



COVID-19 in Croatia

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Abstract

The COVID-19 can be transmitted in areas with hot and humid climates. Regardless of the climate, protective measures must be taken in areas where COVID-19 has occurred. The best way to protect yourself is to wash your hands frequently and thoroughly. This eliminates the viruses that may be on the hands and avoids the infection that can occur by touching the eyes, mouth, and nose.

Keywords

COVID-19; Coronavirus; Infection; Prevention

Introduction

The novel coronavirus pneumonia (COVID-19) that was first reported from Wuhan, China has spread all around China and even to other countries in the world. Confirmed cases of COVID-19 have mounted to a number far exceeding that of SARS in 2003, and its mortality is not negligible [1]. Realizing its “human-to-human” transmission capability, the World Health Organization identified it as a Public Health Emergency of International Concern on January 31, 2020. These facts are enough to illustrate the severity and complexity of the outbreak.

Given the fact that no effective medicine is available for viral infectious diseases, preventive measures including control of the source of infection, early detection of patients, cutting off the transmission, and protecting susceptible population are paramount. Although medical institutions and workers are the main force fighting the disease, public participation is also indispensable for rapid epidemic

control. Therefore, it is extremely important to disseminate relevant information to the public.

Coronaviruses are a large family of viruses that causes not only the common cold but also more serious respiratory illnesses [2]. They are a large family of viruses that are common in people and many different species of animals, including camels, cattle, cats, and bats. Rarely, animal coronaviruses can infect people and then spread between people such as with MERS-CoV, SARS-CoV, and now with this new virus (named SARS-CoV-2). The novel coronavirus (2019-nCoV) was identified as the source of the illnesses on January 7, with the infection traced to the Wuhan seafood market that also sold live animals. The outbreak was first observed on December 31, 2019. The virus has been named “SARS-CoV-2” and the disease it causes has been named “coronavirus disease 2019” (abbreviated “COVID-19”). The SARS-CoV-2 virus is a betacoronavirus, like MERS-CoV and SARS-CoV. All three of these viruses have their origins in bats.

Urgent collaboration and cooperation among all health care sectors, public health, and governments are required globally [3]. It is very important to communicate the epidemiological and clinical data and the risk of COVID-19 infection to health-care workers and the general population and to activate public health education based on evidence sound scientific information to prevent misinformation that might lead to distress and anxiety of the public. The effective approach to the control of COVID-19 is to limit human-to-human transmission through practicing evidence-based community measures, i.e., rigorous hand hygiene with alcohol-based or water and soap, cough etiquette, and face masks only for persons with upper respiratory tract infection. Additionally, distant social measures and international travel based following the country recommendation based on the risk assessment to minimize the social and economic impact of these measures. Infection prevention and control (IPC) measures should be implemented strictly in all health-care facilities to prevent the spread of the infection to vulnerable patients and to protect the health-care workers. Clear protocols for all IPC measures should be in place, i.e., early identification of the suspected cases, early and proper isolation, wearing the appropriate personal protective equipment (PPE), effective terminal cleaning of the room after each COVID-19 patient transfer, educational campaigns, and audits as well as efficient communication with public health.

Infection

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel type of coronavirus of β genus that leads to an emerging infectious disease with remarkable pulmonary involvement in China since December 2019 [4]. The clinical features include fever, dry cough, shortness of breath, normal or low levels of peripheral white blood cells, and inflammatory changes on chest X-ray.

When SARS-CoV-2 infects a person, the lesions are not limited to the lungs [5]. The virus causes viremia after entering the body and the main clinical manifestations are fever, pharyngalgia, fatigue, diarrhea, and other non-specific symptoms. This process includes the incubation phase and the early

phase of the disease. The incubation takes 1–14 days (3–7 days being common). Peripheral blood leucocytes and lymphocytes are not significantly reduced (normal or slightly lower) at this phase. Then, the viruses spread through the bloodstream and mainly in the lungs, gastrointestinal tract, and heart, presumably concentrated in the tissues expressing ACE2, the receptor of SARS-CoV-2. This phase occurs around 7–14 after the onset of the symptoms when the virus starts a second attack, which is also the main cause of the aggravation of symptoms. At this time, pulmonary lesions became worse, and chest CT scans show imaging changes consistent with COVID-19. At this stage, the peripheral blood lymphocytes decrease significantly, involving both T and B lymphocytes. Inflammatory factors in peripheral blood are increased.

The three unprecedented outbreaks of emerging human coronavirus (HCoV) infections at the beginning of the twentyfirst century have highlighted the necessity for readily available, accurate and fast diagnostic testing methods [6]. The laboratory diagnostic methods for human coronavirus infections have evolved substantially, with the development of novel assays as well as the availability of updated tests for emerging ones. Newer laboratory methods are fast, highly sensitive and specific, and are gradually replacing the conventional gold standards. This presentation reviews the current laboratory methods available for testing coronaviruses by focusing on the coronavirus disease 2019 (COVID19) outbreak going on in Wuhan. Viral pneumonia typically do not result in the production of purulent sputum. Thus, a nasopharyngeal swab is usually the collection method used to obtain a specimen for testing. Nasopharyngeal specimens may miss some infections; a deeper specimen may need to be obtained by bronchoscopy. Alternatively, repeated testing can be used because over time, the likelihood of the SARS-CoV-2 being present in the nasopharynx increases. Several integrated, random-access, point-of-care molecular devices are currently under development for fast and accurate diagnosis of SARS-CoV-2 infections. These assays are simple, fast and safe and can be used in the local hospitals and clinics bearing the burden of identifying and treating patients.

Virus

The straightforward scientific answer is that a virus is a packet of infectious genetic material [7]. As such it is almost – but not quite – the odd one out in our list of agents of epidemics, in that it lacks an important property. Bacteria, fungi, and parasites are at least in part capable of independent reproduction. Excluded from this definition those parasites are dependent on specific hosts to ensure their reproduction. The human malaria parasite, for instance, cannot reproduce without both mosquitoes and humans. Nevertheless, it contains the machinery necessary for the task within its structures. This is quite different from the nature of viruses. Some bacteria behave in a similar way to viruses, requiring some constituents of the host to survive and reproduce. The existence of ‘half-way houses’ does not challenge the definition. It simply illustrates the capacity of different types of organisms to explore evolutionary niches.

Viruses can survive but not reproduce on inanimate objects. Research in cancer and haematology wards has demonstrated viable viruses on all kinds of materials, including doors and handles, but the virus cannot multiply in that state. This capacity to survive on non-living material is very important in the transmission of epidemics like SARS and influenza, but viruses can only truly exist by hijacking the machinery of some other living organism to reproduce. That living organism may be the most primitive single-celled amoeba or maybe a plant or a higher animal, but without such a host the virus is at a dead end.

A novel coronavirus was identified as the causative agent of the lung disease severe acute respiratory syndrome (SARS) [8]. The outbreak of SARS in 2002/2003 was associated with high morbidity and mortality and sparked international research efforts to develop antiviral strategies. Many of these efforts focussed on the viral surface protein spike (S), which facilitates the first indispensable step in the viral replication cycle, infectious entry into target cells. For infectious cellular entry to occur, the S protein must engage a cellular receptor, the carboxypeptidase angiotensin-converting enzyme 2 (ACE2). The

interface between ACE2 and S protein, which has been characterized at the structural level, constitutes a key target for vaccines and inhibitors and is believed to be an important determinant of viral pathogenesis and interspecies transmission.

An important aspect of studying viruses involves the ability to alter their genome by reverse genetics and to recover recombinant viruses with defined mutations [9]. Such approaches will help in studying the functions of specific genes and their effects on virus survival and pathogenesis. These strategies will also aid in determining different checkpoints in the progression of virus growth and proliferation and developing therapeutics to prevent pathogenesis.

Genetics

Host genetic resistance to viral infections, as for bacterial and parasitic infections, is usually expressed as a complex genetic trait [10]. The initial approach to mapping, cloning and determining the function of the genes regulating resistance to infections is to dissect complex traits, such as disease susceptibility into simpler phenotypes, such as viral replication, that may be under single gene control. The basic procedure is first to develop an animal model of infection, usually in the mouse, that has a clearly defined trait of resistance and susceptibility. Next, the genetic variation of the selected trait is analyzed in a large panel of inbred strains. A pattern of resistant, susceptible and intermediate phenotypes (continuous variation) is suggestive of a complex trait controlled by multiple genes, whereas a pattern of clearly delineated susceptibility or resistance (discontinuous variation) suggests a single locus with two alternative alleles. A Mendelian analysis is then undertaken on F1 and segregating backcross populations derived from resistant and susceptible progenitors to determine the mode of inheritance and to give an estimate of the number of genes involved. Should the results indicate that more than one gene is acting then further genetic investigation may require the use of recombinant congenic strains or multiple-locus linkage analysis. Should single gene control be confirmed, one of the most frequently used gene mapping methods is linkage analysis in recombinant inbred strains of mice (RIS). The chromosomal location of the unknown

locus is deduced by the concordance in the strain distribution pattern in the RIS panel with markers for previously mapped genes. Once the chromosomal location of the pertinent gene is known, gene cloning may be undertaken by positional cloning and/or by the candidate gene approach.

Coronavirus reverse genetics was performed in the two last decades using defective genomes, as cDNAs encoding full-length genomes were not available due to the large size of the coronavirus RNAs, posing relevant limitations [11]. During the 1990s, reverse genetics in coronaviruses was possible by targeted recombination developed by Paul Master's group. This useful technology enabled the modification of the coronavirus genome by recombination between a replicating coronavirus genome and nonreplicating or replicating RNAs introduced into the same cell. This technology still remains a very useful tool for modifying the coronavirus genome. Significant progress was made in 2000 with the construction of infectious cDNAs encoding coronavirus genomes using a variety of technologies. Historically, the construction of infectious cDNA clones started with the assembly of QB phage (4.5 kb) cDNA, and was followed by the construction of cDNA of RNA viruses with increasing complexity such as brome mosaic virus (with three RNA segments with sizes between 2.1 and 3.2 kb), poliovirus (7.5 kb), closteroviruses (19 kb) and, finally, coronaviruses (27–32 kb). The two main problems associated with the construction of infectious cDNA clones—the fidelity of reverse transcriptase and the toxicity of sequences derived from eukaryotic viruses in bacteria—were aggravated for coronavirus genomes due to their extremely large size. These problems have been overcome by following different strategies. The first infectious cDNA clone was constructed for TGEV in bacterial artificial chromosomes (BACs). These plasmids presented reduced toxicity in bacteria since only a single copy, a maximum of two per cell is produced. Other approaches were the assembly of a full-length cDNA in vitro or the use of poxviruses as cloning vectors.

Epidemics

Because new infectious disease threats usually start

locally, it is important to understand their dynamics in order to deny them the opportunity to spread further among people and overwhelm health systems [12]. The dynamics of epidemic and pandemic diseases typically occur in four phases, although not all epidemic diseases necessarily go through each phase.

The first phase is the introduction or emergence in a community. The second phase is an outbreak with the localized transmission, where sporadic infections with the pathogen occur. In the third phase, the outbreak amplifies into an epidemic or pandemic - the pathogen can transmit from human to human and causes a sustained outbreak in the community, threatening to spread beyond it. The fourth phase is reduced transmission when human-to-human transmission of the pathogen decreases, owing to acquired population immunity or effective interventions to control the disease.

As retrospective studies have demonstrated, SARS presented many of the features that most severely expose the vulnerabilities of the global system [13]. It is a respiratory disease capable of spreading from person to person without a vector; it has an asymptomatic incubation period of more than a week; it generates symptoms that closely resemble those of other diseases; it takes a heavy toll on caregivers and hospital staff; it spreads easily and silently by air travel, and it has a CFR (case fatality rate) of 10 percent. Moreover, at the time it appeared, its causative pathogen (SARS-associated coronavirus) was unknown, and there was neither a diagnostic test nor a specific treatment. For all of these reasons, it dramatically confirmed the IOM's 1992 prediction that all countries were more vulnerable than ever to emerging infectious diseases. SARS demonstrated no predilection for any region of the world and was no respecter of prosperity, education, technology, or access to health care. Indeed, after its outbreak in China, SARS spread by airplane primarily to affluent cities such as Singapore, Hong Kong, and Toronto, where it struck relatively prosperous travelers and their contacts and hospital workers, patients, and their visitors rather than the poor and the marginalized.

International political cooperation to resist epidemics has advanced as well, although many obstacles remain for it [14]. The World Health Organization, founded in 1948 as one of the United Nations' most successful agencies, has coordinated and standardized mortality statistics, drafted international conventions on such responses as quarantines, and promoted cooperative international attacks. Many national governments have active departments and offices for both the promotion of public health and the control of diseases.

To a varying extent, populations in the world share another advantage: by the early twenty-first century many of them (more or less) have been medicalized. That is, popular opinion has accepted the notion that diseases call for responses from the world of biomedicine; when flu strikes one consults a physician. When large numbers of people have accepted medicalization, they will more likely have recourse to the vaccines and antibiotics offered by modern biomedicine. Epidemics, especially those that move by contagion (as most do) from one person to another, may thus run out of susceptible victims.

Pandemics

Pandemic infections are, by definition, global problems that cannot be dealt with exclusively by individual nation-states [15]. Epidemiologists, statisticians, and other professionals working at the World Health Organization (WHO) based in Geneva, Switzerland, have the responsibility for declaring whether or not a pandemic is occurring. Charged with monitoring and protecting human health everywhere on the planet, the WHO is one of the better functioning agencies of the United Nations.

Though the WHO (like any global operation, public or private) has its limitations, only an international organization can (with the help of national agencies) take the ultimate responsibility for declaring that humanity is facing a pandemic. That has to be done with care and must follow established guidelines. The rules have to be clearly thought through and stated, as the ensuing response will require the deployment of substantial administrative and physical resources. Sounding the pandemic alarm can't simply be left to

the ad hoc judgment of a select few key individuals, no matter how wise and well-informed they may be. The turnover rate for WHO officials can be high and even mandatory, given strict rules governing the duration of contracts, retirement at age 60, and so forth. Being part of a global agency, WHO officers may also come from very different cultural and economic backgrounds. What ranks as common sense for one particular group may seem less clear for others.

Therapy

Patients with suspected COVID-19 infection are needed an initial therapy of oxygen as soon as possible if they present several conditions such as severe acute respiratory infection, hypoxemia, respiratory failure, or shock [16]. Oxygen therapy to be given initially is 5 L/min and we need to maintain the oxygen pressure target about $SpO_2 \geq 90\%$ in adult patients and $SpO_2 \geq 92 - 95\%$ in pregnant women patients. The hospital should prepare complete oxygenation systems that only be used one time (nasal cannula, simple masks, and masks with reservoir) and pulse oximetry in all rooms where severe acute respiratory infection patients are treated. When a patient showing some signs of shock with a severe acute respiratory infection, fluid therapy can be given. Antibiotic treatment could be given 1 hour after the patient identified sepsis or an empirical treatment if the patients are on Severe Acute Respiratory Infection (SARI) condition.

Global efforts at this time are focused concurrently on containing the interhuman spread of this virus and mitigating the impact of this virus [17]. Treatments exist. Health officials from WHO has noted that Remdesivir has demonstrated efficacy in treating the coronavirus infection. The US commenced clinical trials in humans to test the safety and efficacy of the drug. The first patient to be administered the drug is an evacuee from the Diamond Princess cruise ship. The National Medical Products Administration of China has approved the use of anti-viral drugs, as a treatment for coronavirus. Favilavir and Umifenovir are approved for marketing in the treatment of influenza and is one of the four drugs showing efficacy against the coronavirus in human trials. The other three are Chloroquine, Remdesivir, and Lopinavir. The

medicines were widely used to treat patients who showed resistance to Tamiflu and Relenza Rotadisk, both of which are medications used to treat and prevent influenza caused by influenza A and B viruses. Favilavir (Avigan) has been adopted by both Japan and China as an experimental drug to treat patients suffering from severe COVID-19. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro and in the latest clinical trials. Already existing antiretroviral Protease Inhibitors might be also effective in this situation. An HIV protease inhibitor, Lopinavir is being studied along with Ritonavir for the treatment of MERS and SARS coronaviruses. The repurposed drug is already approved for the treatment of HIV infection under the trade name Kaletra. The combination is listed in the WHO list of essential medicines. Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the non-human primates (NHP) model of the MERS. Umifenovir (Arbidol) is used primarily as an antiviral treatment for influenza, similar to Tamiflu, but also showed anti-coronavirus activity. Its use is only in China and Russia, since not approved by neither the FDA nor the EMA.

Prevention

At this time, there are no specific vaccines or treatments for COVID-19 [18]. However, many ongoing clinical trials are evaluating potential treatments. WHO will continue to provide updated information as soon as clinical findings become available.

To prevent infection and to slow transmission of COVID-19, do the following:

- Wash your hands regularly with soap and water, or clean them with alcohol-based hand rub.
- Maintain at least 1-meter distance between you and people coughing or sneezing.
- Avoid touching your face.
- Cover your mouth and nose when coughing or sneezing.
- Stay home if you feel unwell.
- Refrain from smoking and other activities that weaken the lungs.

- Practice physical distancing by avoiding unnecessary travel and staying away from large groups of people.

The COVID-19 virus affects different people in different ways. COVID-19 is a respiratory disease and most infected people will develop mild to moderate symptoms and recover without requiring special treatment. People who have underlying medical conditions and those over 60 years old have a higher risk of developing severe disease and death.

COVID-19 in Croatia

The Civil Protection Headquarters of the Republic of Croatia was established by the Government of the Republic of Croatia. The HQ has made several decisions to prevent the spread of coronavirus infection. It is certainly worth pointing out that the vast majority of citizens adhere to these measures, but unfortunately, some do not adhere to them. The measures restrict social gatherings, shops, services, and cultural and sporting events. Measures have been taken to prevent the further spread of COVID-19.

Since COVID-19 is transmitted from person to person, here again, it is necessary to repeat what are the symptoms of COVID-19. These are:

- fever
- cough
- shortness of breath
- muscle pain
- fatigue

In more severe cases such as pneumonia, acute shortness of breath, sepsis, and septic shock can occur which can cause the death of the patient. People with chronic illnesses are more susceptible to serious illnesses. Older people and people with chronic illnesses (such as high blood pressure, heart disease, diabetes, liver disease, and respiratory disease) have a higher risk of developing more serious infectious disease symptoms.

At the beginning of April 2020, Croatian Health Minister Vili Beros stated: "The success so far in the fight against COVID-19 is the result of good preparation and consistent adherence to prescribed

self-protection measures - hygiene, social distance and adherence to self-isolation measures when prescribed. A minority that denies the epidemic or fails to comply with the prescribed measures endangers other members of society and nullifies the advantage we received in this match by timely preparation. We are ready for this epidemic and we are going through it in a team and solidarity. So far, we have been able to prolong exponential growth, and the future depends on each individual. So stay home, protect our loved ones and all those who need to be healthy for us - our health professionals, police officers, firefighters, members of civilian protections and members of the service industry. Therefore, the measures are effective, they are adhered to by the citizens, but they should continue to be adhered to until the spread of COVID-19 is stopped.

It is very important to point out the following: There are a large number of citizens in the Republic of Croatia who have pets. So far, it has not been proven that COVID-19 can be transferred from a pet to a human, but pet owners should avoid risky situations and prevent possible health problems. Should the situation arise that the owner must be in isolation, the care of the pet should be arranged in advance.

Amid the COVID-19 epidemic, on March 22nd, 2020., the capital of the Republic of Croatia, Zagreb, it has hit a major earthquake in which hospitals and other health care institutions have suffered significant damage. In spite of this additional problem, the measures adopted by the Civil Protection HQ continue to be implemented without major difficulties.

Isolation and Self-isolation

Measures that produce results in the fight against COVID-19 are isolation and self-isolation.

Isolation means that a person is accommodated and staying in a separate room to prevent the spread of an infectious disease. The same goes for self-isolation, only the term isolation is used for sick people, and self-isolation or home quarantine for the healthy. Isolation is a measure of isolation of a person from other people, which is used in the treatment of people who are sick and have symptoms of the

disease, in this case, they are symptoms of acute respiratory infection with fulfilled epidemiological criteria (stay in countries affected by the epidemic or close contact with the person who is probable or confirmed case of illness). People suspected of having a COVID-19 virus infection are hospitalized using isolation, diagnosis and treatment measures.

Self-isolation is a special measure of health care that is implemented based on the decision of the Minister of Health. Applicable to healthy persons (without symptoms) who have been at risk of infection, or who have been in close contact with the affected person or who have been in the last 14 days in areas/countries with the local or widespread transmission (transmission) of COVID-19 coronavirus disease lasting 14 days of leaving the affected area or contacting the affected person. The basic rule is that you should stay at home (quarantined / self-contained, and in certain areas foreign nationals in organized quarantine) and avoid physically close contact with other people. The duration of health surveillance or self-isolation is 14 days because the incubation of COVID-19 disease (from infection to the onset of symptoms) can last from 2 to 14 days. The procedures for checking passengers entering Croatia are defined in such a way as to ensure the highest possible protection of the health of the population and passengers, with minimal disruption to international traffic.

Unfortunately, some situations have happened which should not have happened.

Situation-1:

When she heard that her son-in-law had been infected with the COVID-19, the mother-in-law immediately went to see him. The COVID-19 spread from him to her, and when she returned home, she infected her family and another family.

Situation-2:

The businessman knew he was infected with the virus, and he never told anyone. He contacted other people as if nothing had happened. It is unknown how many people became infected.

Situation-3:

A young woman has publicly stated that she is a doctor and spreads misinformation related to the COVID-19. Police have determined that she is not a doctor and the resulting damage from her appearances will not be quickly remedied.

Situation-4:

A group of young people has publicly opposed the implementation of the COVID-19 protection measures adopted by the Government of the Republic of Croatia. The police asked them to split up, and three of them refused to do so. They were brought to police and a criminal investigation was initiated against them.

Conclusion

The COVID-19 can infect people of all ages. According to the epidemiological picture so far, the elderly and people with health complications (such as asthma, diabetes, heart disease) appear to be more susceptible to the virus. Healthcare organizations advise people of all ages to take steps to protect themselves against the virus, primarily by adhering to adequate hand hygiene and the use of precautionary measures in the event of coughing and sneezing.

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