Tabari Biomedical Student Research Journal

OPEN ACCESS

EDITORIAL: The Second Pandemic I Have Ever Seen, COVID-19 Infection, An Overview

Mohammad Ali Ebrahimzadeh

Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran.
Email: zadeh20@gmail.com
ORCID: 0000-0002-8769-9912

10.18502/tbsrj.v2i1.2575 **Published: 31 Mar 2020**

Since the declaration of WHO on 11th March 2020, after AIDS (2005-2012, killing > 36 million people), COVID-19 was the second real pandemic disease I have ever seen in my life. As of 28th March, 35,480 people have been affected with COVID-19, 2,517 people have died of COVOD-19, and 11,679 people have recovered in Iran (1).

Coronaviruses are a group of related viruses that cause diseases in mammals and birds. Coronaviruses were first discovered in the 1960s. This name is derived from Latin corona, meaning crown, based on the appearance of the virus (***Figure 1***). They cause respiratory tract illnesses, from the simple common cold to more serious ones.

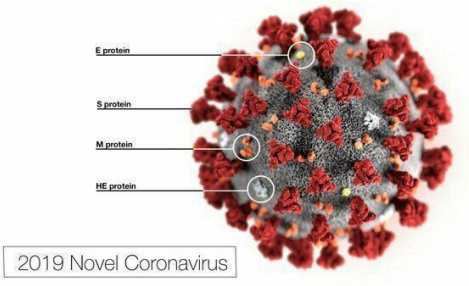


Figure 1. Appearance of Coronavirus-19

SARS-CoV-2, the virus that causes COVID-19, is thought to have first jumped from bats to humans in Wuhan, China. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), also both caused by coronaviruses. SARS emerged in 2003, affecting > 8000 people, killing 774 in 26 countries. MERS was isolated in 2012 and has seen over 2400 cases reported to WHO to date, and >850 deaths (2).

Incidence of many infectious diseases, including human coronaviruses have seasonal patterns. A simplified model that shows a zone at increased risk for COVID-19 spread has proposed recently (3). Based on this model, it may be possible to predict the areas most likely to be at higher risk of COVID-19 in the upcoming weeks. It can lead to concentrate of public health efforts on surveillance and containment. It initially appeared in a series of patients with pneumonia of unknown etiology in the Hubei, China, and subsequently spread to many other regions in the world such as South Korea, Japan, Iran, Italy, and USA.

Age distributions and sex ratios

To date (28th March), COVID- 19 has already confirmed to have affected almost 620,731, with more than 28,650 deaths and 137,348 recovered in the world. COVID-19 has been affected 199 countries. A list of the eleven countries most affected by COVID-19 is shown in ***Table 1*** (4). Iran is the sixth in the table. The number of affected people in Italy and America is rising rapidly. USA got the rank of first in the list. Fortunately, China as a primary source of virus is on the decline.

Incubation period and death rate

The incubation period (time from exposure to the development of symptoms) for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately four to five days after exposure (1). WHO reported an incubation period between 2 and 10 days,

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[DOI: 10.18502/tbsrj.v2i1.2575]

Table 1. Rank of the eleven countries most affected by COVID-19 until March 28, 2020.

Rank	Country	Total Cases	New Cases	Total Deaths	New Deaths	Total Recovered	1st case
-	World	620,731	+24,419	28,650	+1,309	137,348	Jan 10
1	USA	104,906	+780	1,715	+19	2,537	Jan 20
2	Italy	86,498		9,134		10,950	Jan 29
3	China	81,394	+54	3,295	+3	74,971	Jan 10
4	Spain	72,248	+6,529	5,690	+552	12,285	Jan 30
5	Germany	53,340	+2,469	399	+48	6,658	Jan 26
6	Iran	35,408	+3,076	2,517	+139	11,679	Feb 18
7	France	32,964		1,995		5,700	Jan 23
8	UK	17,089	+2,546	1,019	+260	135	Jan 30
9	Switzerland	13,377	+449	242	+11	1,530	Feb 24
10	Netherlands	9,762	+1,159	639	+93	3	Feb 26
11	South Korea	9,478	+146	144	+5	4,811	Jan 19

China's National Health Commission had initially estimated an incubation period from 10 to 14 days and United States' CDC estimates the incubation period for COVID-19 to be between 2 and 14 days (4). The case fatality rate with seasonal flu in the United States is less than 0.1%. The mortality rate for SARS was 9.6%, and for MERS 34%, for Swine Flu was 0.02%, and for COVID-19 was 2%. The early estimation of mortality by WHO was 2% (1). Now, the death rate of COVID-19 is about 3.4% worldwide, according to the WHO, but that number does not fully capture how deadly the virus could be for older populations. The death rate in the US is above 10% for those over 85 (5). Americans over 85 make up the largest portion of coronavirus cases when the data is adjusted for population size. The data suggests person's chances of dying from COVID-19 increase with age. Most (>93%) coronavirus deaths in the US have been among people 55 and older (5). Italy is one of the countries most affected by the coronavirus pandemic. Its population is the second oldest on average, after Japan's (***Table 2***) (5).

South Korea has also seen higher death rates among older age groups, though it has reported lower death rates overall than most countries. South Korea's total death rate was about 0.97%. That's far lower than the death rates in other countries. A major factor could be the country's comprehensive coronavirus-testing policies. The death rate in South Korea is 7.2% for those over 85. The rate of death is a little more in males.

Age distribution and sex ratio of all confirmed COVID-19 cases in China have been shown in ***Figure 2***. The male-to-female ratio was 0.99:1 in Wuhan, 1.04:1 in Hubei, and 1.06:1 in China overall (6).

One study of 140 patients with COVID-19 in China, found the sex distribution equal; whereas, in a study of critically ill patients, more men were affected (67%) than women. In the latest report of 1099 patients with COVID-19 from 552 hospitals in 30 provinces in China, 58% of the patients were men. Taken together, these data seem to

Table 2. Ranking of COVID-19 death rate in a few countries with confirmed deaths and more than 1,000 cases. Based on Johns Hopkins reports in March 17, 2020 (5).

Rank	Country	Cases	Deaths	Death rate
1	Italy	31,506	2,503	7.94
2	Iran	16,169	988	6.11
3	Spain	11,309	509	4.50
4	China	81,058	3,320	3.98
5	UK	1,960	55	2.81
6	Netherland	1,708	43	2.52
7	France	6,664	148	2.22
8	USA	5,702	96	1.68
9	Switzerland	2,700	27	1.00
10	South Korea	8,320	81	0.97

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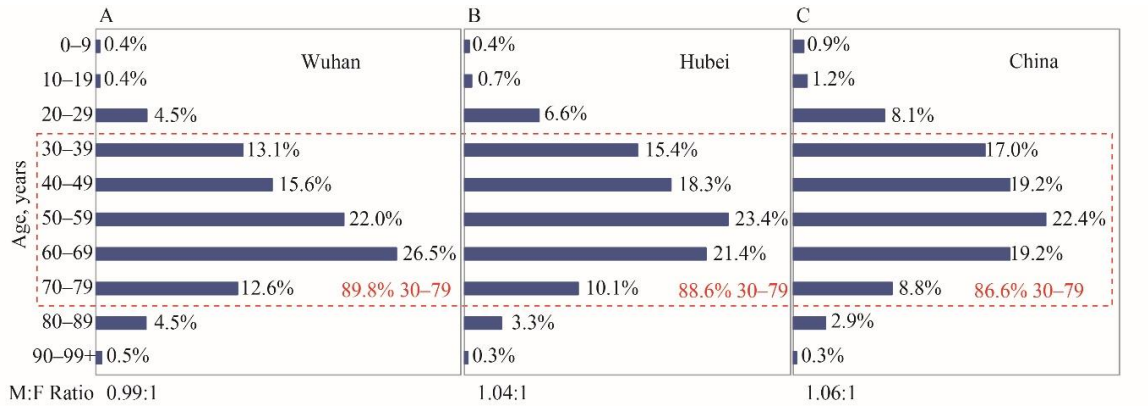


Figure 2. Age distribution and sex ratio of all confirmed COVID-19 cases in China. (A) patients diagnosed in Wuhan only; (B) patients diagnosed in Hubei Province; and (C) patients diagnosed in China overall. Dashed red line highlights the proportion of patients in the 30–79 years age range. Sex ratio (i.e. male-to-female [M:F] ratio) is shown below each graph (6).

indicate that there might be a sex predisposition to COVID-19, with men more prone to being affected (7).

Pre-existing medical conditions (comorbidities)

The presence of some pre-existing medical conditions predisposes patients and mortality rate will rise (***Table 3)*** (6).

Among a total of 72 314 case records, 44 672 were classified as confirmed cases of COVID-19 (62%). 98% of infected patients were >20 years of age. The overall fatality rate was 2.3%. The fatality rate was elevated among those with pre-existing comorbid conditions, 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6%for cancer (8).

According to one report, 191 patients in China were included in a study, of whom 137 were discharged and 54 died in hospital. 48% of patients had comorbidity, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%) (9).

People with blood group A have a significantly higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O has a significantly lower risk for the infection compared with non-O blood groups (10).

Transmission

Although bats are expected reservoir hosts for COVID-19, Malayan pangolins were identified as intermediate hosts that might have facilitated transfer to humans. The similarity of pangolin coronavirus to COVID-19 suggests that pangolins should be considered as possible hosts in the emergence of COVID and should be removed from wet markets (11).

The reports, published online in Gastroenterology, found that > 53% of people infected with COVID-19 have the virus in their stool; some patients have vomiting and diarrhea; and some test positive for virus in stool even after respiratory samples test negative for the pathogen. This may suggest a new hypothesis regarding the ways the virus is transmitted (12).

In another report, live virus was detected in feces. It means that COVID-19 may be transmitted by the fecal route (13).

Table 3. COVID-19 fatality rate by comorbidity (Pre-existing medical conditions):

Pre-existing condition	Death rate, confirmed cases	Death rate, all cases
Cardiovascular disease	13.2%	10.5%
Diabetes	9.2%	7.3%
Chronic respiratory disease	8.0%	6.3%
Hypertension	8.4%	6.0%
Cancer	7.6%	5.6%
No pre-existing conditions		0.9%

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Ocular involvement has not been described with either MERS or SARS. Based on WHO guidance on personal protection equipment in infection prevention and control when COVID-19 is suspected, Eye protection (goggles) or facial protection (face mask) should be worn, and healthcare workers are advised against touching any mucosal membranes (eyes, nose or mouth) (2).

The WHO is considering "airborne precautions" for medical staff. The virus is transmitted through droplets, or little bits of liquid, mostly through sneezing or coughing. Researchers found the virus was detectable in aerosols for up to 3 hours, up to 4 hours on copper and up to 24 hours on cardboard. COVID-19 can also last up to three days on plastic and stainless steel, the scientists concluded (14).

Diagnostic tools

The diagnostic value and consistency of chest CT as compared with comparison to the reverse-transcription polymerase chain reaction (RT-PCR) assay in COVID-19 was investigated in 1014 patients in Wuhan, China. RT-PCR or gene sequencing for respiratory or blood specimens is a key indicator for hospitalization. Of 1014 patients, 59% had positive RT-PCR results, and 88% had positive chest CT scans. The sensitivity of chest CT in suggesting COVID-19 was 97% based on positive RT-PCR results. In patients with negative RT-PCR results, 75% had positive chest CT findings. Chest CT has a high sensitivity for diagnosis of COVID-19. Chest CT may be considered as a primary tool for the current COVID-19 detection in epidemic areas (15). Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) of nasopharyngeal swabs typically has been used to confirm the clinical diagnosis (13).

Unfortunately, the WHO does not possess a database for COVID-19 testing data, so gathering the data is so hard. ***Table 4*** shows the estimates of testing levels in some countries (as of 20th March 2020) (16). Countries with higher ability to test are in lower levels of infections and death rates (Compare with data of ***Table 2***). Doing more tests means we can expect the number of confirmed cases/ positive tests, is closer to the real number of infected people.

Signs and symptoms

Eight studies on the clinical characteristics of COVID-19 infection were collected for meta-analysis (5732 patients). According to the data, among the clinical characteristics of patients with COVID-19 infection, fever (90.9%), cough (70.8%), and muscle soreness or fatigue (41%) were the most common symptoms in patients with COVID-19 infection. The incidence of abnormal chest CT was 95.6%. Some people have muscle soreness or fatigue, ARDS. Diarrhea, hemoptysis, headache, sore throat, shock, and other symptoms only occur in a small number of patients. The mortality rate of patients was 6.4% (17).

Of 138 hospitalized patients with COVID-19 infected pneumonia (NCIP), the median age was 56 years, and 54.3% were men. Common symptoms included fever 98.6%, fatigue 69.6%, and dry cough 59.4%. Lymphopenia occurred in 70.3%, prolonged prothrombin time in 58%, and elevated lactate dehydrogenase in 39.9%. Chest CT scans showed patchy bilateral shadows or ground-glass opacity in the lungs of all patients (18).

Table 4. Total estimated number of COVID-19 tests in some countries (as of 20 March 2020).

Entity	Total COVID-19 tests	Tests per 1,000,000 people
United Arab Emirates	125000	12,738
South Korea	316664	6,148
Australia	113615	4,473
Germany	167000	2,023
United Kingdom	64621	960
Iran	80000	957
France	36747	559
United States	103945	314
Japan	14901	118

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Results of data regarding 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces in China showed that the median age of the patients was 47 years; 41.9% of the patients were female. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). On admission, ground-glass opacity was the most common radiologic finding on chest CT (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with no severe disease and in 5 of 173 patients (2.9%) with severe disease. Patients often presented without fever, and many did not have abnormal radiologic findings. The mortality rate of patients was 1.4% (19).

All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. Forty-one admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection. Most of the infected patients were men (73%); 32% of infected patients had underlying diseases including diabetes (20%), hypertension (15%), and cardiovascular disease (15%). Common symptoms were fever (98%), cough (76%), and myalgia or fatigue (44%); less common symptoms were sputum production (28%), headache (8%), and diarrhea (3%). Dyspnea developed in 55% of patients. All 41 patients had pneumonia with abnormal findings on chest CT (20).

Diarrhea and loss of appetite could be early signs of coronavirus as scientists find almost half of patients experience one or more digestive symptoms. One study of 204 Wuhan residents revealed 48.5% showed digestive symptoms. Most had normal respiratory issues. Only seven people did not. Digestive problems such as diarrhea, vomiting and loss of appetite could be a symptom of COVID-19 (21).

Anosmia and/or dysgeusia are frequently reported as signs in COVID-19. Anosmia, in particular, has been seen in COVID-19 positive patients with no other symptoms (22).

Recently, the neutrophil-to-lymphocyte ratio (NLR) was recognized as the independent risk factor for severe illness in patients with 2019-nCoV infection. Patients with age ≥ 50 and NLR ≥ 3.13 facilitated severe illness, and they should rapidly access to ICU if necessary (23).

Platelet-to-lymphocyte ratio (PLR) provided as a new indicator in the monitoring in patients with COVID-19. The PLR of patients means the degree of the cytokine storm. A single-center case series of the 30 hospitalized patients with confirmed COVID-19 reported that the number of platelets and their dynamic changes during the treatment might have a suggestion on the severity and prognosis of the disease (24).

Asymptomatic infections have also been described many times. In a COVID-19 outbreak on a cruise ship, about half of the 619 confirmed COVID-19 cases were asymptomatic at the time of diagnosis. In a study of 24 patients with asymptomatic infection whom all underwent CT, 50% had typical ground-glass opacities and another 20% had atypical imaging abnormalities. In another study of 55 patients with asymptomatic infection identified through contact tracing, 67% had CT evidence of pneumonia (25). Documents reported by China showed more than 43,000 people had tested positive for COVID-19 by the end of February, did not show any symptoms (26). Role of such an asymptomatic carrier of COVID-19 in China in spread of infection has been reported elsewhere (27). Children with COVID-19 show milder symptom pattern (28).

Vaccines and treatment

The first step, the simplest and the most effective way for prevention of COVID-19, is maintaining personal hygiene such as washing hands, avoiding touching face and coughing into sleeves (***Figure 3***).

While there are several therapeutics currently in clinical trials in China and more than 20 vaccines in development for COVID-19, there are currently no licensed vaccines or therapeutics for COVID-19 (29).

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Figure 3. Personal ways for prevention of COVID-19

A Canadian company says it has made a breakthrough in the fight against the COVID-19 outbreak, claiming to have developed a COVID-19 vaccine candidate that could begin human testing as early as this summer (30). Chinese scientists claim they have developed an oral vaccine to beat coronavirus using baker's yeast, but this product was still 'far from' being sold on the market. It would take at least six months for the vaccine to pass tests and evaluations (31).

Although no definitive cure for this disease has been found to date, there is promising evidence of the efficacy of some drugs against COVID-19 in the literature. Receiving 600 mg of Hydroxychloroquine daily is significantly associated with viral load reduction/ disappearance in COVID-19 patients. This preliminary result also suggested a synergistic effect of the combination of Hydroxychloroquine and azithromycin (32). Chloroquine can inhibit COVID-19 with IC50 of 1-5 µM (9 µM for SARS). Hydroxychloroquine was much more potent than chloroquine at inhibition of COVID-19 in cell lines (EC50 of 0.7 µM). They recommended a regimen of 400 mg twice daily for the first day, followed by 200 mg twice daily for the following four days (33). Combination of two HIV drugs, Lopinavir-Ritonavir; antiviral drug Remdesivir; Japanese anti-flu drug Favipiravir is effective in the treatment of this disease (33,34). A brief overview of off label use of drug against COVID-19 has been shown elsewhere (33). It seems that Neuraminidase inhibitors (such as Oseltamivir) do not seem to be effective against COVID-19 (33). Tocilizumab (***Figure 4***) is a recombinant humanized monoclonal antibody that binds to the interleukin-6 (IL-6) receptor and blocks it from functioning. It is most commonly used to treat rheumatoid arthritis. It may also be used to treat cytokine release syndrome. It is effective in patients with COVID-19 who develop a cytokine storm (which involves elevated levels of IL-6, a major pro-inflammatory cytokine.

On 20th March, Swiss healthcare company Roche wins approval for Actemra (Tocilizumab) to treat patients developing severe complications from COVID-19 (35). Siltuximab is an alternative drug with similar clinical effects. Siltuximab is an anti-IL6 monoclonal antibody (33).

Some observational studies suggest that statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients admitted with influenza and/or pneumonia. Therefore, it is conceivable that patients admitted with viral respiratory illnesses including COVID-19 could derive a beneficial effect from the continuation of their statin therapy. One randomized controlled trial (RCT) showed possible beneficial effects of oral administration of statin in reducing mortality in those with ventilator-associated pneumonia. In contrast, the results of another RCT do not support statin administration in those with ventilator-associated pneumonia (36). Atorvastatin 40-80 mg, PO, daily, Pravastatin 80 mg, PO,



Figure 4. Tocilizumab in drug market

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daily, and interferon-beta B1 also reported being effective against COVID-19 (33). Stages of illness and timing of suitable therapies have been shown in ***Scheme 1***. For relief of fever, avoid administration of ibuprofen, naproxen, and other NSAIDs.

Acetaminophen 650 mg PO every 4-6 hours (max dose of 2 g/day) can be used. Azithromycin 500 mg PO on day 1, then 250 mg PO on days 2-5 or Oseltamivir 75 mg PO twice daily for five days, can be used in some stages of infection (37).

Canadian researchers launched a study recently into the use of a powerful anti-inflammatory drug to reduce the risks of pulmonary complications and death related to the new coronavirus. Recently, colchicine has been shown to be effective against CIVID-19 (38).

Camostat mesilate, a drug currently approved in Japan to treat pancreatic inflammation, may block COVID-19 infection. It seems camostat blocks entry of the virus into lung cells (39).

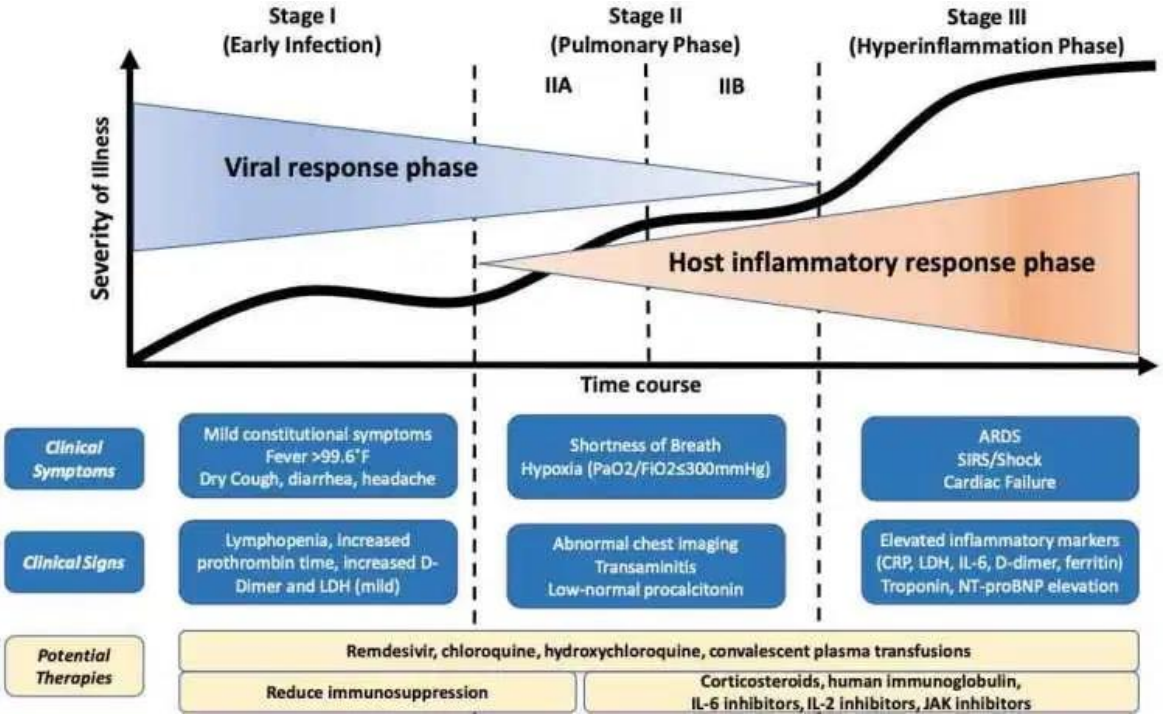
Although Moderna's COVID-19 vaccine (mRNA vaccine) is at least a year away from a widespread rollout, the company may provide the vaccine to a few people, which could include healthcare workers, as early as fall of 2020 (40). The tuberculosis vaccine (The Bacille Calmette-Guerin vaccine, also known as BCG) could help protect health workers from COVID-19 (41).

Passive antibody therapy has been suggested as a new therapeutic hope. Hospitals in New York City are trying to use the blood of people who have recovered from COVID-19 as a possible antidote for the disease (42).

The role of vitamin D3 (the active metabolite of vitamin D; 1,25(OH)2D3; Calcitriol) in immunoregulation is clear. Altered levels of vitamin D3 cause higher susceptibility to immune-mediated disorders. Nearly every tissue in the body has receptors for vitamin D3. Vitamin D3 dramatically induces genetic expression of antimicrobial peptides (AMPs). The AMPs display a broad-spectrum of antimicrobial and antiviral activities including the influenza virus (43).

Persistence of coronaviruses on inanimate surfaces

The analysis of 22 studies reveals that human coronaviruses such as SARS coronavirus, MERS coronavirus or human coronaviruses (HCoV) can persist on inanimate surfaces like metal, glass or



Scheme 1. Stages of illness & timing of therapies.

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plastic for up to 9 days, but can be efficiently inactivated by disinfectants such as 62–71% Ethanol, 0.5% Hydrogen Peroxide or 0.1% Sodium Hypochlorite within one minute. Other biocidal agents such as 0.05–0.2% Benzalkonium Chloride or 0.02% Chlorhexidine Digluconate are less effective (44).

The aerosol and surface stability of SARS-CoV-2 was analyzed and compared with SARS-CoV-1, the most closely related human coronavirus. SARS-CoV-2 remained viable in aerosols throughout experiment (3 hours), with a reduction in infectious titer from 103.5 to 102.7 TCID50 per liter of air. This reduction was similar to that observed with SARS-CoV-1, from 104.3 to 103.5 TCID50 per milliliter. SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 hours after application to these surfaces (45).

Furthermore, finally, I think we should wait for another outbreak, Hantavirus! Hantavirus is a member of Bunyavirus family. This group was first identified as causing hemorrhagic fevers with renal failure. Hantavirus pulmonary syndrome became more prominent when it was first described in USA.

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