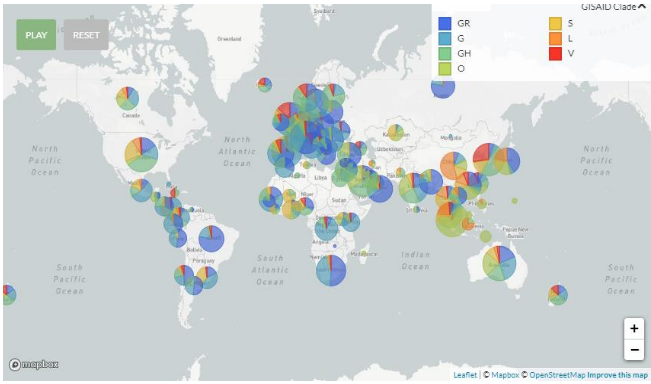


Figure 1: *Genomic epidemiology of hCoV-19 [13]*

2- SARS-CoV-2 characteristics

SARS-CoV-2 belongs to the family of Coronaviridae, the suborder of Cornidovirineae, the order des Nidovirales, the genus Betacoronavirus and realm Riboviria. As all coronaviruses, it is an enveloped, with positive-stranded RNA virus and having a diameter ranging from 80 to 200nm. The genome, ranging from 27 to 32 kb, is packed inside a helical capsid formed by a nucleocapsid protein (N) and further surrounded by an envelope. Three structural proteins are associated with the viral envelope: membrane protein (M), envelope protein (E) and spike protein (S) which forms large protrusions on the virus surface, giving to coronaviruses a crown appearance so their name. The skipe protein mediates virus entry into host cells; it binds to the angiotensin-converting-enzyme-2 (ACE2) receptor, present on the surface of several human cells such as type II pnemocytes, enterocytes and macrophages. It is also a major inducer of host immune responses, allowing production of specific antibodies with probable neutralizing activities [14]. The genome structure of SARS-CoV-2 showed specific characteristics of known coronaviruses; the 5’ end (the two-thirds of the RNA) encodes for non-structural proteins, the viral polymerase (RdRp), and other proteins involved in the transcription and the replication of the virus. The latest 3’ one-third part of the genome encodes for the four structural proteins (spike, envelope, membrane and nucleocapsid) and other helper proteins [15].

3- What are the probable origins of SARS-CoV-2?

Many early cases of COVID-19 were linked to the Huanan market in Wuhan, where, in addition to fish and shellfish, a variety of live wild animals (including hedgehogs, badgers, snakes, and birds) were available for sale as well as other animal carcasses [16]. However, no bats were available for sale. Until now, the origin of the newly emergent SARS-CoV-2 remains debatable and under investigations [17]. Primary investigations done on six patients at the beginning of the epidemics showed a high homology between SARS-CoV-2 and SARS-CoV genome sequences (80% identity in nucleotide acids) and relatively poor homology with that of MERS-CoV (50%). Thus, it is reasonable to suspect that bats are the natural host of SARS-CoV-2, considering its similarity with SARS-CoV. Both of them are classified under the subgenus Sarbecovirus of the genus Betacoronavirus which ancestor origin is a bat [18]. Researchers first started looking for what bat coronavirus could match with the newly discovered virus. In consequence, phylogenetic analysis of SARS-CoV-2 as compared to a collection of many coronaviruses revealed that the virus was closely related to Bat CoV-RaTG13 (96.2% overall genome sequence identity), a bat coronavirus detected in a Chinese bat (*Rhinolophus affinis*) isolated in Yunnan province, in 2013 (Figure 2) [17].

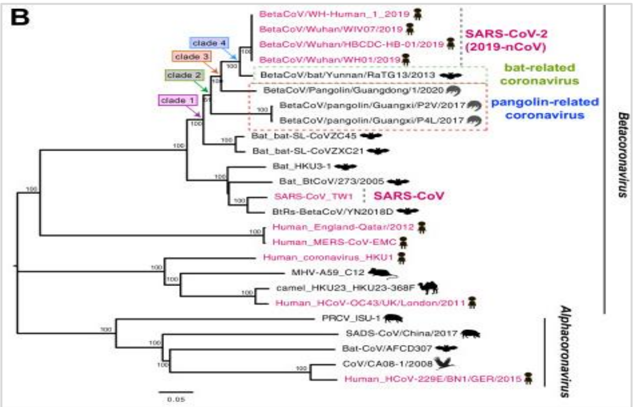


Figure 2: *Phylogenetic relationships between SARS-CoV-2 and other coronaviruses in bats, birds, mice, camels, swine, pangolins and humans. Red color indicates the human-origin coronaviruses. The scale bar represents the number of nucleotide substitutions per site (subs/site) [19].*

Despite current evidences pointing out to the evolutional origin of SARS-CoV-2 from the bat viruses, the virus transmission to humans must be understood. For that, researchers have emitted three hypothesis [20-22].

Hypothesis 1 (Figure 3a): A bat mutant virus infects a non-human host; after adaptation, the new virus was easily transmitted to humans and replication in humans has led to the epidemic viral strain. This is how previous coronavirus outbreaks have emerged, with humans contracting the virus after direct exposure to civets (SARS) or camels (MERS). For COVID-19, Pangolins were among the first animals suspected of being the intermediate host. Indeed, two teams reported in China that they had found similarities in the genomes (approximately 85.5% to 92.4%) of SARS-CoV-2 and coronaviruses isolated from tissues of Malayan pangolins (*Manis javanica*); such similarities were lower than that with the bat coronavirus RaTG13 (96.2%). It is important to note that trading pangolins is illegal in China.

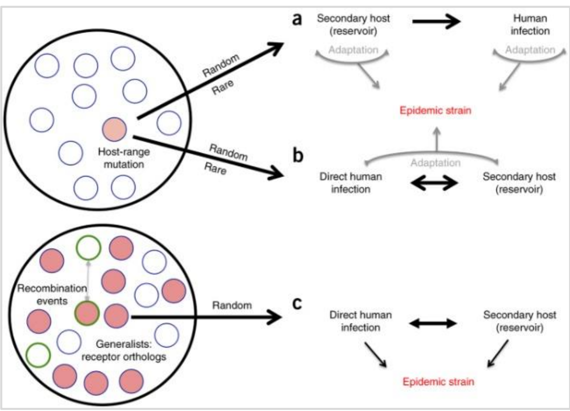


Figure 3: *Probable ways of SAR-CoV-2 emergence [23].*

The pangolin coronaviruses turned out to be too distant from the direct ancestors of SARS-CoV-2, but the fact that they are the only wild mammals besides bats, known so far to be living with coronaviruses similar to SARS-CoV-2, suggests they cannot be ruled out as an intermediate source. Finally, the roles played by bats and pangolins, as respective natural reservoirs and intermediate hosts, still need further investigations.

Hypothesis 2 (Figure 3b): A bat mutant virus can be directly transmitted to human without any intermediate host. Viral selection will happened into human population, with closely related viruses that have already replicated in a secondary host, permitting continued viral persistence and adaptation in both population.

Hypothesis 3 (Figure 3c): A direct contamination of humans from bats after viral recombination of SARS-CoV, particularly spike genes, allowing efficient viral attachment to human cells.

The hypothesis of direct transmission from bats to humans was rejected for the following reasons [23, 24] : RaTG13 bat virus cannot bind efficiently to human cells,

- Until now, there are no documented cases of direct bat-human transmission, suggesting that an intermediate host was likely to be involved;
- Most bat species in Wuhan are hibernating in late December;
- No bats in Huanan Seafood market were sold or found;
- MERS, SARS and other human-infecting coronaviruses that originate from bats need an intermediate host to be able to infect humans (Figure 4) [24].

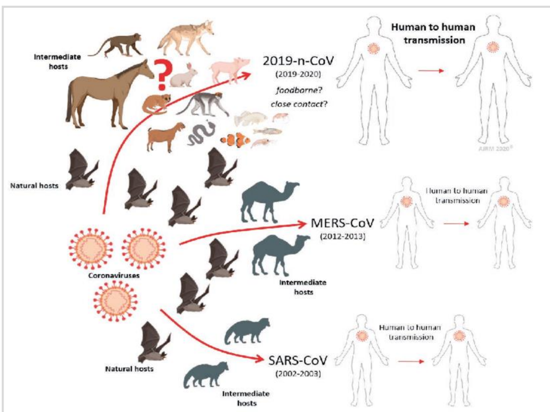


Figure 4: *Potential animal origins of human coronaviruses [25]*

While available, genetic sequences suggest that the SARS-CoV-2 virus emerged from an animal source and there is currently not enough scientific evidences to identify precisely either the source or the route of transmission from the original animal reservoir to a putative intermediate host and then to humans (Figures 4 and 5).

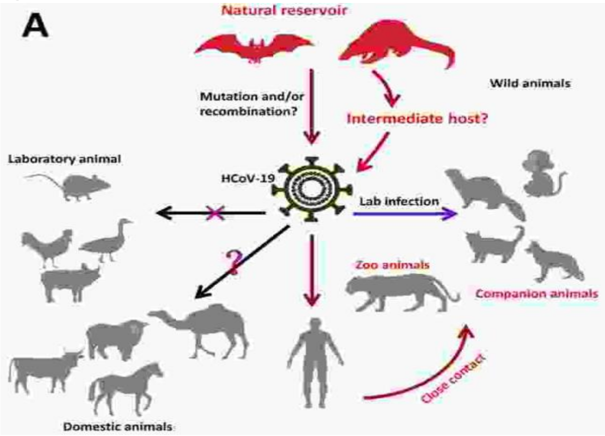


Figure 5: *Putative zoonotic origin, transmission and infection of HCoV-19 in humans and animals [26]*

4- Why we are getting more and more emergent CoVs?

During the last decades (Figure 6), the frequency of animal-to-human transmission of new viruses has increased, within a brief timeframe. Indeed, In less than 20 years, three human CoV epidemics have occurred and knowing as SARS-CoV (2002), Mers-CoV (2013) and Sars-CoV-2 (2019). The mysterious phenomena has arisen some questions to understand what the key drivers of virus spillovers are. Perhaps, we know now the human behaviors, including heavy trade and consumption of high-risk wildlife, land-use changes leading to deforestation and conversion, expansion of agriculture with unsustainable intensification and animal production, are being the main culprit. Thus, increasing the chance of close contacts between wild animals and humans facilitates, in consequence, the spill-over of zoonotic agents (Figure 7) [12].

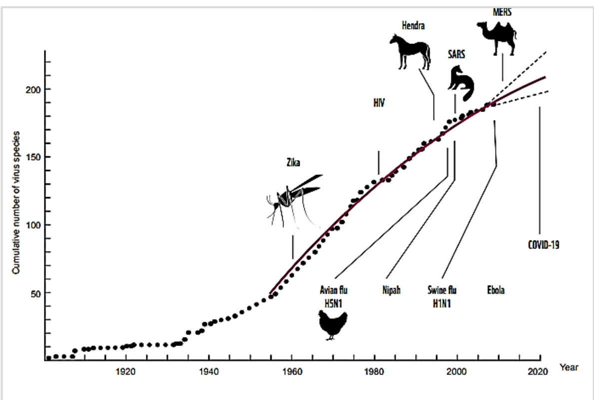


Figure 6 : *Cumulative discoveries of zoonotic diseases [27]*

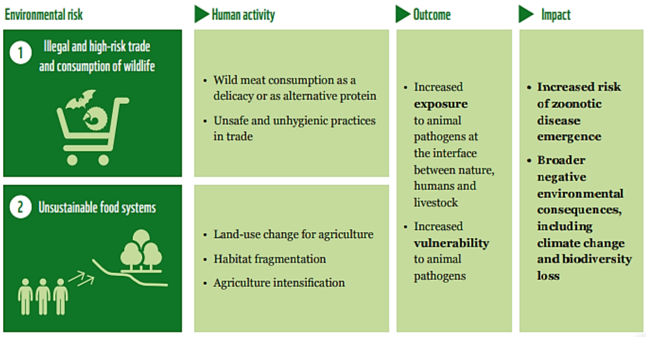


Figure 7 : *Key drivers of New zoonotic diseases [27]*

Worldwide infectious disease experts believe that the source of the next human pandemic is likely to be zoonotic, and wildlife as the primary source. This should remind us to be vigilant and prepared to the next deadly pandemic disease as a result of currently unknown zoonotic agents or one of the thousands of genetically identified agents of currently unknown pathogenic potential [28].

5- SARS-CoV-2 and animal health

5-1- SARS-CoV-2 events in animals

Infection with SARS-CoV-2 is not a World Organization of Animal Health (OIE) listed disease. However, it meets the criteria of an emerging disease as specified in Articles 1.1.4. and 1.1.6. in Chapter 1.1 of the OIE Terrestrial Animal Health Code. Therefore, OIE member countries should report infection of any animal with SRAS-CoV-2. Positive results obtained from experimental infection are not notified [29, 30].

OIE case definition [31]: Although, current investigations regarding different species susceptibilities are ongoing; clinical representation of an animal infection with SARS-CoV2, suggests that it may include (but not limited to) nasal discharge, respiratory distress, coughing, vomiting or gastrointestinal disease. In humans, mild or asymptomatic infections are likely to occur and should be considered during epidemiological investigations. The following case definitions are duplicated from OIE fact sheet regrading “Considerations for sampling, testing, and reporting of SARS-CoV-2 in animals” (Version 1, 7 May 2020).

<u>**Suspected case**</u>: SARS-CoV-2 infection can be suspected in an animal if:

- The animal has clinical signs suggestive of SARS-CoV-2 infection as described above and a veterinarian has effectively ruled out all other likely differential diagnostic etiologies.

AND

- The animal has an epidemiological link with a confirmed human COVID-19 patient, SARS-CoV-2 infected animal or suggestive case history indicating potential exposure.

Confirmed case: The followings define a laboratory confirmed case of SARS-CoV-2 infection in an animal (with or without clinical signs):

- SARS-CoV-2 has been isolated from a sample*, taken directly from an animal;

OR

- Viral nucleic acid has been identified in a sample*, taken directly from an animal, giving cause for a suspicion of previous association or contact with SARS-CoV-2, by:

a) Targeting at least two specific genomic regions at a level indicating the presence of infectious virus;

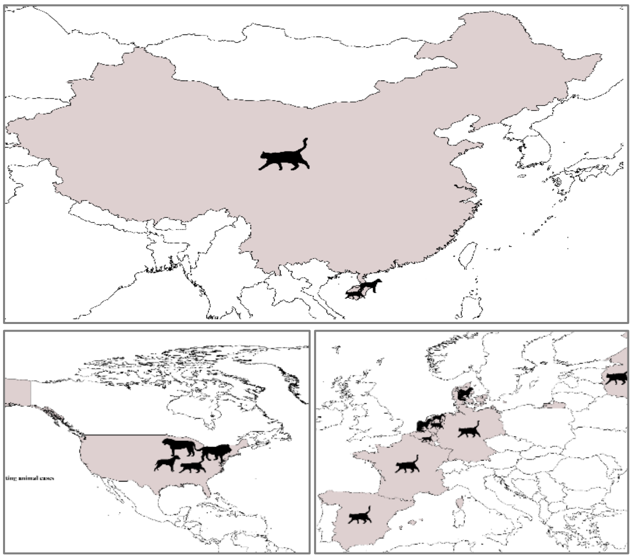
OR

b) Targeting a single genomic region followed by sequencing of a secondary target.

* Samples for virus isolation and viral nucleic acid detection are preferably: nasal swab, oropharyngeal swab, nasal washing, tracheal swab and/or rectal sample may be taken; a fecal sample may be used in situations where direct sampling is not possible due to risks to the animal or the testing staff; or post-mortem collected internal organs.

a- Natural Infection

Infections of pets (Table I), captive wild cats and farmed minks with SARS-CoV-2 in natural conditions have been reported by several countries: China, United States of America, Hong Kong, Belgium, France, Spain, Germany and Russia (Map 1) [32].



Map 1: *Countries having reported animal infections with SARS-CoV-2 (As of June 30, 2020)*

a-1-Infections of pets:

The Table I (Annex 1) summarizes findings related to natural infection with SRAS-CoV-2 in pets.

a-2- Infection of captive wild cats and farmed minks

- **The United States of America**

On April 6, the United States Department of Agriculture (USDA) reported to the OIE a positive tiger (*Panthera tigris jacksoni*) housed at the Bronx Zoo in New York. This Tiger was housed with four other tigers and three lions (*Panthera leo*) in two distant enclosures at the zoo. Clinical signs of mild respiratory disease (dry cough and some wheezing) were observed, over the course of a week, in four of these tigers and all the lions. On April 17, the USDA notified to the OIE that one of the three lions has also been confirmed by the National Veterinary Services Laboratory to be infected with SARS-CoV-2. The Wildlife Conservation Society (WCS), announced on April 22, that all the tigers and lions described above were tested positives for SARS-Cov-2. Fecal samples tests were applied without the need for general anesthesia. These large captive cats were long-term residents of the zoo without any chronic medical conditions, and no new animals had been introduced to the groups for several years. The zoo also houses other large cats. They did not develop clinical signs related to COVID-19 [36]. The source of infection was presumed to be from a zookeeper, who at the time of exposure was asymptomatic. Biosecurity protocols have been implemented for zookeepers caring for these large felids [32, 36].

- **Netherlands**

From the end of April, respiratory disease and increased mortality were reported in minks in two farms of the Netherlands. The mink necropsies revealed interstitial pneumonia, and organ and swab samples tested positive for SARS-CoV-2 RNA by qPCR. The sequences obtained from the two farms are closely related to known human sequences, and the distance between the sequence clusters from the two farms suggests separate introductions. The most likely explanation of the widespread infection in the mink farms is introduction of the virus by humans and subsequent transmission amongst the minks [42, 43]. In addition, pets staying in the vicinity of these farms were tested for SARS-CoV-2 and a total of 24

Feral and semi feral cats around the mink farms have been tested positive (Table I). Farm owners have been advised to ensure that new cats cannot enter their mink farms nor existing cats leave, waiting for the results of the studies and confirming the role played by cats in the transmission of the virus [32]. In order to detect additional infections in mink companies, a mandatory screening of all Dutch mink farms was implemented [44]. Since 25 May to June 9, thirteen farms were infected. Eleven are located in the province of Noord Brabant and two located in Limburg. Five farms among the 13 had clinical signs. Few minks, in these farms, showed symptoms of the disease, where minks are kept in separate pens, which means that there is little or no contact between these animals. In the 8 remaining farms, the infection was mainly subclinical [44].

On June 3, 2020, the competent authority decided a culling policy of infected premises. Culling operation started on June 6, 2020. This decision was taken because, according to the Outbreak Management Team for Zoonoses and the Administrative Coordination Consultation for Zoonoses, the virus may continue to circulate in mink farms for a long time and therefore may pose a risk to public and animal healths. Therefore, this measure would also reduce the risk of mutations of the virus in minks, which may facilitate its passage to humans [44]. National measures, such as the hygiene protocol, the transport ban for minks, and the visitors' ban are applied. In 2016, the top Dutch court ordered to phase out mink farming by 2024 [38].

- **Denmark**

On June 17, the Danish competent authority in animal health has reported to OIE the first finding of SARS-CoV-2 in animals. Denmark is the second country, after the Netherlands that has reported infection with SARS-CoV-2 in farmed minks. The infected farm is located in Northern Jutland (municipality of Hjørring). The animals did not exhibit clinical signs related to COVID-19 and no increased mortality was registered. Samples were collected, because the Danish Veterinary and Food Administration was informed about a person, in the farm, that has tested positive. To reduce the risk of the virus spread, the government has decided to cull all animals in the infected farm [32]. Denmark has been, for decades, the world's top mink producer. The Danish industry produces 40 per cent of the world's pelts, with an estimated fur and mink skins export value of about EUR 0.5 billion, annually [45].

b- Experimental Infection

Knowledge about the susceptibility of different animal species to SARS-CoV-2 in laboratory settings has been updated in this section. Diverse experimental infections, done respectively in separate institutions, have generated these preliminary findings:

-**Poultry (chickens, ducks and turkeys) and pigs** : all findings of the experimental infection studies conducted by different institutions, indicated that these species are not susceptible to and cannot transmit SARS-CoV-2 [32]

-**Dogs** exposure to SARS-CoV-2, in laboratory settings, has proven that this species remains asymptomatic, unlike cats [46]. Besides and in experimental conditions, dogs conversely to cats do not shed the virus following infection [47].

-**Cats** are the most susceptible species to SARS-CoV-2 and can exhibit clinical signs (Table 1). In an experimental laboratory setting, cats were able to transmit infection to other cats [46, 48]. The virus can replicate effectively in cats with more receptivity among juvenile [46]. Cats also develop a robust neutralizing antibody response that prevents re-infection with a second viral challenge [47].

-**Ferrets** are susceptible to infection and able to transmit infection to other ferrets, in experimental conditions [30].

-**Golden Syrian hamsters, cynomolgus and Rhesus macaques** can be infected by SARS-CoV-2 and show clinical signs [30].

- **Egyptian fruit bats** are also infected during an experimental laboratory setting but do not show any signs of the disease. The infected fruit bats are also able to transmit infection to other fruit bats [30].

Clinical trials currently available are done on a small number of animals and do not demonstrate if the animals may transmit the virus to humans [36]. However, experimental findings suggest that cats and ferrets could serve as an appropriate animal model for the study of SARS-2 infection as well as for the development of vaccines and therapeutic products for use in both animals and humans [30].

5-2-Human-Animal interface

On May 19 and 25, 2020, the Dutch Minister of Agriculture announced, in two letters, to the House of Representatives that it is plausible that two care workers have likely contracted COVID-19 from a mink farm.

- First Case: the virus isolated from the employee has shown similarity with the mink virus found in the same farm. Based on genome sequence comparison and phylogenetic analysis, it became plausible that the employee of the mink farm has been infected by infected mink [49].

- Second case: The virus was detected in three persons in an infected mink farm. The genetic code of the isolated viruses showed high similarity with those found in the mink living in the farm. Based on the available information, it is most likely that at least one of the 3 infected persons has got the virus from a mink [50].

The virus RNA has been detected in dust particles in the stables. This could explain the way of exposure of the mink keepers working at the farms [43]. According to the World Health Organization (WHO), these two plausible cases of Dutch mink contamination could be the first known cases of transmission of the new coronavirus from animals to humans.

Actually, the ongoing pandemic of SARS-CoV-2 remains the result of human-to-human transmission, through respiratory droplets from coughing, sneezing, and talking [30]. Events regarding contamination and/or infection of domestic and wild animals remain sporadic. Even, if animal infections were reported in some countries, they remain the result of a close contact with humans infected or suspected to be infected with SARS-CoV-2 [30].

Referring to the latest report (May 26, 2020) of the OIE about COVID-19, the recent evidence of mink to human transmission does not change the recommendations of the Animal-Human interface ad hoc Group (AHG). It is mentioned that there is no evidence that animals play a significant epidemiological role in the spread of the human disease. In the light of the recommendations of the OIE ad hoc group of experts, it is not justified to take measures in relation to animals, in particular pets, which might compromise their welfare [51].

5-3-Impact of COVID-19 on animal health

In Tunisia as in different other nations, different prohibitive measures has been taken against COVID-19 expansion, which have directly or indirectly perturbed all animal production activities to keep livestock healthy, by preventing and controlling animal diseases and maintaining good biosecurity. Movement restrictions and quarantine measures have also limited farmers' ability to access veterinary services and the following consequences:

- Challenges for veterinary and veterinary paraprofessionals to visit the farms;
- Difficulties for farmers to reach out to their veterinarians when animals are suspected to be sick and particularly due to financial hardship;
- Limited access to animal health inputs, such as veterinary drugs, vaccines…;
- Disrupted animal disease surveillance, reporting and reduced testing and diagnostic capacities;
- National animal disease control programs reduced or even suspended such as vaccination campaigns ;
- International animal health activities delayed and not implemented as planned.

5-4-Essential services provided by the Tunisian veterinarians in the context of COVID-19

- **Food safety services**

  - Veterinarians fulfill a critical role in the safe food supply chain. Thus, their activities of control continued to be ensured throughout the COVID-19 shutdown for both food safety and security.
  - Private and public veterinarians provide essential services that help optimizing productivity and quality of animal food products. Maintaining sanitary control in slaughterhouses as well as dairy products, eggs and other livestock products, has been a priority for the Veterinary Services. Consequently, food safety and security are not been compromised.

- **Livestock veterinary services**

In addition to their role in food safety, veterinarians have the missions of diagnosing, treating and monitoring food products. They are at the forefront of detection and response to emerging and exotic animal diseases. Their responsibilities have to be ensured throughout the year despite any impediment. The Tunisian veterinary services were able to maintain their capacities to detect and respond to endemic (rabies…) and exotic diseases (Rift Valley Fever…) during the COVID-19 epidemic.

- **Companion animal veterinary services**

Given that many Tunisian are staying at home, confined with domestic pets, and the fact they should both remain healthy, veterinarians in pets practice have played an important role in advising their clients:

- On the public health implications of COVID-19 by assessing and interpreting available information around the risks of potential pet transmission of the disease.
- About other potential zoonoses, pet handling and hygiene, and surveillance for any significant emerging diseases (eg. rabies), which could further affect humans at any time. Veterinary practices were available to provide emergency treatment as well as essential medical and surgical cares to any sick pet since animal welfare should not be compromised.

- **Animal welfare**

Veterinarians fulfilled many roles to ensure that animal welfare standards are maintained. This became even more important in the COVID-19 situation, given the potential for domestic pets and livestock to be abandoned or mistreated in the mistaken belief that they play some role in COVID-19 transmission. Ongoing veterinary presence ensured that the public has provided the public with access to accurate, scientifically based information and ongoing animal care.

- **One Health**

Through its mission to set animal health and welfare standards, to inform, and to build capacity, the OIE is fully mobilized to accompany Veterinary Services across the world to address any epidemic, even COVID-19. Given that COVID-19 and about 70% of emerging infectious diseases in humans, over the last 30 years, have been zoonotic, veterinarians need to be constantly engaged in a "One Health" capacity. Thus, the OIE liaises closely with its partners, WHO and FAO. With the World Veterinary Association (WVA), the OIE has released on March 18, 2020, a statement advocating of the absolute requirement that veterinarians, worldwide, would be designated as an essential service provider, in the context of the COVID 19 pandemic. For this, several OIE expert groups are developing scientific advice on research priorities, sharing results of on-going researches in animals, and developing scientific opinions on implications of COVID-19 in animal and public health. The OIE has also developed a high-level guidance for veterinary laboratories, working with public health services, to support testing of human samples. Besides, It is currently developing guidance on the circumstances under which exceptional testing of animals might be justified. Looking to the future, the OIE is working with its Wildlife Working Group, Member Countries and International partners to develop an ambitious work program, aimed at reducing and managing risk of spillover events between wildlifes, livestock and humans. In addition, in April 2020, FAO published the policy brief on "Mitigating the impacts of COVID-19 on the livestock sector", which discusses how to plan for and address difficulties at the policy level, regarding the livestock production and products.

6- SARS-CoV-2 and public health: focus on epidemiology, virus characteristics, clinical and radiological features.

6-1- Worldwide situation

According to the European Center for Disease Prevention and Control (ECDC), since December 2019 and as of 30 June 2020, 10 273 001 cases of Covid-19 were registered, including 505 295 deaths. The highest numbers were reported in America (5 226 063 cases), Europe (2 427 670 cases) and Asia (2 215 784 cases). The United States and Brazil were the countries with the highest number of Covid-19 cases (Figure 8 and Table II)[52, 53].

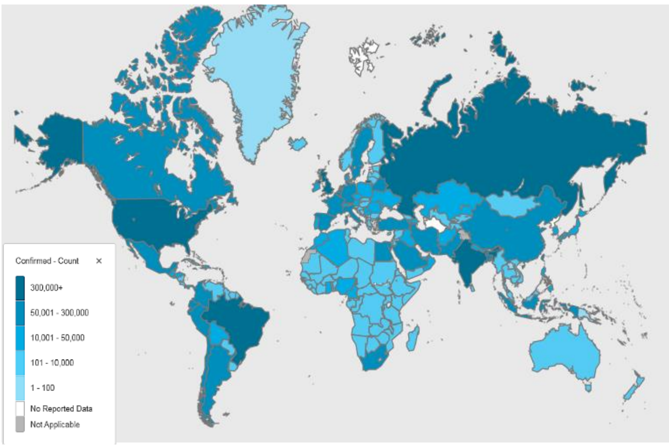


Figure 8 : *Worldwide distribution of Covid-19 cases, as of 3 June 2020 (Source: World Health Organization) [52]*

***Table II:** Distribution of Covid-19 cases by continent and the five countries reporting the highest number, as of 30 June 2020 (Source : European Center for Disease Prevention and Control) [53].*

Continent and countries		Numbers of Covid-19 cases
America		**5 226 063**
	United States	2 590 552
	Brazil	1 368 195
	Peru	282 365
	Chile	275 999
	Mexico	220 657
Europe		**2 427 670**
	Russia	641 156
	United Kingdom	311 965
	Spain	248 970
	Italy	240 436
	Germany	194 259
Asia		**2 215 784**
	India	566 840
	Iran	225 205
	Pakistan	209 337
	Turkey	198 613
	Saudi Arabia	186 436
Africa		**393 444**
	South Africa	144 264
	Egypt	66 754
	Nigeria	25 133
	Ghana	17 351
	Algeria	13 571
Oceania		**9 344**
	Australia	7 767
	New Zaland	1 178
	Guam	257
	French Polynesia	62
	Northern Mariana Islands	30
Other*		**696**

* International conveyance in Japan

Table III reports the list of the most affected countries concerning the number of deaths; the highest number was registered in America e with more than 248 672 deaths [53] .

***Table III :** Distribution of Covid-19 deaths by continent and countries, with the highest numbers registered, as of 30 June 2020 (Source : European Center for Disease Prevention and Control) [53]*

Continents and countries		Numbers of Covid-19 deaths
America		**248 672**
	United States	126 140
	Brazil	58 314
	Mexico	27 121
	Peru	9 504
	Canada	8 566
Europe		**191 411**
	United Kingdom	43 575
	Italy	34 744
	France	29 813
	Spain	28 346
	Belgium	9 747
Asia		**55 194**
	India	16 893
	Iran	10 670
	Turkey	5 115
	China	4 641
	Pakistan	4 304
Africa		**9 878**
	Egypt	2 872
	South Africa	2 529
	Algeria	905
	Nigeria	573
	Sudan	572
Oceania		**133**
	Australia	104
	New Zealand	22
	Guam	5
	Northern Mariana Islands	2
Other*		**7**

* International conveyance in Japan

At the beginning, the measures taken were based on active surveillance of confirmed and suspected cases, contact tracing and self-isolation at home when signs of severity are absents. Covid-19 circuits were also created within hospitals and services when the disease is confirmed. Subsequently, on March 2020, with the aim at reducing viral transmission, several countries adopted national lockdown, with curfews and border closures, in addition to hygiene measures and social distancing. Consequently to all these measures, the reproduction number (Rt) dropped from 2-3 to below one, in countries with the largest number of cases such as United States, United Kingdom, Italy, France and Spain (Table IV) [54]. Globally, the numbers of Covid-19 cases and deaths decreased in many regions but it remains high in America; confirmed cases exceeding the 100 000 in the United States and Brazil, from 28 May to 2 June, 2020 [54]. Since May 2020, many countries started raising the lockdown restrictions and some of them planned reopening their frontiers, in the late of June.

***Table IV :** Covid-19 reproduction number estimated in the most affected countries, before and after lockdown measures, up to April 29, 2020 [54].*

Countries	Numbers of Covid-19 cases	R_0	Rt Post-lockdown
United States	1 551 853	3.6 [3.4-3.8]	0.97 [0.97-1.00]
United Kingdom	248 818	2.1 [1.8-2.3]	0.99 [0.96-1.02]
Italy	227 364	2.2 [2.0-2.4]	0.89 [0.87-0.91]
France	143 845	2.0 [1.8-2.1]	0.76 [0.72-0.82]
Spain	233 286	2.2 [2.1-2.4]	0.74 [0.71-0.78]

6-2-Tunisian situation

In Tunisia, the first confirmed case of Covid-19 was declared on March 2, 2020; it was an imported case from Italy. The first local case was reported on March 9, 2020, and the first death was registered on March 18, 2020 [10]. Since then and as of June 30, 2020, 1 175 were confirmed Covid-19 cases of which 88.3 % (1038 cases) have recovered. Fifty deaths (4.2%) were reported and Kebili Governorate has shown the highest cumulative incidence of Covid-19 cases per 100,000 inhabitants (Figure 9).

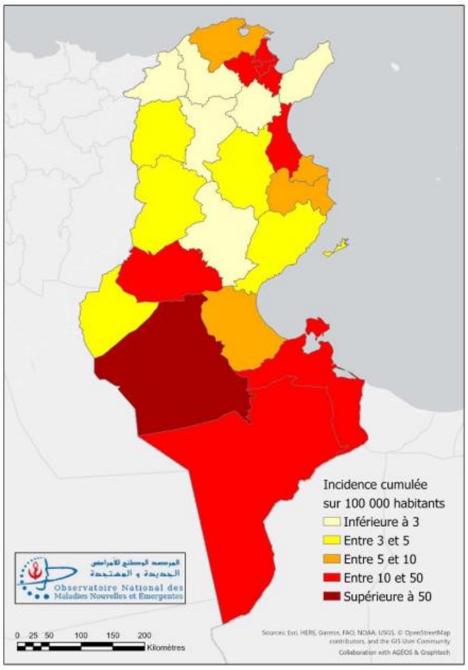


***Figure 9** : Cumulative incidence of Covid-19 cases by 100 000 inhabitants by Tunisian Governorate, as of June 30, 2020 (Source : National Observatory of New and Emerging Diseases) [55]*

A peak of the outbreak was registered during the week 13, with a gradual decline since then (Figure 10). A slight increase of the case numbers was observed on April 15 and 16, 2020, following the repatriation of residents abroad. After that, the number of cases showed a continue and slow decrease [55]. The Tunisian Ministry of Health has started its preparedness plan for response to the crisis since January 2020. As of January 28, 2020, the government authorities have implemented early prevention measures, including screening in the points of entry along with a systematic 14 days isolation for travelers returning from risky areas. On March 12, 2020, Tunisia has proceeded to the progressive closing of its frontiers with the high-risk countries. On March 12 and 13, 2020, schools, universities, coffees and restaurants were ordered to close. On March 18, 2020, a curfew was applied, and four days after, the government launched strict measures of general lockdown, border closure and quarantine in dedicated locations for all returnees. Tunisia started the first phase of targeted lockdown on May 04, 2020. In early ~~of~~ June, the government announced the possible re-opening of the borders at the end of May. Consequently to curfew and lockdown interventions, the Rt has decreased, at first, from 3.18 [95% CI 2.73–3.69] to 1.77 [95% CI 1.49–2.08] and then to 0.89 [95% CI 0.84–0.94]), following the national lockdown measure [56].

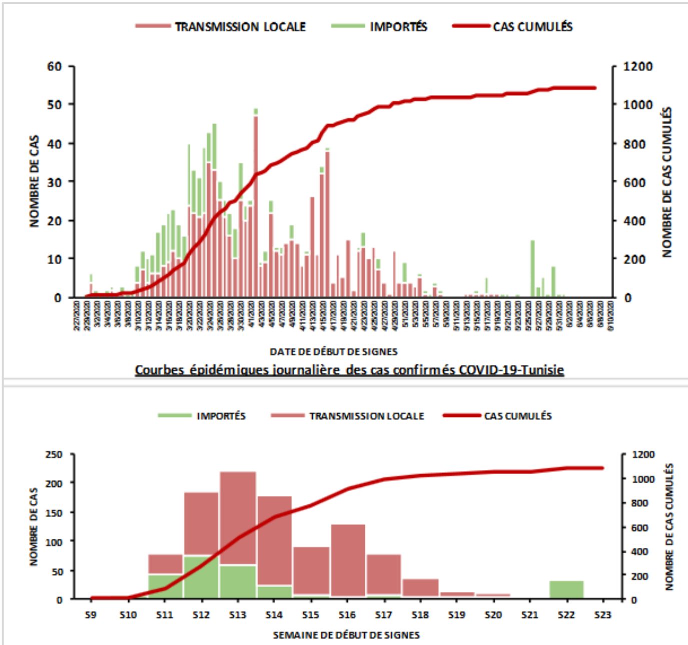


***Figure 10 :** Daily and weekly epidemic curves of confirmed Covid-19 in Tunisia, as of June 7, 2020 (Source : National Observatory of New and Emerging Diseases) [55]*

6-3- Human to human viral transmission

The main source of SARS-Cov-2 is infected patients. The transmission from person to person occur with close contact (less than 1.8 meters), mainly by respiratory droplets through sneezes, coughs or talks [5, 57, 58]. Virus can penetrate into the human body (lungs) via inhalation through the nose or the mouth. Recent studies showed that viable virus could be detected on copper up to 4 hours, on cardboard up to 24 hours and on plastic and stainless steel up to 2-3 days [59]. This indicates that transmission can also happen after contact with contaminated surfaces by rubbing ears, nose and may be eyes after direct contact. In general, respiratory viruses have the highest transmissibility when the patient is symptomatic [5, 58]. Virus transmission can occur 1-2 days before symptom onset and at least 8-10 days after symptom onset [60]. Transmission of SARS-Cov-2 was also reported from asymptomatic individuals [61]. Therefore, we can assume that transmission of this virus may occur during the illness onset and even with mild or without any symptoms. SARS-CoV-2 was detected in stool samples and some biological fluids; however, the possibility of transmission via each of them is still unknown. Further studies are required to understand virus transmission by other routes than airborne [62-64]. There is no evidence of vertical transmission of Covid-19 in women who developed pneumonia during pregnancy [65].

6-4- Clinical features

The incubation period of Covid-19 was similar to SARS and MERS but longer than influenza; it varied from 2 to 14 days. The mean incubation period was 5.2 days (95% confidence interval [CI], 4.1-7.0) [66-68]. Clinical aspect of Covid-19 varied largely, from asymptomatic to fatal pneumonia (Table V) [69].

Table III: *Clinical characteristics of Covid-19 types [68]*

Type	Clinical characteristics
Asymptomatic	No clinical symptoms and chest imaging findings.
Mild	Mild clinical symptoms No abnormal chest imaging findings
Moderate	Mild or moderate clinical features. Chest imaging showed mild pneumonia manifestation
Severe	Suspected respiratory infection symptoms + Shortness of breath/RR ≥ 30 breaths/min / Oxygen saturation ≤93%/ $PaO_2/FiO_2 \leq 300$ mmHg Lesion progression of more than 50% in chest imaging, within 24-48 hours
Critical	Rapid progress of disease + Respiratory failure that needs mechanical ventilation/ Shock/other organ failure requiring intense care unit and monitoring treatment.

*RR: Respiratory rate; PaO_2 : Arterial partial pressure of oxygen; FiO_2 : Oxygen concentration

The severity of the clinical signs is based on the strength of the immune response against the infection. Infected patients suffering from other pathology such as diabetes, hypertension, or other cardiovascular diseases (CVD), are at a greater risk for developing a severe disease. A large Chinese study reported that among 72 314 Covid-19 patients, 81.4% had mild symptoms, common to other viral infections ("flu-like syndrome"), 13.9% had severe presentations and 4.7% were in a critical situation [70]. In adults, the most common symptoms of Covid-19 are fever, dry cough and fatigue [5, 71, 72]. Extra-respiratory symptoms had also been reported; they may represent the initial or sole presentation of Covid-19 (Table VI) [72].

Table IV: *Summary of the main extra-respiratory Covid-19 manifestations [72]*

Organ/System	Symptoms/Signs (reported prevalence in patients)
Cardiac	Acute cardiac injury (8-12%), heart failure (23-52%), arrhythmia (8.9-16.7%), shock, acute myocarditis, chest tightness
Gastrointestinal	Anorexia (26.8%), diarrhea (12.5%), nausea/vomiting (10.2%), abdominal pain/discomfort (9.2%)
Hepatic	Abnormal aspartate aminotransferase or alanine aminotransferase values (16.1–53.1%)
Kidney	Acute kidney injury (overall 0.5%; 2.9–23% in severe cases)
Neurological	Dizziness (16.8%), headache (13.1%), skeletal muscle injury (10.7%), impaired consciousness (7.5%), acute cerebrovascular disease (2.8%), ataxia (0.5%), seizures (0.5%), meningoencephalitis, Guillain–Barré syndrome
Olfactory and gustatory	Hyposmia (5.1–20.4%), anosmia (79.6%), dysgeusia (8.5%), ageusia (1.7%)
Ocular	Acute conjunctivitis (31.6%)
Cutaneous	Erythematous rash (15.9%), hives rash (3.4%), vesicles (1.1%), acro-ischemia, transient unilateral livedo reticularis
Hematological	Lymphopenia (56.5%), thrombocytopenia (16.4–32.3%), coagulation disorders, thrombotic events, anti-phospholipid antibody

The infection can be expressed by only change in smell or/and taste or conjunctival congestion [73-75]. A European study concerning 1 420 Covid-19 cases, has reported headache in 70.3% of cases, anosmia (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), dysgeusia (54.2%) and sore throat (52.9%). Elderly patients had often fever, fatigue and dysgeusia while the youngest one complained from oto-laryngological manifestations [76]. In a New York study, the most common shown symptoms were cough (79.4%), fever (77.1%), dyspnea (56.5%), myalgia (23.8%), diarrhea (23.7%), and nausea and vomiting (19.1%) [77]. Huang et al. (year) have reported that SARS-CoV-2 infection may cause acute respiratory distress syndrome and requirement for admission in an intensive care unit, with death in some cases [78].

Covid-19 affects children less than adults, with milder symptoms and better outcome, assuming thus, that they could spread the virus as a reservoir [79, 80]. The most common symptoms in children were fever, cough and sore throat (51.6%, 47.3% and 17.9%, respectively). Dyspnea is rare in children but it seems to be the most common reported in neonatal age, followed by fever and feeding intolerance (40%, 32% and 24% respectively)[81]. Recently, many reports of an increased rate of Kawaski disease were published, but further studies are needed to evaluate its association with SARS-Cov-2 infection [82].

Characteristic laboratory findings are normal white blood cell count or mild leukopenia and marked lymphopenia. Elevated C-reactive protein (CRP), pro-calcitonin, lactate dehydrogenase (LDH), and D-dimer are commonly found in Covid-19 severe cases [83, 84].

6-5-Virological diagnosis

The virological gold-standard for the diagnostic of COVID-19 is based on the detection of viral RNA in nasopharynx sample, using Real-Time Polymerase Chain Reaction (RT-PCR) [85]. However, the virus may also be detected in other body sites. The sensitivity of the test can be improved by taking samples of lower respiratory tract secretions. According to recent analysis of 1070 specimens, collected from 205 patients with COVID-19, broncho-alveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 out of 104; 72%), nasal swabs (5 of 8; 63%), fibro-bronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%) [86]. SARS-CoV-2 RNA was detected in respiratory tract samples, 1-2 days prior to symptom onset and could persist for 7-12 days in moderate cases, and for up to two weeks in severe cases. It has also been detected in whole blood, saliva, feces and urine by RT-PCR. Testing of specimens from multiple sites may improve the sensitivity and reduce the false-negative test results. Viral loads are high, shortly after symptoms onset, and they are significantly more elevated in severe Covid-19 case, with a longer period of viral shedding than in mild cases [64]. RT-PCR is only suitable for diagnosis and cannot judge on the severity and the progression of Covid-19. Its limitations are low detection and high false negative rates [85].

Serological tests are also available; they detect specific IgA, IgM and/or IgG. Median day for seroconversion was 10-13 days post-onset. Up to now, these tests are recommended only for sero-epidemiological studies or to identify high clinical suspected Covid-19, with false negative PCR [87].

6-6- Radiologic characteristics

Computed tomography (CT) has an important role in both the diagnosis and the evaluation of Covid-19. Typical chest CT imaging features show multiple patchy ground glass opacities in bilateral and multifocal lung lesions, with peripheral distribution, crazy paving appearance (Figure 11) [88], air space consolidation, traction bronchiectasis while pleural effusion, pericardial effusion, cavitation and thoracic lymphadenopathy, are uncommon [85]. Rodriquez-Morales et al; (year) reported through a meta-analysis that, respectively, 25% and 72.9% of Covid-19 cases have unilateral opacity and bilateral opacities on chest radiography, while 68.9% have ground glass opacity on CT [89]. Radiographic findings of consolidation and ground-glass opacity were statistically associated with increased mortality rates [90]. Some study reported higher sensitivity of Chest CT over RT-PCR (98% vs. 71%, p< 0.001), justifying its use as a standard method for Covid-19 diagnosis. However, CT cannot identify or differentiate between different viral etiologies [85].

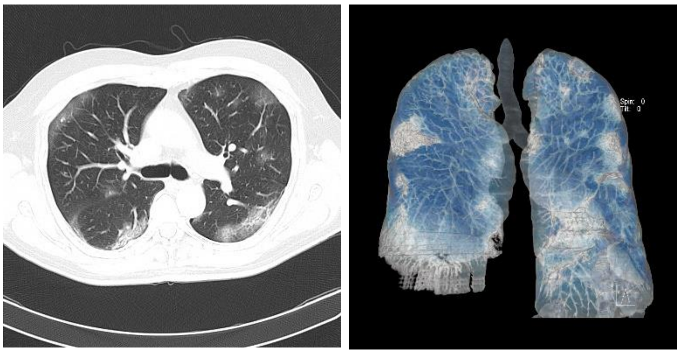


Figure 11 : *Chest CT features of COVID-19 pneumonia (multifocal and bilateral ground-glass opacities scattered in both lungs, predominantly at peripheral and posterior regions) [87].*

6-7-Prognosis

The severity of Covid-19 is associated with gender, age, comorbidities and disparity in the immune response. Patients with chronic obstructive pulmonary and cardiovascular diseases and hypertension were at at higher risk of severe illness and for intensive care unit admission [91]. Obesity is suspected to be a risk factor for respiratory failure, leading to invasive mechanical ventilation [77].

It is also suggested that male gender and advanced age associated with comorbidities, such as asthma, diabetes, cardiovascular diseases or cancer, are risk factors to higher rates of death.

6-8- Prevention and treatment

Up to now, there are neither vaccines nor specific antiviral medicine for treatment of Covid-19. Standard care is based on isolation and prevention measures, as well as symptomatic treatment. Several clinical studies have been carried out and in progress throughout the world. According to online Covid-19 clinical trial trackers, there are 1476 trials registered worldwide, on June 7, 2020 [92]. WHO outlined four potential therapeutic drugs for Covid-19 in their Solidarity project: Remdesivir, Lopinavir/Ritonavir, Interferon beta-1a, and Hydroxychloroquine and Chloroquine. Of these, Remdesivir currently seems to be the most promise drug [93]. The efficacy of chloroquine and hydroxychloroquine, the anti-malarial drugs, in the control of SARS-CoV-2 infection, is highly debated; some authors think that it can decrease the disease severity and reduce the viral load [94, 95]. However, others suggested the absence or the limited effect and even their severe side effects [93]. Randomized trial studies have reported the safety and the efficacy of Interferon-α and Lopinavir-Ritonavir in Covid-19 treatment [96]. This association reduced SARS-CoV-2 viral load and improved clinical symptoms, during the treatment of Covid-19 patients. Other treatments are under investigations. Tocilizumab's preliminary data showed an improvement of the clinical outcome, immediately in severe and critical Covid-19 patients [96]. Attempts with convalescent plasma therapy showed an early-stage recovery and a reduced mortality rate in infected patients [62].

Even if there is still no licensed Covid-19 vaccine, several trials are under development; some of them are in early clinical trials and the vaccine could be available as soon as possible [93].While waiting for an effective vaccine, the only measure to reduce the risk of viral transmission remains prevention by hand washing, mouth and nose covering when coughing or sneezing, social distancing, wearing personal protective equipment, specifically surgical face masks, and having minimal contact with patients to limit public transmission [97].

Conclusion

During the COVID-19 outbreak (January 1 – June 30, 2020), including the fourteen weeks that follow the March 11 declaration by the WHO of a global pandemic, and despite the fact that, the number of people confirmed with COVID-19 exceeded 6 million, globally, and 1 175 in Tunisia.

In addition, there has been fewer than 21 reports (as of June 30, 2020), from around the world, on pets (dogs and cats) and other species (tigers, lions, minks) being infected with SARS-CoV-2. However, none of these reports have suggested that pets are a source of infection for people. Based on the limited information available to date, the risk of animals spreading COVID-19 to people is considered low.

To date, evidences from the few domestic animals that have tested positive for SARS-CoV-2 indicate these infections are typically a result of their close contact with people with COVID-19. In laboratory experimental infections with SARS-CoV-2, ferrets, Syrian hamsters and cats - animals that may be kept as pets – have shown their potential to serve as animal models for human infection; but dogs, pigs, chickens, and ducks do not. Besides, although molecular modeling and *in vitro* studies suggest that multiple animal species may theoretically be able to be infected with SARS-CoV-2, a definitive intermediate host has not been identified, yet. There is little to no evidence that domestic animals are easily infected with SARS-CoV-2 under natural conditions and no evidence to date that they may transmit the virus to people. The primary mode of COVID-19 transmission to humans is person-to-person spread.

Finally, during this COVID-19 outbreak, substantial knowledges and progresses have been made on Covid-19, as well as on pathogen monitoring, source identification, basic etiology and therapy.

Nevertheless, different points remain unclear. Worldwide, normative institutions and pharmaceutical companies are working hard for effective vaccines and drugs against SARS-Cov-2. Until then, respecting hygiene measures and physical distancing measures, as well as close monitoring, early identification of Covid-19 along with higher vigilance are very important to prevent viral transmission and disease complications.

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Annex

Table I : Findings related to natural infection with SRAS-CoV-2 in pets (As of June 30, 2020)

Country	Report date	Species (number)	Clinical signs		COVID19 Owner	Laboratory Diagnosis				References
			Yes/ No	Other information		RT-PCR	Virus isolation	Gene sequencing	Neutralizing antibodies	
United States of America (New York)	June 25, 2020	Dogs (3)	Not reported	-	YES	Not reported	Not reported	Not reported	YES	[33]
United States of America (Illinois)	June 10, 2020	Cat (1)	Yes	Clinical signs included fever, oral lesions and ulcerations on the tongue. The cat tested negative by feline respiratory panel test, for FIV and FeLV, and positive by feline coronavirus serologic test, a common finding.	YES	Positive	Not reported	Positive	Not reported	[32, 34]
Spain (La Rioja)	June 8, 2020	Cat (1)	No	The cat suffered from chronic diseases. The animal lived in a house with another cat tested negative to SARS-CoV-2. Both of them did not show clinical symptoms. The owner of both animals has been diagnosed with COVID-19, with severe pneumonia.	YES	Positive	Not reported	Not reported	Not reported	[32, 35]
United States of America (Minnesota)	June 3, 2020	Cat (1)	YES	Clinical signs included depression, fever, and harsh lung sounds. The cat tested positive for both *mycoplasma felis* and SARS-CoV-2, at the initial testing laboratory.	YES	Positive	Not reported	Positive	Not reported	[32, 34]
United States of America (New York)	June 2, 2020	Dog (1)	No	No clinical signs of the disease	YES	Negative	Positive	Positive	Positive	[32, 34]
United States of America (New York)	June 2, 2020	Dog (1)	Yes	Clinical signs included severe lethargy, diagnosed as hemolytic anemia.	YES	Positive	Positive	Positive	Positive	[32, 34]
Russia (Moscow)	May 26, 2020	Cat (1)	Not reported	-	Not reported	Positive	Not reported	Not reported	Not reported	[32]

The Netherlands	May 15, 2020	Dog (1)	YES	The dog has exhibited breathing problems. However, it is unknown whether the dog has respiratory problems linked to an infection with SARS-CoV-2 or due to another cause.	YES	Negative	Not reported	Not reported	Positive	[36]
The Netherlands (Noord Brabant)	May 15 and May 25, 2020	Cats (7)	Not reported	24 feral or semi-feral cats, living in the first two infected farms (municipalities of Gemert-Bakel and Laarbeek), were tested positive. The way of contamination of the cats was unknown (from infected minks or infected farm workers).	-	Positive (1 cat only)	Not reported	Not reported	Positive (n=7)	[32, 36]
Germany (Bavaria)	May 13, 2020	Cat (1)	NO	Two other cats were housed in the same nursing home. None of the cats showed any symptoms. Samples were negative for the two other cats.	YES	Positive	Not reported	Not reported	Not reported	[32]
France (Bordeaux)	May 12, 2020	Cat (1)	YES	The owner is suspected of having got COVID-19. The animal exhibited respiratory distress (coughing).	Suspected	Positive	Not reported	Not reported	Not reported	[37]
Spain (Catalogna)	May 11, 2020	Cat (1)	YES	The animal lived in a household where several people were COVID-19 positive. He had exhibited respiratory symptoms, but his veterinarian has questioned its link to the SARS-CoV2; the animal was suffering from an hypertrophic cardiomyopathy. The finding of SARS-CoV-2 in this animal is therefore considered to be incidental.	YES	Positive	Not reported	Not reported	Not reported	[32, 38]
France (Ile de France)	May 2, 2020	Cat	YES	This cat showed mild respiratory and digestive signs.	YES	Positive	Not reported	Not reported	Not reported	[39]
USA (New York)	Apr 22, 2020	Cats (2)	YES	Two cats from separate households were sampled for respiratory illness. Clinical signs included sneezing and ocular discharge. One cat is from a household with a known COVID-19 affected person; the other from a household in an affected	YES	Positive	Not reported	Positive	Not reported	[32, 36]

				neighborhood and allowed to go outdoors.						
Hong Kong (Hong Kong)	Apr 3, 2020	Cat (1)	No	-	YES	Positive	Negative	Not reported	Positive	[32]
China (Wuhan)	April 2, 2020	Cats (3)	Not reported	On April 3^{d}, 2020, a preprint posted on the bioRxiv site described a serological survey of cats conducted during the initial outbreak of COVID-19 in Wuhan.	YES	Not reported	Not reported	Not reported	Positive	[40]
Belgium (Not reported)	Mar 18, 2020	Cat (1)	YES	The cat expressed digestive and respiratory clinical signs one week after the return from Italy of his owner. The Belgian Scientific Committee as well as an OIE expert group indicated that these elements do not indicate a productive viral infection, but only to suspect it.	YES	Positive	Not reported	Not reported	Not reported	[32, 38]
Hong Kong (**Hong Kong)**	Mar 21, 2020	Dog (1)	No	The dog was kept in the same household as a confirmed COVID-19 patient and another dog. Only this dog was tested positive. Both animals did not show any relevant clinical signs.	YES	Positive	Positive	Not reported	Positive	[32, 41]
Hong Kong (Hong Kong)	Feb 29, 2020	Dog (1)	No	The test results confirmed the dog's infection with SARS-CoV-2. However, no clinical signs were detected during the quarantine. The animal was returned to its owner at the end of the quarantine, following consecutive negative test results. The dog died two days after its release from the quarantine. However, his death was not considered to be a direct consequence of its prior infection.	YES	Positive	Negative	Not reported	Positive	[32, 41]

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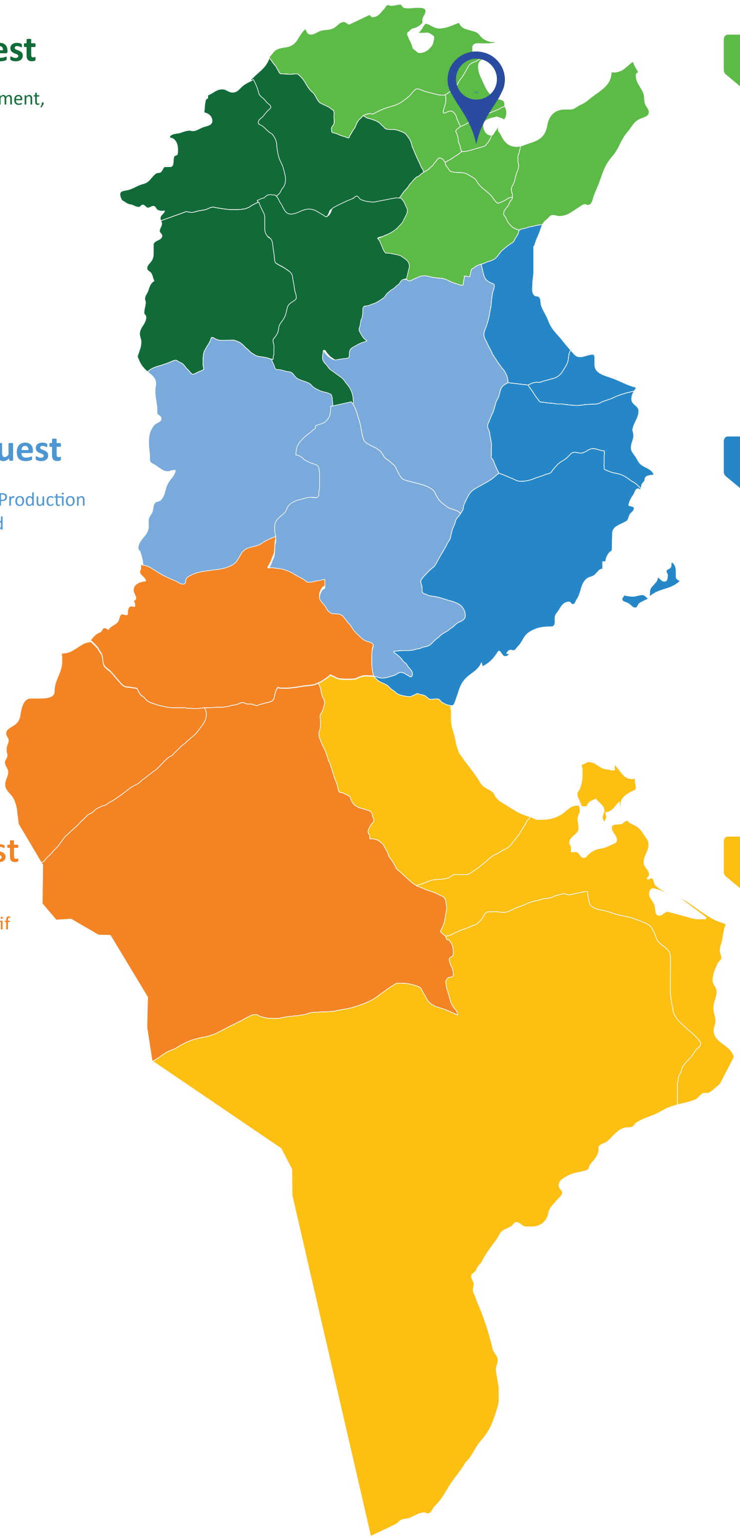

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