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COVID 19 - THE CHALLENGE OF CORONAVIRUSES

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Abstract
About corona viruses many discusses were occur in the last two years because of Covid 19, the pandemic disease of our days. The Family of coronaviruses includes the positive sense single-stranded RNA viruses with helical symmetry of enveloped nucleocapsid, which determine respiratory or intestinal infection in humans and animals and causing disorders of different organs. The name of viral genus derives from their surface with club-shaped spikes like solar corona.
SARS-CoV-2 causes the COVID-19 disease and spread all over the world. The scientific communities analyse this virus and investigate the effects about the human organisms. The threat of the coronavirus become seriously enough in 11 March 2020, when the World Health Organization (WHO) declared a pandemic.
No doubt the world was not prepared for this important problem of public health. Till May 2021, 1055265 cases of infection were registered in Romania. In Arges County the number of infection was 26476 in the same period.

Keywords: COVID-19, pandemic, public health

1. INTRODUCTION

The entire world was warned at the end of 2019 that the spread of the coronavirus outside China.
Because the virus came from outside the Europe, the population did not feel in danger at the beginning of pandemic. But the threat of the coronavirus become seriously enough in 11 March 2020, when the World Health Organization (WHO) declared a pandemic.
No doubt the world was not prepared for this important problem of public health.
The poor capacity of laboratory diagnosis and the unknown principles of clinical treatment for severe coronavirus infections were the major issues in this period.

The features of coronaviruses

The Coronaviruses are part of Order Nidovirales, which are the enveloped viruses with genome composed by a positive sense single-stranded RNA. The Human Coronaviruses (HCoV) are integrated in Suborder Cornidovirineae, Family Coronaviridae, Subfamily Orthocoronavirinae, genera Alphacoronavirus and Betacoronavirus, according ICTV 2020 Master Species List (https://talk.ictvonline.org/files/master-species-lists/m/msl/12314). Subfamily Orthocoronavirinae is divided up into four genera: Alphacoronavirus, Betacoronavirus, Deltacoronavirus, Gammacoronavirus (Figure 1), but HCoV are part just of Alphacoronavirus (Human coronavirus

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229E: HCoV-229E; Human coronavirus NL63: HCoV-NL63) and Betacoronavirus (Human coronavirus OC43, part of Betacoronavirus 1: HCoV-OC43; Human coronavirus HKU1: HCoV-HKU1; virus of Severe Acute Respiratory Syndrome: SARS-CoV; virus of Middle East Respiratory Syndrome: MERS-CoV; virus of Severe Acute Respiratory Syndrome 2 or Covid-19: SARS-CoV 2).

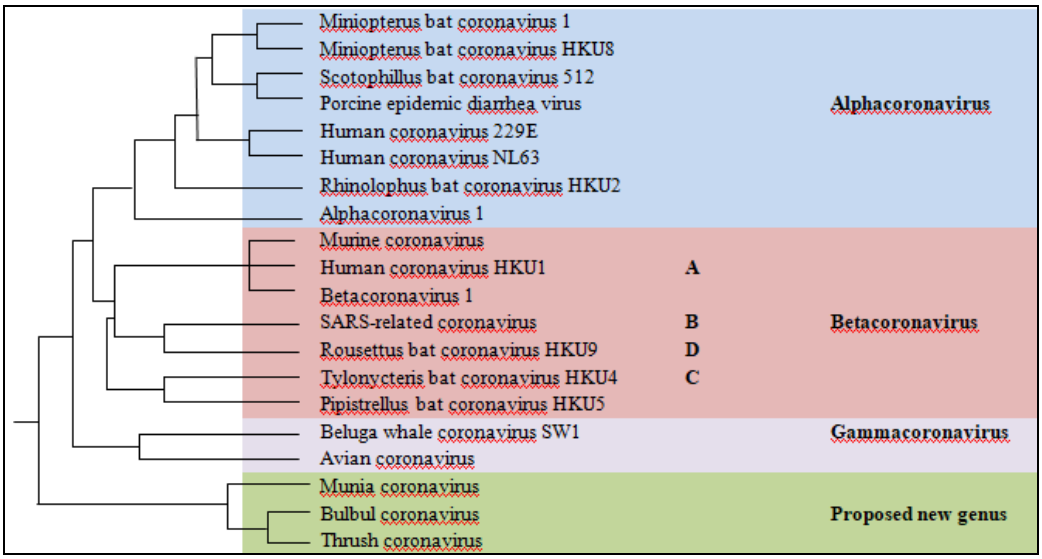

Figure 1. The taxonomy of Subfamily Orthocoronavirinae
(https://talk.ictvonline.org/ictv-reports/ictv_9th_report/positive-sense-rna-viruses-2011/w/posrna_viruses/223/coronaviridae-figures)

Coronaviruses naturally infect man and a large category of animals, causing a wide variety of diseases involving different organ systems (respiratory, hepatic, gastrointestinal and neurological systems). Some of them are responsible for about 15% of common colds (the second cause behind rhinoviruses, clinically indistinguishable), the majority of adults having antibodies against viral antigens. Some of coronaviruses were studied a long time ago. For instance, mouse hepatitis virus was grown in tissue culture in the laboratory and was used to provide the model for human liver viral disease (Weiss, 2020). The human coronaviruses subject was a topic of conference in 1980 in Germany, especially by genome point of view, because of its replication strategy and some information about the human coronavirus 229E was presented.

It is well known that the coronaviruses are the viruses with the largest genome ssRNA between the human viruses, more than 30kb (Cernescu, 2012). This is the source of the high genetic variability of these viruses and lead to many genetic variants that could cause the human illness.

The certain studies demonstrated the particularities of the viral replication of coronaviruses. By fingerprinting methods was shown the presence of nested subgenomic RNAs during the transcription of genomic RNA of coronaviruses, like other nidoviruses; these subgenomic RNAs contain a cap-structures of their 5' ends (Lai et al., 1982), derived from the 5' end of the genome. The genomic and subgenomic RNAs contain also the 3' polyadeniylated end. Another studies, published in 2010 by Hung-Yi Wu and David Brian, refer to the subgenomic mRNAs that are transcribed from negative RNAs (synthesized from the genomic RNA) by a unique mechanism. They described a discontinuous transcription of the genome, involving a viral polymerase.

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The high rate of recombination may involve an interspecies infection, too.
Also, coronaviruses have a special structure of particles with antigenic features that increase the capacity of these viruses to attach to the cellular receptors and to entry in the host cells.
These viruses present a characteristic morphology; they appear medium-sized (120 - 160 nm diameter), round and moderately pleomorphic, with an outer envelope club-shaped surface projections like a crown (glycoprotein spikes). Under the electron microscope spikes could seen as clear projections on the virion surface (20 nm length) (Davies and Macnaughton, 1979) and are grouped into trimers to determine the distinctive ”corona” (Belouzard et al., 2012).
The viral genome encodes 16 non-structural proteins (NSP) and 4 structural proteins (spike protein S, membrane protein M, envelope protein E and nucleocapsid protein N (Yadav et al., 2021).
The most important protein of coronaviruses is protein S. The spike protein (S) is synthesized as a precursor in the endoplasmic reticulum, and is transported to the plasma membrane; it is split into S1 and S2 subunits by cellular enzyme, the process being dependent both by cell type and virus strain. The interaction of glycoprotein S and host cell receptors induces the host range, the cell tropism and the pathogenesis of coronaviruses. But the proteolytic activation of spike protein seems to play an important role in the infection process (Millet and Whittaker, 2015), because the spike proteins contribute both in cell receptor binding and fusion with target cellular membranes. So, it is clear that the coronaviruses have many strategies to affect the host cells; they can enter both by virus-cell fusion and by receptors mediated endocytosis.
The S glycoprotein of coronaviruses is a type I transmembrane protein, between 1200 and 1400 amino acids, with a large ectodomain (with a N-terminal domain S1 for cell receptor binding, composed by two subdomains and the C-terminal domain S2 for fusion with cell membrane, the most conserved region of S protein), a transmembrane domain and the small cytoplasmic endodomain (Millet and Whittaker, 2015).
The coronaviruses spike protein is a class I viral fusion protein and has relatively large HR (heptad repeat) regions in S2 domain (Bosch et al., 2003). The class I viral fusion proteins contain HR region, usually two as a number: HR1 (N-terminal HR region) and HR2 (C-terminal HR region), involved in viral fusion.
The spike protein of coronaviruses is activated by cell proteases like furin (a Golgi-resident host protease), trypsin (active at neutral pH), cathepsins (degradative protease found in endosomes and lysosomes, important in antigen processing), transmembrane protease serine 2 (TMPRSS2), elastase (especially pancreatic elastase) and plasmin (produced from its precursor plasminogen, but more selective than trypsin). Cathepsin L is known to activate viral glycoproteins of coronaviruses at low pH (3.0 to 6.5) and cathepsin B is involved in coronavirus entry at higher pH (Kawase et al., 2009).
For certain coronaviruses the cleavage of S protein can occur at two different sites (Belouzard et al., 2012), at the S1/S2 boundary or within S2. The moment for S protein cleavage is important in pathogenicity, host range and cell tropism of coronaviruses, during biosynthesis of protein or during virus entry (Millet and Whittaker, 2015).
The coronaviruses are various according to surface glycoproteins with enzymatic activities; some of them, like mouse hepatitis viruses, as well as human coronavirus OC43, have a receptor-destroying enzymes (RDEs) similar to influenza virus C, named hemagglutinin-esterases (Klausegger et al., 1999). This similitude suggests that coronaviruses acquired the hemagglutinin through recombination with influenza virus C and the increase of virulence may occure through interspecies infections.

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The receptors for coronaviruses are different dependent on type of virus and a host species. For SARS-CoV was identified as cell receptor angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) was identified as cell receptors for MERS-CoV. SARS-CoV 2 is able to use ACE2 as cell receptor, demonstrated on HeLa cells (Zhou et al., 2020).
After the spike proteins bind to the cellular receptors and the virus entry in host cell, it is replicated in ciliated and nonciliated cells. The viruses will be released from cell through budding, with the envelope derived from cell membrane.

Clinical diseases
The severe acute respiratory syndrome related coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV 2) are causes of severe upper or lower respiratory tract infections, with or without multiorgan failure. In 2003 SARS-CoV and in 2012 MERS-CoV caused life-threatening infections (mortality rate was 5-15% depending on age for SARS), and SARS-CoV 2 caused the pandemic of our days.
Many coronaviruses induce common cold symptoms after 2-3 days of incubation period: sore throat, rhinorrhea, cough and headache.
SARS-CoV infections had various symptoms like: fever, headache, myalgia, nonproductive cough, and severe atypical pneumonia, mostly in elder patients and underlying diseases (diabetes, cardiac and hepatic disease). MERS-CoV infections could lead to respiratory and multiorgan failure. SARS-CoV 2 determine infection named COVID 19 disease, with symptoms similar to SARS-CoV: fever, myalgia, fatigue, nonproductive cough, and severe pulmonary disease with acute respiratory distress. These viruses stimulate cytokines and a hyperproduction of inflammatory response, important for the pathology of respiratory diseases.
The treatment of coronavirus infections is no specific. Some antivirals were used, but they were controversial. As antiinflammatory agents the steroids were useful, other therapies could reduce the intensity of symptoms during the disease.
Quarantine of contacts of COVID 19 cases and intensive infection control procedures were necessary. In pandemic strict measures to prevent public exposure after the outbreak of the virus were taken, restrictions means: restricted public gatherings, schools and religious services, restricted travels, business closures.
Nowadays the vaccines are available and the infections could be prevented.

2. MATERIALS AND METHODS
Genetic studies of coronaviruses were made to point out viral pathogenesis of the emerging coronaviruses SARS-CoV and MERS-CoV. After during six or seven month SARS caused over 8000 infections and over 700 deaths, were identified HCoV-NL63 and HCoV-HKU1 viruses. MERS-CoV emerged in 2012 and caused more deaths and SARS-CoV-2 caused the last outbreak; this suggests the coronaviruses may spread all over the world in different ways and get over differnt patterns (Weiss, 2020).
A laboratory diagnosis tests are available nowadays. It can be made by isolation of viruses in tissue culture, detection of viral RNA genome by reverse transcription PCR (RT-PCR), serological investigations by evidence of antibodies in patients' sera. In Romania the reverse transcription PCR (RT-PCR) tests were used to confirm the COVID 19 infections. This technology amplifies the specific sequence of nucleic acids (viral RNA) through a complementary DNA, using oligonucleotides for viral nucleocapsid protein genes.

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3. RESULTS AND DISCUSSIONS

The surveillance of COVID 19 infections in Romania were made by the beginning of pandemy. During one year, since April 2020 to May 2021, were registered 1056572 cases (Figure 2). In the first six months the number of cases increases slowly, but after that the number increases very fast.
In according to the number of infections, the number of deaths increased too after six months of pandemy (Figure 3). During one year, 28194 deceases were registered in Romania (the mortality rate were 2.66% in that period).

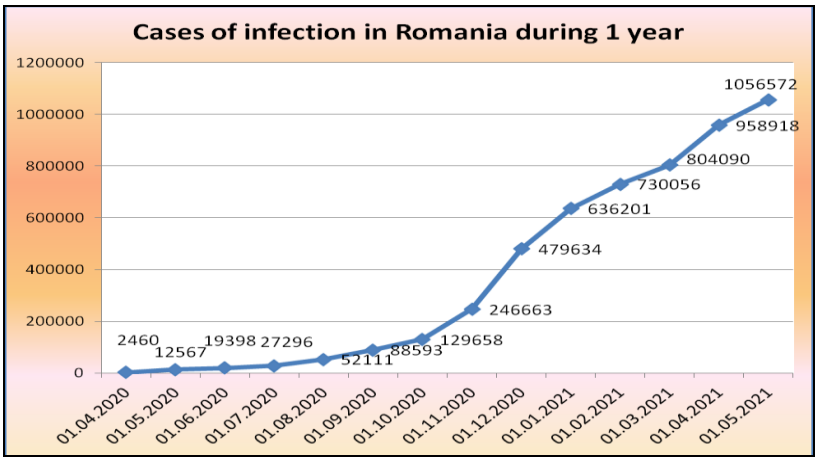

Figure 2. Number of COVID 19 cases in Romania during one year

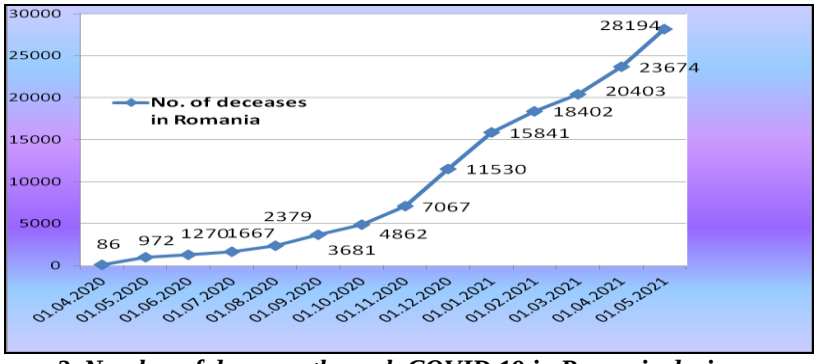

Figure 3. Number of deceases through COVID 19 in Romania during one year

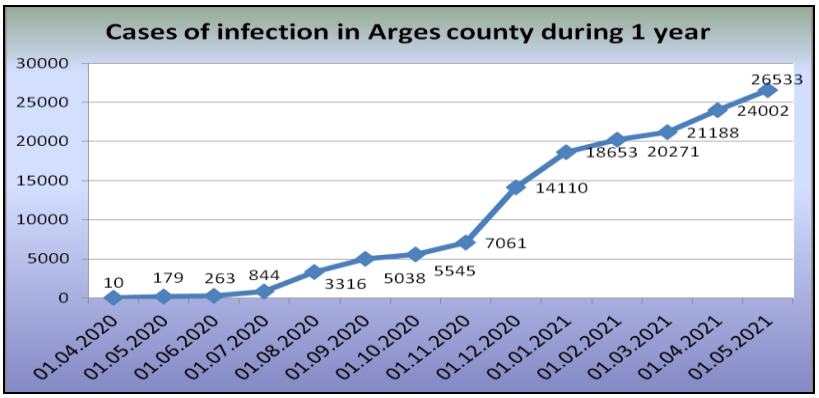

Figure 4. Number of COVID 19 cases in Arges County during one year

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In Arges County the surveillance of COVID 19 infections were made by authorities and the number of infections were established by RT-PCR test for confirmation of viral infection. The data are presented in Figure 4. Between April 2020 and May 2021 26533 cases were registered in Arges County; 2.51% of Romanian cases of COVID 19 were in this region.

4. CONCLUSIONS

The emergence of the coronavirus SARS-CoV 2 had a major impact on the world population, both in terms of economic relations, social tensions, tourism and so. Another concern are underlying diseases in the general population which may exacerbate the severity of COVID 19 - induced diseases and may lead to death.

Various pharmaceutical companies tried to obtain potential therapeutic drugs for COVID 19, but also plasma therapy (with polyclonal antibodies produced by recovered patients) and monoclonal antibodies were used to treat this illness.

Also, mRNA-based vaccines and vaccines with non-replicated viral vector are used now to preevnt the infection with SARS-CoV 2 and stop the pandemy.

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