

General evaluation of the COVID 19 pandemic from an Infectious Diseases perspective

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ABSTRACT

Coronavirus 2019 (COVID 19) has caused mortality and morbidity both in our country and around the world. It has been declared as a pandemic by the World Health Organization. Infectious disease specialists are among the departments that played the leading roles in the pandemic. In this review, it was aimed to evaluate the COVID-19 outbreak in perspective of the infectious diseases physicians in the light of the current literature.

Keywords: COVID-19, epidemic, pandemic.

Infectious disease: Infectious diseases are diseases transmitted from person to person under special circumstances and characterized by pathologic symptoms caused by the infectious agent or its toxins as a result of local and general localization of the infectious agent by entering the human body through any path.^[1] As in the past and today, infectious diseases will continue to be a problem in the future. The importance of infectious diseases stems from the fact that they threaten public health in varying degrees, especially outbreaks and the ongoing COVID-19 pandemic.

Infectivity: Infectivity is the ability of the pathogen to be transmitted to a healthy person, to settle in the host's body and to reproduce.^[1] Current studies mention the high infectivity of COVID-19.

Virulence: Virulence refers to the severity of the disease caused by the pathogen.^[1] Some agents cause mild infections, while others cause severe disease. Studies on COVID-19 report that it causes moderate-severe disease.^[2]

Transmissibility: Transmissibility is the ability of an infectious agent to leave a host and spread to another.^[1] Although it is not as high as smallpox, transmissibility of COVID-19 is quite high.^[2]

Modes of transmission: Pathogens can enter the new host's body in a variety of ways. Transmission may occur directly or indirectly, and especially through digestion, respiration, contact, and vectors. In regards to the modes of transmission of COVID-19, when mucous membranes of healthy individuals come into contact with respiratory secretion droplets containing the virus from sick individuals which spread to the surroundings

Received: January 05, 2021 **Accepted:** January 18, 2021 **Published online:** May 05, 2021

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Cite this article as:

Dindar Demiray EK, Alkan Çeviker S, Yılmaz M, Alırcı İD. General evaluation of the COVID 19 pandemic from an Infectious Diseases perspective. D J Med Sci 2021;7(1):82-90.

during coughing, sneezing, laughing, and speech, transmission occurs. Transmission occurs through contact, respiration, and droplets. These modes of transmission from person to person requires close contact (closer than 1 meter).^[1]

In terms of epidemiology, since the first case in Wuhan, 132 million COVID-19 cases (May 30, 2020 - WHO) have been reported, including all laboratory-confirmed cases in China at the end of 2019, as well as clinically diagnosed cases in the Hubei Province.^[1-3] An increasing number of cases have also been reported in countries on other continents except for Antarctica. The World Health Organization (WHO) declared COVID-19 as a pandemic, as the rate of new cases outside of China exceeded the rate in China. Surveillance methods for the management of pandemics have been implemented.^[1] Infectious diseases occur as a result of the chain of infection consisting of the source of infection, the healthy person, and the transmission route. Infection is prevented by taking precautions against one or more of the components of the chain.^[1]

In the epidemiology, an outbreak is a disease that seems like a series of new cases over a period of time in a certain population, but displays a much higher impact than expected compared to previous experiences. Depending on what is expected, the definition of the outbreak may be subjective. An outbreak may be local, more generalized, or global.^[4] In order to be called an outbreak, the number of cases must be higher than normally expected. This number may vary depending on the type of disease and regions that are affected. According to the American Food and Drug Administration (FDA), When two or more people acquire illness from the same contaminated food or drink, the event is called a foodborne outbreak. According to the criteria of the American Center for Disease Prevention (CDC) for measles, the presence of ≥ 3 verified cases of measles in a certain region was defined as an outbreak. The World Health Organization (WHO) has defined a >2 -week period and an incidence of $\geq 15/100,000$ in a certain region as the outbreak criteria for invasive meningococcal disease. The outbreak criteria for invasive meningococcal C disease were defined by the CDC as ≥ 3 cases in the same region without close contact in a ≤ 3 -month

period, and incidence of $\geq 10/100,000$ in the region.^[5]

Some diseases may be observed at standard rates in certain populations (endemic), while others occur at persistent yet higher rates (hyperendemic). When referring to an outbreak, it is understood that there are clearly more cases in that region or among the population than the expected rate. Outbreaks can be examined as “outbreaks” in foreign literature, referring to outbreaks that occur in a localized region, “epidemics” which are outbreaks which affect a large region or country, or “pandemics” which encompass many countries and/or continents. However, the terms “outbreak” and “epidemic” are usually used interchangeably. According to the Turkish Language Association, the terms outbreak and epidemic are synonymous.^[5]

Pandemic: Many infectious agents can lead to epidemics through different transmission routes. These epidemics may limit themselves over time depending on the virulence of the agent. However, they may also produce short- or long-term effects due to high infectivity. Theoretically, pandemics (from ancient Greek pan: all + demos: people) refer to the general name of epidemic diseases that spread and impact a very broad area such as a continent, or the entire world.^[2,4,5]

The degree of impact of a pandemic on humans especially varies according to the infectivity and virulence of the virus, community immunity, lifestyles and socioeconomic conditions of individuals, the convenience of traveling distances between cities and countries, risk factors that individuals carry in their life and working life, the quality of health services provided by the country people live in, and the positive and negative effects of climate on the outlook of the infectious agent.^[2,4,5]

World Health Organization influenza pandemic preparedness plan: The WHO conducts studies related to infectious diseases. Their long-term health planning aims to organize national preparation and foresee a number of scenarios, especially in the face of viral infections in which an effective or rapid cure or vaccine cannot be procured. For this reason, the “Checklist for Influenza Pandemic Preparedness Planning” was prepared and published by the WHO,^[2] for when caught unprepared in a pandemic scenario, and comprises of the following:

- The country's Ministry of Health is notified of X outbreak from X country.
- During this period, cases are identified in neighboring regions.
- A team is sent to investigate the region.
- Factor X is detected in necessary samples obtained from patients.
- Factor X, which has never been found in humans before, is identified
- Genetic analysis of Factor X is conducted as rapidly as possible
- Factor X begins to make major headlines.
- The outbreak begins to be seen in neighboring countries
- Travel restrictions are initiated.
- Schools are closed.
- Drug resources are limited.
- An effective vaccine is not yet available.
- The general population begins to panic.
- Illness is observed in airline passengers from countries with outbreaks.
- There are news of outbreaks in other continents.
- Phonelines of health institutions are disrupted.
- Vaccination and antiviral drugs cannot be obtained.
- There is a major shortage of staff among all institutions because of disease.
- There is no room in intensive care units.
- Respiratory devices are insufficient for the ongoing outbreak.
- In about eight weeks, the pandemic puts the world in a difficult situation
- Institutions providing health and public services become insufficient.

Historical overview of outbreaks specific to coronaviruses

Outbreaks have been the cause of great consequences and losses throughout human history. Among those which have had the greatest impact on human history, plague, cholera, typhus, smallpox, ebola, and flu are the most well-known. In recent history, SARS 2003, Influenza A H1N5 2007, Influenza A H1N1 2009, MERSCoV 2012, Influenza A H7N9 2013, Ebola 2014, Zika 2015 have been observed (Table 1).

Outbreaks are health events that have led to major global consequences, resulting in changes in daily life and administration. In the 1300s, 75-125 million people lost their lives due to the Black Death, which occurred in Italy and is considered the largest epidemic in Europe. The epidemic caused the collapse of feudalism in Europe due to its social, economic and political effects. Moreover, society has been shaped over the traumatic consequences faced by societies that have halted production, even when they have money. From a medical standpoint, the development of the concept of public health has progressed due to these epidemics. The Spanish Flu of 1918-1920 infected about half a billion people, causing the deaths of 17-50 million people. Today, COVID-19 is the first infectious epidemic disease of this scope and magnitude faced by the world after the Spanish Flu. In 1965, a group of English researchers led by Dr. David Tyrell studied the common cold, and the team examined a seemingly new virus found in tissue culture under an electron microscope and noticed its similarity to a virus isolated from chickens with bronchitis in the 1930s. The recognition of this virus began the journey to the discovery of coronaviruses.^[2,4]

Dr. Kenneth McIntosh, a member of the Harvard Medical Faculty, stated that research continued on these viruses seen in animals and known as avian bronchitis and that vaccines would be available. In 1968, McIntosh's team discovered another common respiratory coronavirus today with the code OC43. These viruses were called "Coronaviruses" due to their crown-like structure when viewed under the electron microscope.^[2]

Although coronaviruses have been extensively researched since the SARS outbreak, it is still unclear why the three major Coronaviruses

Table 1. Recent epidemic factors^[2]

SARS 2003
Influenza A H1N5 (avian flu) 2007
Influenza A H1N1 (swine flu) 2009
MERS-CoV 2012
Influenza A H7N9 2013
Ebola 2014
Zika 2015
COVID 19 2019

(SARS-CoV-1, MERS-CoV, and SARS-CoV-2, the source of the COVID-19 pandemic), spread with a more severe clinical presentation. It has been observed that the previously isolated Coronaviruses were ineffective next to the last three, and the latest Coronaviruses have more severe symptoms and higher mortality rates. In this context, research is still ongoing.

New global viral outbreaks: The most commonly encountered coronaviruses are RNA viruses that can infect humans and several animal species. They cause a wide variety of respiratory tract infections in humans, ranging from the common cold to pneumonia. Every year in autumn and winter, Coronaviruses cause colds with symptoms of sore throat, dry cough, runny nose, and fatigue. These coronaviruses have a short incubation period, of about 3-5 days, the disease is self-limiting within 4-6 days, and patients recover rapidly. Clinically severe pneumonia may develop in very few cases, especially in those among the risk group. Since 2002, novel coronaviruses, have begun to show more severe flu-like respiratory symptoms, different from the common cold. Coronaviruses that cause infections in humans belong to the alpha or beta genera.

SARS-CoV: SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) infection, originating from the Guangdong region of China in February 2003, was first transmitted from bats to palm civets and then thought to have transmitted to humans. In eight months, the disease was mostly seen in China and affected about 8,000 people, and about 800 people lost their lives from the disease. Since the virus can cause epidemics, especially as a result of close contact, protective measures are of great importance to prevent infection. Health personnel constitute the highest risk group due to the mode of transmission.

MERS-CoV: Another new coronavirus infection is MERS-CoV (Middle Eastern Respiratory Syndrome Coronavirus). It first emerged in Saudi Arabia in 2012. It is an enveloped RNA virus thought to specifically infect humans, bats, and camels. In the MERS-CoV epidemic that continued until June 2018, 2,229 cases and 791 deaths were reported.

While the mortality rate of SARS-CoV is 10.9%, this rate reached 35% in MERS-CoV. In

both SARS-CoV and MERS-CoV infections, the incubation period can be as short as 3-5 days, and can extend to up to 10-14 days. This suggests that the disease can be transmitted to others for up to 10-14 days even in the asymptomatic stage before symptoms appear. The disease is thought to be transmitted by close human-to-human contact, especially by touching the mouth, nose, and eyes with the hands after contact with surfaces contaminated with the virus, and by breathing droplets spread to the air by sick people during sneezing, coughing, and speaking.^[2,6]

SARS-CoV-2 (COVID-19): Today's ongoing viral pandemic is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), an enveloped RNA virus like SARS-CoV and MERS-CoV that causes severe respiratory failure, was isolated from humans on January 7, 2020. The first case was reported on December 31, 2019, in the city of Wuhan, which has a population of 11 million, in the Hubei province in China. This virus is also thought to be transmitted from other members of the family to a zoonotic infection such as SARS-CoV and MERS-CoV.^[2,3,6]

COVID-19 was first detected in humans in the seafood market in the city of Wuhan in China, in December 2019. Although scientists thought that COVID-19 was transmitted from bats, considering that bats were not sold in the market, it was suggested that a kind of intermediate animal was a carrier in the transmission of the virus to humans. Today, the disease has rapidly spread among humans, spreading to Europe, America, and Asia, the number of patients has increased day by day, reaching millions and the number of deaths reaching tens of thousands. The outbreak still continues as an ongoing pandemic (as of June 2020).^[2,3,6]

According to researchers, the virus can survive on different materials such as wood, paper, aluminum, plastic, and glass for about 4-5 days. According to a study published in The Lancet Magazine in 2019, the most common symptoms of COVID-19 were determined to be fever, coughing, and shortness of breath. Sore throat was observed in 5%, while diarrhea, nausea and vomiting were observed in 1-2% of cases. Pneumonia, severe acute respiratory failure, multiple organ failure and death have been observed in patients with

severe clinical manifestation. It was determined that the virus is generally transmitted from person to person, usually through droplets formed as a result of cough-speech. Transmission also occurs by the person touching contaminated surfaces and then touching their face with their hands. In addition, viral particles may be found in human feces and transmission may also occur through the fecal-oral route. The shortest incubation period is around 2-4 days, and the shortest disease duration is determined to be 5 days for those with good clinical progress.^[2,6,7]

Verifying an outbreak: An epidemic is suspected as a result of examining the data obtained through the surveillance of diseases for the management of infection. The available data are discussed by the health institutions. With the cooperation and coordination of the central and auxiliary health institutions, information, materials, and equipment are prepared for the epidemic. The literature is scanned in this context. The presence of a statistically significant increase ($p < 0.05$) in endemic rates for the disease is defined as an outbreak. To verify the outbreak, observed and expected cases are compared. In order to establish the expected number of cases, the current number of cases is usually compared with the previous case numbers, for example at the same time of the year. When the current infection rate is statistically higher compared to the times before the outbreak, and statistically high detection of a previously unseen disease supports the diagnosis of an outbreak. An answer is sought for the question, 'How can this be explained in a clinical and laboratory setting?'.^[1,5]

Case diagnosis: Cases are reviewed individually in terms of all possible diseases; diagnostic criteria

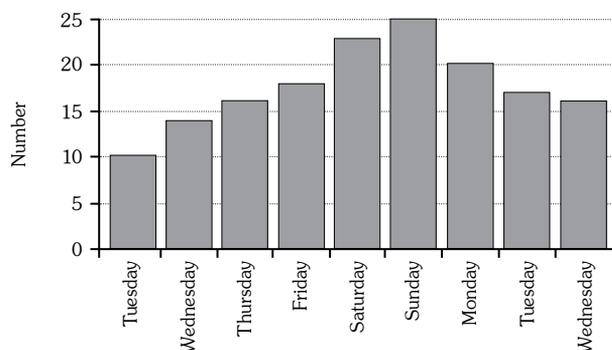


Figure 1. Example of a histogram.

are defined for probable, highly probable, and definite cases.^[1,5]

Evaluating the individual health status of cases: Cases are investigated according to the characteristics of the disease. Thus, all cases are determined and their numbers and characteristics are identified.^[1,5]

- Demographic data (age, sex, address, occupation, etc.)
- Clinical data (symptoms, presence of fever, physical examination findings, laboratory results, onset and severity of symptoms, etc.)
- Data pertaining to possible risk factors (presence of chronic disease, drugs used, foods ingested, etc.)

Defining the person, place, and time characteristics of an outbreak: Certain characteristics of the outbreak such as person, place, and time are examined. The epidemic curve drawn by the Histogram method (Figure 1) is useful in determining the type of outbreak. Point maps (Figure 2) provide visuality regarding the places where cases live or where they may have encountered the pathogen. Those at risk are determined by examining personal characteristics with these methods.^[1,5]

Forming hypotheses with reviewed data: A hypothesis is formed to explain the possible source of the disease, the possible route of transmission, and exposure to the pathogen.^[1,5]

Evaluating the hypothesis: Hypotheses can be compared with the results of all available

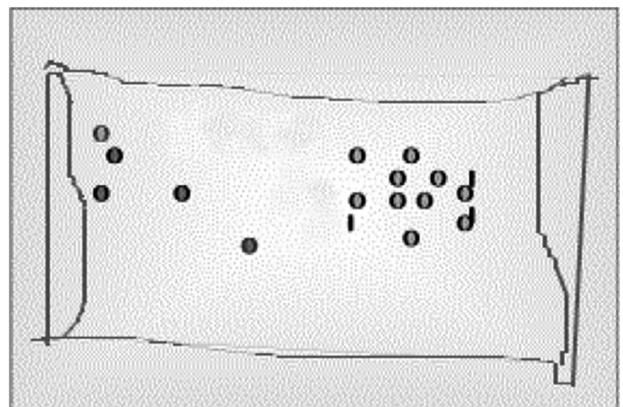


Figure 2. Example of a dot distribution map.

data. Analytical epidemiological methods and the relationship of variables can be assessed. For instance, with case-control studies, the odds ratio is calculated by investigating the exposure of both patients and those without disease, and an analysis of the relationship between the disease and the pathogen is made.^[1,2]

Determining the cause of the outbreak: Filiation methods consisting of additional samples collected from cases with detected exposure, and susceptible and high risk groups are used to determine the cause of the outbreak, possible sources, and mode of transmission. Filiation means analysis of the chain of contact, by reaching and examining everyone the person diagnosed with COVID-19 was in contact with for the last 14 days. This filiation is conducted to break the chain of infection.^[1,2]

Taking precautions: Absolute precautions are taken against the source of the outbreak. Contamination is attempted to be prevented. All cases are treated and differentiated. Susceptible people are attempted to be protected.^[1,2]

Reporting of available findings and results of evaluation: A detailed report consisting of an introduction, general information, method, findings, discussion, and recommendations is written. Surveillance continues. The authorities are notified for outbreak management. The epidemic is announced and the community is informed in detail.^[1,2]

Important points in combating epidemic diseases: Physicians, especially infectious disease specialists, family physicians, and emergency room specialists, are the first to encounter epidemic diseases. For this reason, the physician has a major role in early detection of outbreaks. During an outbreak, physicians may be faced with a large patient population, vaccination, and antibiotic prophylaxis. Meanwhile, they must take an active role in hospital and community work to inform the public and control the epidemic. Therefore, physicians should also be involved in the preparation and development of medical and social preparedness and response plans together with local and national authorities.^[2,8]

The most important point in dealing with epidemics is the installation of a strong health system infrastructure. It is necessary to fulfill fundamental public health services (disease

surveillance, support of laboratory services) in order to establish a rapid response to epidemic threats, to effectively identify them and investigate them in detail. Early diagnosis of naturally occurring infectious diseases and reemerging diseases will become easier with a more effective global surveillance program. It is especially important for clinicians to be aware and responsive to unusual cases of infection and their aggregation, to consult with infectious diseases specialists regarding diagnosis, and to report the cases to public health specialists.^[2,8]

The cooperation of primary health care physicians with public health officials is fundamental. While healthcare providers are trying to cope with epidemics, they require the cooperation of emergency management units, lawmakers, health institutions, and many other institutions that provide community services. In order for these groups to work together effectively, an advanced planning system should be implemented. In addition to surveillance programs, informing and training healthcare professionals, public health workers, and primary health care personnel about agents that can be used is also important. In addition, in order to rapidly diagnosis the source of the epidemic, expand laboratory capacity, and manage the epidemic, it is necessary to effectively provide medicine, vaccines, medical services, and hospital services.^[2,8]

Prevention and control measures in infectious diseases

Prevention and management measures must be taken during an epidemic. Protection and control measures involving the source, the route of transmission, and healthy people can be discussed under different headings:

- *Measures towards the source:* involves identifying the source, reporting the disease, definitive diagnosis, treatment of patients, isolation, carrier search, surveillance of suspects, health training, and extermination of animals in a zoonotic disease
- *Measures towards routes of transmission:* involves effective improvement of environmental conditions (disinfection), adequate control of food and beverages, health training for the community and

healthcare workers, generalizing of the use of personal hygiene and protective equipment, improvement of housing conditions, and restricting population mobility. Measures oriented towards the healthy population include vaccination, seroprophylaxis, chemoprophylaxis, quarantine observation, and ensuring healthy nutrition.

The importance of surveillance in protection and management methods

Surveillance is ongoing systematic collection, analysis, and interpretation of health data that are essential to the planning, implementation, and evaluation of public health practice. The purpose of surveillance is to quickly provide information that can be analyzed to determine the incidence and answer the questions of person, place, and time. In other words, it is used to determine the existing pattern of disease formation and potential in order to effectively investigate, manage, and prevent infection in a region.^[1,2,6]

“Passive surveillance” is a method of surveillance in which data sent for a specified period of time are analyzed, interpreted and reported through the system determined by the people who make the diagnosis, without actively collecting data from the person or units obliged to make notifications. “Active surveillance” is a method of surveillance in which the data is collected, analyzed, and interpreted by the authorized units without waiting for the self-report of the person or units responsible for reporting data. Active surveillance is used during outbreaks when the current situation and time are important. ‘Syndromic management’ is a surveillance method in which data consisting of nonspecific diagnoses or symptoms are collected, analyzed, and interpreted. It aims to create an algorithm for physicians to track which factors to consider first and which samples and diagnostic tests should be sent and when. The World Health Organization recommends this approach to countries with limited resources. “Sentinel surveillance” refers to a surveillance method in which data is collected, analyzed, interpreted, and feedback is made in a selected sample to detect cases in the earliest manner, to access sufficient information about the disease, and to collect quality and accurate data.^[1,2,6]

Within the scope of surveillance, studies included in the table below are carried out in relation to notifiable infectious diseases. In addition, some or all of these studies can be carried out during unusual or unexpected situations or public health threats that are not within the scope of notifiable disease, depending on the nature of the event (Table 2).

How does an outbreak end?

Three main requirements are needed to declare the end of an outbreak:

- A significant portion of the community encounters the disease and develops protective antibodies
- Reducing the population that can get sick through the use of vaccinations or preventive drugs
- Decrease in infectivity and pathogenicity of the agent

In regards to COVID-19, there is no indication of the third requirement as of yet. The second requirement, vaccination and prophylactic drug-Ig, has not yet been found, although research is ongoing. Only the first point remains, however, this method also carries a risk of mortality due to the disease.^[2,8,9]

DISCUSSION

Coronaviruses, which we have encountered as the sources of Severe Acute Respiratory Syndrome (SARS), followed by Middle East Respiratory Syndrome (MERS-CoV), and finally 2019 Coronavirus Disease (COVID-19), can cause a variety of infections that can be fatal in humans. The pathogenesis of COVID-19 is not fully known and new studies are required on this subject. Continuing his scientific research, Dr. McIntosh pointed out that “Coronaviruses will continue to surprise researchers”. He emphasized that the molecular structure of coronaviruses is not fully understood and can easily mutate at a genetic level, and that it has the largest RNA genome of any zoonotic virus and carried many secrets. Effective infection control is currently regarded as the only method to prevent the spread of SARS-CoV-2. The most appropriate treatment method for patients diagnosed with COVID-19 is still unknown. Therefore, treatment protocols should be followed within the framework of

Table 2. Surveillance studies carried out in health institutions

Case notification	Report	In a specific situation and in the case of suspected, possible, or definitive diagnosis, health authorities are notified over the phone without waiting for normal notification
	Notification	The process of reporting suspected, probable or definitive cases within 24 hours with the help of forms or systems determined by the health authorities.
	Field investigation/filiation	Field investigation/filiation is the study of determining the source and the agent after the notification of the case and/or taking protection and control measures including those who were in contact with the agent.
After case notification	Case investigation	In cases that do not show clustering or epidemic characteristics, the patient is diagnosed at the health institution, the case study form is filled out and sent, and other studies are carried out to confirm the diagnosis.
	Outbreak investigation	In cases of clustering or epidemics, outbreak investigation consists of all studies aimed at identifying the epidemic at the place where the disease was seen, determining the source, agent, and people who were exposed. In events when a single case is considered an epidemic, it is also necessary to fill in the case data form regarding the disease.

current health regulations. Since the first case in Wuhan, 132 million cases of COVID-19 cases (30 May 2020 - WHO) have been reported.^[1-3] An increasing number of cases have also been reported in countries of every continent, except for Antarctica. The WHO recognized COVID-19 as an intercontinental epidemic-pandemic, as the rate of new cases outside of China exceeded the rate in China. The degree of impact of a pandemic on humans especially varies according to the infectivity and virulence of the virus, community immunity, lifestyles and socioeconomic conditions of individuals, the convenience of traveling distances between cities and countries, risk factors that individuals carry in their life and working life, the quality of health services provided by the country people live in, and the positive and negative effects of climate on the outlook of the infectious agent.^[2,4,5]

The pandemic has taught us to reflect upon ourselves in several aspects, or in other words, it has been observed that some countries, especially those with low socioeconomic status, are unprepared for a major health emergency of this global magnitude. It is also acknowledged that if these countries fail to control the epidemic, the global threat will continue to grow. Recently, the concept of “One World, One Health” has come to the foreground as a result of the initiatives in the USA and the EU, especially due to the global effects of new zoonotic diseases emerging in recent years on human, animal and environmental health and international trade, and economy. Studies related to planning in this

regard have demonstrated how appropriate this decision really is. Again, within the scope of protection, operating institutions of countries may be expected to assume a part of the responsibility of protecting their personnel. Failure to do so may result in negative consequences.^[2,6]

The risk of epidemics is rising mainly due to nationalist policies, and political and social factors. The support and resources provided to international organizations that provide epidemic planning and support are decreasing. Skeptical approaches to vaccination and insensitivity to insensitivity to protective services developed against preventable diseases increase the risk of the continuity of epidemic. To oppose the increased risk of epidemic, the importance of healthcare professionals and those with authoritative positions in important institutions can be mentioned. In this regard, countries are obligated to provide prevention, education, testing and treatment facilities, to develop all forms of effective methods for the treatment of the disease, and to allocate resources to support clinical research to obtain and organize preventive vaccines.^[2,8,9]

In Turkey, after the first confirmed case was detected on March 11, 2020, local measures have been taken across the country to gradually prevent and reduce the spread of the virus in the community. The most important aspect in dealing with epidemics is the establishment of a strong health system infrastructure. Fundamental public health services (disease surveillance, support of laboratory services) should be fulfilled in order

to initiate a rapid response to epidemic threats, to identify them effectively, and to investigate them in detail, and the physician has an immense role in early detection of outbreaks. During an outbreak, physicians may be faced with a large patient population, vaccination, and antibiotic prophylaxis. Therefore, they must take an active role in hospital and community work to inform the public and control the epidemic.^[2,5,7]

Outbreaks, the onset of which may be anticipated but require effective treatment and protective health services for its end, reveal the need for many changes in society. Infectious diseases units play an active role throughout the process, unlike the diseases they normally monitor. It should be ensured that health and other business lines, which are in close interaction with each other in every regard, participate in the entire process, and further studies with randomized controlled trials must be conducted as soon as possible in order to achieve global success in future epidemic scenarios.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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