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Matemathical modelling and numerical simulations of COVID-19 spreading – example of Bosnia

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ABSTRACT

Introduction: Mathematical modeling of coronavirus disease spread and computer simulations are currently one of the main tools in public health that can give important indicators for prevention planning. Based on mathematical projections and daily updates of information, the measures are either tightened or reduced, in order to protect the health of the population.

Aim: The aim of this paper is to present a computer system based on an adequate mathematical model that allows frequent execution of various scenarios of spread severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in any period in the future. Also, the aim of this article is to point out the importance of measures for the prevention of coronavirus disease 2019 (COVID-19) in Bosnia through examples of computer simulation models.

Methods: Software solution based on the USLIRD model (Unpopulated - Susceptible - Latent - Infectious - Recovered - Deceased) was developed, with a number of variable parameters ‘reproduction number, delay period, infectivity period, hospital capacity, characteristics of population). By setting these parameters in accordance with the existing and available data, the model is brought to an optimized state with the possibility of a realistic assessment of the course of the infection curve in any future period. Data from the beginning of the pandemic are collected at the Faculty of Mechanical Engineering, University of Sarajevo and updated several times a day. The set of measures is divided into two types. 'Intervention 1' is a measure to close institutions that are at high risk for pandemics, working from home, wearing face mask, enhanced hygiene when entering facilities with a larger number of people. 'Intervention 2' presents restrictive measures that has been introduced as mandatory in Bosnia. The period 01.03.2020 to 01.09.2020 was observed.

Results: Without epidemiological measures, Bosnia's health system would quickly collapse. Restrictive measures reduce the intensity of the spread of the infection, save human lives and keep the health system functional, but with consequences on other aspects of society - reduction of economic activities, collapse of the service industry and companies and disorders in mental health status of the population. Four different scenarios of the situation were analyzed. Scenario number three is current condition with measures that are currently in Bosnia. The reintroduction of restrictive measures leads to a decrease in the number of infected population and suppression of the spread of the pandemic, which is shown in scenario 4.

Conclusion: Self-discipline, adherence to measures, while trying to avoid restrictive measures should be the way to fight the COVID-19 pandemic. Whatever the consequences, the initiation of restrictive measures to preserve the health of the population should be imperative.

Keywords: Coronavirus, Virus Spreading, Computer Simulation

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1. Introduction

In early December 2019, a large number of patients with pneumonia of unknown cause, were reported in Wuhan City, Hubei Province, Central China. Common clinical picture was described as coronavirus disease 2019 (COVID-19) [1,2]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Due to the large number of infected, COVID-19 has paralyzed the world, with no clear guidelines for treatment [3,4,5,6,7,8,9,10,11,12]. Incubation of the virus is 5 to 6 days, up to 14 days [13,14]. A person is the most virulent when the symptoms are pronounced, but there are indications that some people may transmit the virus without having symptoms or before they appear [15,16]. Polymerase chain reaction (PCR) is the gold standard in the diagnosis of infection, although its specificity and sensitivity are not 100% [17]. All of the above leads to the conclusion that the only way to fight against COVID 19 are preventive measures, which must be implemented thoroughly, throughout society, with the aim of survival and functionality of the health system. Although isolation, self-isolation and complete quarantine measures in most countries of the world have effect of slowing down the pandemic, there have been a major problem with a modern society lifestyle and with economic losses which forced governments to reduce these measures and try to live with virus [18,19]. Healthcare professionals and hospitalized patients, residents and staff of homes for the elderly and infirm, symptomatic people with increased risk of severe illness and complications, people aged 65 and over and people with chronic diseases are target groups for testing, all in the aim to save healthcare system [20,21]. Although the phylogenetic pattern of SARS-CoV-2 has been detected in Bosnia, a large number of imported cases, with opening of the borders will certainly bring new problems not only to the health system, but also to the scientific community [22].

Bosnia consist of two entities (entity Federation of Bosnia and Herzegovina and the entity Republika Srpska) and the Brcko District. The structure of the health system of the Federation of Bosnia and Herzegovina consists of 11 ministries of health (10 cantonal and 1 federal), 11 health insurance institutes (10 Cantonal and 1 Federal Health Insurance and Reinsurance Institute) and 11 public health institutes (10 Cantonal and 1 Federal). The health system in the entity Republika Srpska is centralized with all competencies within the Ministry of Health and Social Welfare, the Institute for Health Protection and the Health Insurance Fund. Brcko District is organized through four health institutions: Brcko Hospital, Brcko City Health Center, Bijela Health Center and Maoca Health Center [23,24,25]. Official data for 2019 and 2020 on the status of human and infrastructural resources of the health system are not available, which further complicates the story of COVID-19, and puts the focus on prevention as the most significant measure that the health sector of Bosnia can offer. The health community must play a major role in prevention itself, through programs from the primary to the tertiary level of health care.

The fight against the further spread of the virus, which has been accepted by almost all countries, presents personal hygiene, as well ‘physical distancing’ and self-isolation [26,27,28]. These measures have resulted in a reduction in the percentage of newly infected, but, in most countries, the total number of infected and newly infected is still increasing [28,29,30]. Therefore, one of the key questions is what is the predicted course of the infective curve, when will the moment of reaching its maximum occur and what is the period of duration of infection. At the same time, despite the fact that the new SARS-CoV-2 virus has an extremely high degree and great ease of transmission, its spread is mainly accompanied by a course similar to other infections (influenza, Ebola and measles) [28,29,30,31]. For this reason, a number of mathematical modeling is largely applicable to the case of COVID-19. Scientific research related to mathematical modeling of coronavirus spread problems has intensified greatly in recent months. However, in addition to the unprecedented transparency and ease of its spread, the new virus has one important exception, and that is that there is still no drug or vaccine that would help in battle against him.

The vast majority of the adopted models are based on the SIR methodology (Susceptible-Infectious-Removed), which is well known and perfected on the experience of spreading the infection of other types of viruses. For example, recently Nesteruk [32], using the SIR model, developed a new method by which he determined the optimal values of parameters based on statistical analysis, thus enabling effective prediction of the percentage of infected population as a function of time [32]. Mathematical models are the main tool in the hands of public health, and they are used to plan activities to stop the spreading of infectious agent. Based on mathematical projections and daily updates of information, measures are either tightened or reduced, all with the aim of a better quality of life for the population [33[.

2. Aim

The aim of this paper is to present a computer system based on an adequate mathematical model that enables interactive derivation of various scenarios for the spread of SARS-CoV-2 coronavirus infection in any period in the future. Also, the aim of this article is to point out the importance of measures for the prevention of COVID-19 in Bosnia through examples of computer simulation models.

3. Material and methods

In this paper, we use the well known and widely used model of spreading of infection known as SIR (Susceptible - Infectious - Recovered). However, during this research we developed the more comprehensive USLIRD (Unpopulated - Susceptible - Latent - Infectious - Recovered - Deceased) model, which is somewhat similar to the SEIRUS (Susceptible - Exposed - Infectious - Removed - Undetectable - Susceptible) model, often used in modeling and preventing the spread of AIDS. In doing so, we adopt the following adjustable model parameters: basic reproductive number R_0, delay period, mortality rate, vaccination rate (when available), population density, interaction radius, initial degree of infection, population size.

By adjusting the above parameters in accordance with existing (known) data, we optimize the model in such a way that, starting from the existing (known) situation with the total number of infected, mortality rate, etc., we can reliably estimate the spread of infection in the future. It is a deterministic endemic model where a class of suspected (S) persons is defined as a set of individuals who are not yet, but could be infected through interaction with members of class (I) continuously. An infected individual (class I) is one who has been infected with the coronavirus and is in some stage of infection. A removed individual (class R) is one who has been confirmed to have the expected symptoms of the virus, the outcome of which is cure and discharge from the hospital or consequent death. Basic reproductive number (R_0) is defined as the number of secondary infections that one infectious individual would develop during the infectious period, provided that all other individuals are suspected. Here, $R_0 = 1$ represents the threshold below which the generation of secondary cases is not sufficient to maintain infection in a given community. In case $R_0 < 1$, the number of infected individuals will decrease over time and the infection disappears, and if $R_0 > 1$ the number of infected individuals will increase and the infection will spread over time.

Mathematically, the model is defined by the following variables and parameters:

Variable	**Description**
$S(t)$	Number of susceptible to becoming infected at time t
$E(t)$	Number of exposed at time t
$I(t)$	Number of infected through contact with someone already infected at time t
$R(t)$	Number of recovered (no longer infected or died) at time t

Schematically (Figure 1), the simulation is based on the following flow:

- suspected (potentially infected) individuals, ie. those who do not yet have immunity (for now it is the complete population) are exposed/infected by contact with infectious individuals. Each infectious individual causes an average of R_0 secondary infections, as long as that individual is contagious. In this case, the transmission of the virus can have a seasonal variation which is determined by the parameter "seasonal forcing" (amplitude) as well as the parameter "seasonal peak" (month of the most intensive transmission of the virus),
- after an average latency time, exposed individuals progress to a symptomatic / infectious condition. It is modeled that this process takes place in three phases, which ensures that the distribution of time spent in the exposed state is more realistic than a simple exponential flow,
- infected people recover or become seriously ill. The ratio of recovery to severe phase depends on the age of the infected person,

- severely ill individuals recover or their condition worsens and they become critically ill. And that process depends on the age of the infected person,
- critically ill persons are admitted to intensive care units or placed in a temporary isolation ward,
- critically ill individuals return to regular hospital accommodation after successful signs of recovery or die from the effects of the infection.

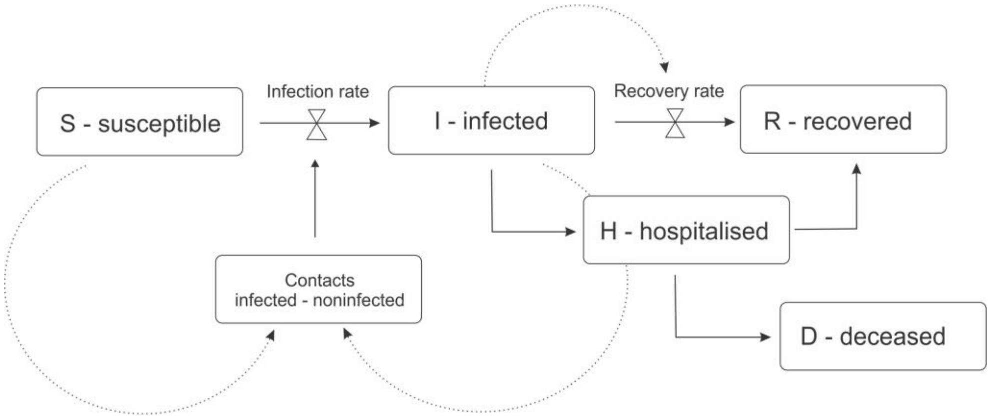

Figure 1. Schematic representation of the basic model. S denotes 'suspected' population, E 'exposed', I 'infected', R 'recovered / deceased', H 'severe' (hospitalized) and D are deaths.

In order to create an effective computer system, individual model parameters can be changed interactively to allow the investigation of different virus spread scenarios. The presented mathematical model, among other things, enables the introduction of parameters that reflect the measures taken to control the infection in a given community and which generally contribute to the reduction of transmission. Here we support measures such as social distancing, suspension of regular classes in educational institutions, restriction of population movements and the like. Several scientific studies have attempted to assess the impact of different aspects of social distance (social distancing) and infection control on the rate of virus transmission.

Mathematically, the presented model can be described as a set of the following differential equations:

$$\frac{dS(t)}{dT} = -\frac{\beta}{N}S(t)I(t) \tag{1}$$

$$\frac{dI(t)}{dT} = \frac{\beta}{N}S(t)I(t) - \gamma I(t) \tag{2}$$

$$\frac{dR(t)}{dT} = \gamma I(t) \tag{3}$$

where N is the total population number, β is the contact rate of the disease and γ is the mean recovery/removal rate. If at t = 0 we have the initial values given by S_0, I_0 and R_0 then by solving the above set of equations we get

$$S(t) = S_0 e^{-\frac{\beta}{N\gamma}(R(t)-R_0)} \tag{4}$$

with parameters β and γ to be determined in some way.

The charts shown bellow are the result of execution of a propriatory in-house developed solution, optimized for use in any standard web platform. The data is collected by the Faculty of Mechanical Engineering of the University of Sarajevo and can be seen on https://mef.unsa.ba/Home/Coronavirus. The data is updated several times on a daily basis since the beginning of the desease.

4. Results

4.1. Recorded data for Bosnia

Taking into account the official data on infected persons available from the World Health Organization (WHO), below-average growth of infection was recorded in Bosnia - until recently (Figure 2). This is apparently the result of timely and rather strict measures taken, including the decision of the Crisis Staff of the Federal Ministry of Health of 11.03.2020, as well as by declaring the state of the accident on the territory of FBiH from March 16, 2020 to May 25, 2020. These decisions resulted in the suspension of regular classes in educational institutions, the introduction of the obligation of social distancing and restrictions on the movement of the population, as well as the decision to ban the work of business and other entities. However, in the last month, there has been a very sharp increase in the number of infected people, and this is a new, very worrying phenomenon. As we can see from Figure 2, on August 8, 2020, the total number of infected people in Bosnia was 13,687, while the number of active cases increased to 5,920. Also, the relative position of the actively infected inhabitants of Bosnia in relation to other countries has shifted significantly towards the most critically affected countries (Figure 3).

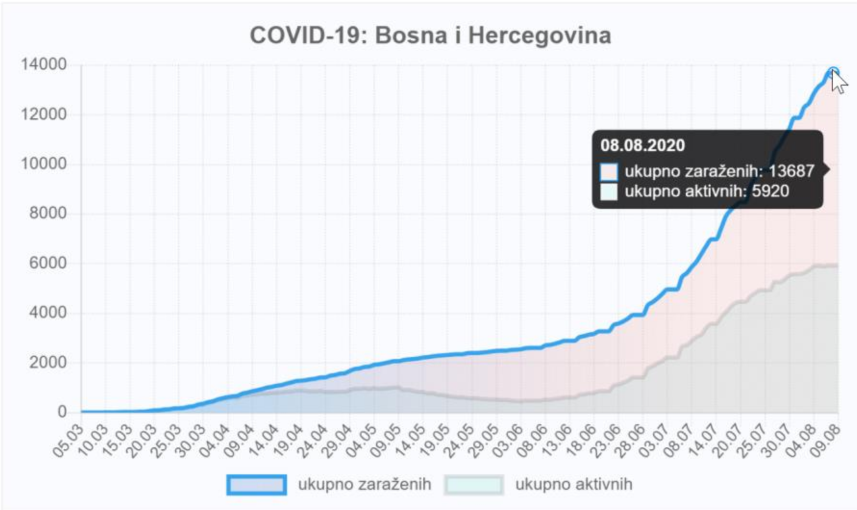

Figure 2. Distribution of the total infected population of Bosnia from the beginning of the infection 05.03.2020 to 09.08.2020 (source: https://mef.unsa.ba/Home/Coronavirus)

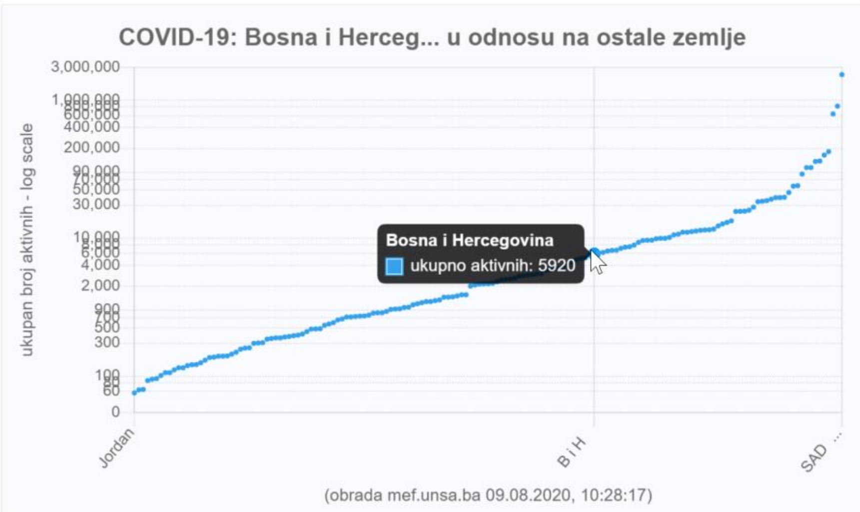

Figure 3. Relative position of actively infected inhabitants of Bosnia in relation to other countries (source: https://mef.unsa.ba/Home/Coronavirus)

4.2. Virus spread scenarios

Measures to prevent the spread of the infection are divided into two forms:

- Measure *'Intervention 1'* means a measure that is the closure of institutions that are at high risk for pandemics, restricting the work of facilities that perform service activities, forcing work from home, wearing self-protective masks indoors, enhanced hygiene when entering any facility where many people). This measure was introduced in Bosnia on March 16, 2020 and is still in force today.
- Measure *'Intervention 2'* is a restrictive measure (restriction of movement, closure of borders and other restrictive measures). This measure was introduced in Bosnia on April 1, 2020, but was abolished on May 25, 2020.

For the adopted mathematical model, we analyze four different scenarios of virus spread:

- '**Scenario 1'** implies a situation in which no restrictive measures have been taken
- '**Scenario 2'** implies the introduction of restrictive measures for the entire simulation period, ie. 'Intervention 1' (with a procedural decrease in the intensity of the spread of infection in the interval 33% - 40%) and 'Intervention 2' (with a percentage decrease in the intensity of the spread of infection in the interval 10% - 30%),
- **'Scenario 3'** implies the introduction of restrictive measures 'Intervention 1' for the entire simulation period (with a percentage reduction in the intensity of the spread of infection in the interval 33% - 40%) and 'Intervention 2' for the period from 01.04.2020 to 25.05.2020 reducing the intensity of the spread of infection in the interval 10% - 30%),
- **'Scenario 4'** implies the introduction of restrictive measures 'Intervention 1' and 'Intervention 2' as in 'Scenario 3', where the third measure 'Intervention 3' is introduced for the period from 01.08.2020 to 01.09.2020 (with procedural reduction of intensity spread of infection in the interval 10% - 30%).

We emphasize that in Bosnia, the current (valid) scenario is the 'Scenario 3', given that the measure 'Intervention 1' is still valid, but that the measure 'Intervention 2' has ceased to be valid as of 25.05.2020.

The basic parameters that determine the mathematical model are the same for each scenario and take into account the population, initial number of cases at the beginning, simulation time span, annual interval of average values of basic reproductive number R_0 and projected latency in days (Table 1). These parameters were determined in a repetitive cycle of computer simulations in an effort to reconcile the output results with the recorded results on the actual numbers of total infected, cured, and deceased.

Table 1. Basic model parameters

Total population number	3,324,000
Initial number of cases at the beginning of the simulation period	150
Simulation time span	01.03.2020 - 01.09.2020
Basic reproductive number R_0 (annual average)	1.6 – 2.2
Latency [in days]	3

4.2.1. Scenario 1 (without measures)

In this scenario, we assume that no restrictive measures have been introduced. Solving the system of differential equations (1) – (3) and taking into account the values of the basic parameters from Table 2, the computer simulation results in the following graph (Figure 4):

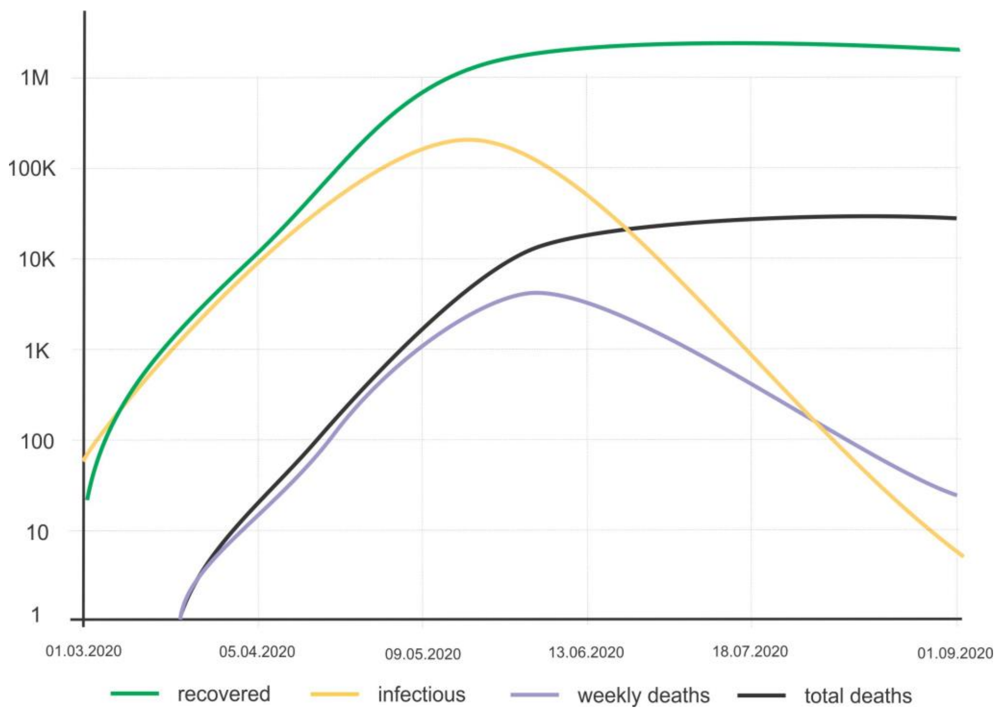

Figure 4. Simulation of the number of infected, actively infected and deceased in a scenario in which no measures have been introduced

As we can see from Figure 4 in this scenario, in which no measures have been taken for the entire simulation range, an intensive spread of infection with maximum effect is predicted in mid-May 2020 when the total number of infected falls. This phenomenon is often referred to in the literature as 'herd immunity', but it is evident that the risk posed by this scenario is potentially catastrophic for the population. The total number of infected reaches a huge number of over 200,000.

4.2.2. Scenario 2 (introduced two restrictive measures for the entire simulation period from 01.03.2020 to 01.09.2020)

In this scenario, we assume that the two restrictive measures 'Intervention 1' and 'Intervention 2', described in the previous chapter, have been introduced for the entire simulation period. In doing so, we assume that the reduction in transmission for the first measure is in the range of 33% - 40%, while the second measure reduced transmittion by 10% - 30% (Table 2). These values were determined in a way that the model was in line with the actual data (the total number of infected and deceased) in the previous period, which is known from the data collected in the database. https://mef.unsa.ba/Home/Coronavirus:

Table 2. Measures taken

Measure name	Date interval	Effectiveness
'Intervention 1'	20.03.2020 to 01.09.2020	33% - 40%
'Intervention 2'	01.04.2020 to 01.09.2020	10% - 30%

In doing so, we first create two separate simulations for the start and end values of the specified intervals, and then determine the mean value of the final diagrams. The result is shown in Figure 5.

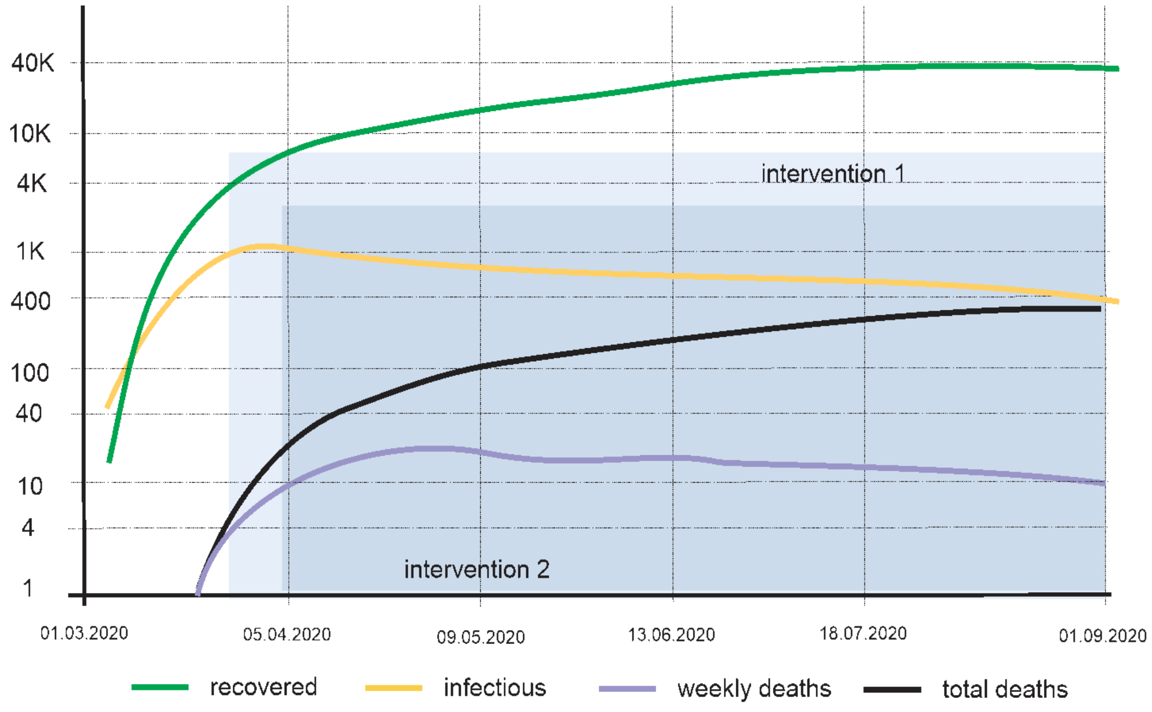

Figure 5. Simulation of the number of infected, actively infected and deceased in the scenario in which two restriction measures were introduced for the entire simulation period (01.03.2020 to 01.09.2020)

As we can see from Figure 5, according to this scenario, there would be a very large reduction in all the consequences of the infection, and it would take a stable form at the beginning of May 2020. The total number of actively infected individuals would not exceed 1,200, while the weekly death toll would stabilize below 25.

4.2.3. Scenario 3 (two restrictive measures were introduced, but not for the entire period - the existing situation)

In this scenario, we assume that the two restrictive measures ‘Intervention 1’ and ‘Intervention 2’, described in the previous chapter, have been introduced, but this time the ‘Intervention 2’ was active only for a shorter period of time, ie. from 01.04.2020 to 25.05.2020. This is exactly in line to what was happen in Bosnia (existing situation). The details of those two mesures are given in Table 3:

Table 3. Measures taken

Measure name	Date interval	Effectiveness
'Intervention 1'	20.03.2020 to 01.09.2020	33% - 40%
'Intervention 2'	01.04.2020 to 25.05.2020	10% - 30%

The results of the computer simulation are shown in Figure 6:

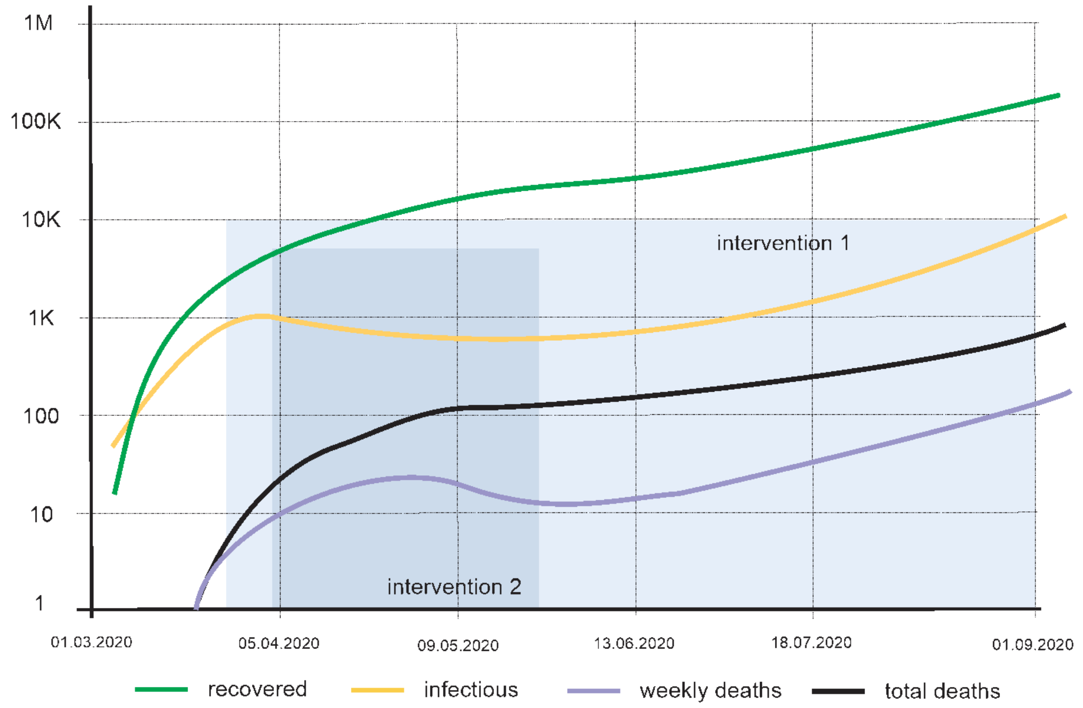

Figure 6. Simulation of the number of infected, actively infected and deceased (current situation)

As we can see from Figure 6, the mathematical model predicts a significant increase in all tracked numbers. It is clear from the graph that, after the initial reduction in the total number of infected since the beginning of May 2020, there is a renewed increase that coincides with the time of the abolition of the second restrictive measure. We can mark this new trend as the beginning of the 'second wave of infection', which is constantly intensifying until the end of the simulation period.

The total number of actively infected at the end of the simulation period reaches a value of over 9,000. What is particularly worrying in this scenario is that the diagram does not show any sign of the weakening or mitigation of the spread of the infection in the following period, because all the diagrams shown in the graph continue to have an increasing form.

4.2.4. Scenario 4 (the previously mentioned measures were retained and a new restriction measure was introduced)

In this scenario, the restrictive measures listed in the previous scenario are retained, but a new measure 'Intervention 3' is introduced on 01.08.2020 which lasts until the end of the simulation period. In character, this third measure is identical to the 'Intervention 2' measure (Table 4). The aim of this simulation is to determine what would happen if the measure 'Intervention 2' was reintroduced, which was abolished in Bosnia on 25.05.2020.

Table 4. Measures taken

Measure name	Date interval	Effectiveness
'Intervention 1'	20.03.2020 to 01.09.2020	33% - 40%
'Intervention 2'	01.04.2020 to 25.05.2020	10% - 30%
'Intervention 3'	01.08.2020 to 01.09.2020	10% - 30%

The results of this simulation are shown in Figure 7:

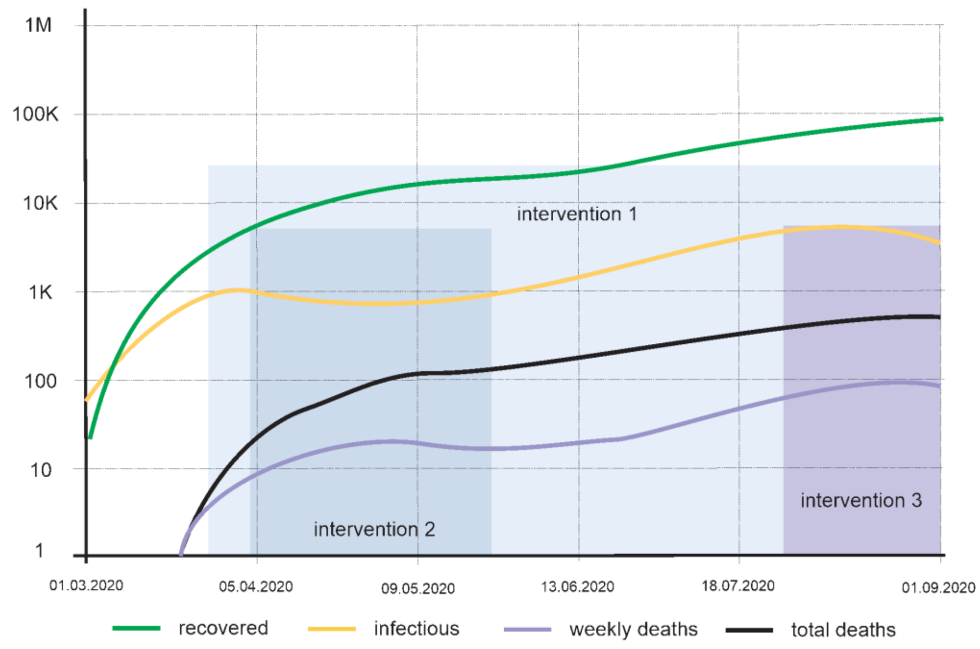

Figure 7. Simulation of the number of infected, actively infected and deceased in the scenario in which three restrictive measures were introduced

As we can see from Figure 7, the mathematical model in this scenario predicts a reduction of all monitored numbers. Thus we see that soon after the introduction of the third measure, the total number of actively infected begins to weaken, and the curve takes an evidently descending form.

5. Discussion

Coronaviruses (CoVs) belong to the family Coronaviridae, subfamily Orthocoronavirinae, and the order Nidovirales. SARS-CoV-2 is 17th specimens of CoVs that are known to have an effect on the human population. It is thought to represent a zoonosis, with an as yet unclear Intermediate host, as well as a rather dubious reservoir host (3). The virus is pathogenic for the complete population regardless of age, and the clinical picture is more severe in those patients with comorbidities (cardiovascular disease, presence of diabetes, chronic obstructive pulmonary disease) (4). Mechanisms of action of SARS-CoV-2 alone are on human angiotensin-converting enzyme 2 (ACE2) and human dipeptidyl peptidase 4 (DPP4) receptors and these additionally led to dubiosis in pharmacological properties as well as the pharmacological modality of the most common diseases of modern world (4,5). The virus is believed to be of animal origin (middle East respiratory syndrome related coronavirus (MERS) is from camels, while severe acute respiratory syndrome (SARS) from civets), SARS-CoV-2 origin s also associated with markets with wild animals, and the mode of transmission is human to human (6,7,8). Although the first cases were recorded in December 2019, it is interesting that the analysis of wastewater in Milan and Turin from December 2019, and wastewater samples from Barcelona on March 12, 2019, also proved the presence of SARS-CoV-2 (9,10). Fatality rate of 3.4%, lower than that of SARS (9.5%) and MERS (34.4%) (11).

By mid-May 2020, a set of restrictive measures in Bosnia was introduced. Closed borders, restriction of movement, reduced working hours, closed restaurants, shopping malls, mandatory wearing of protective masks etc. limited the number of people infected with SARS-CoV -2, and the crisis itself seemed to be under control. After two months of restrictions though, the measures were relaxed and with the opening of borders, as well as of places for public gatherings, an increase of infected individuals was noted. Two months after, the average number of newly infected individuals ranges between 300 to 350 per day. However, the measures are still not restrictive, except that gathering of large number of people is not allowed. An important question to be answered is what to do, with the note that health of the population is the most important.

This article introduced four different scenarios. The first scenario indicated what would have happened without any measures. Overcrowding and possible collapse of the state's health care system will be guaranteed. Large number of population would be infected, with increased mortality.

Second scenario showed what would happen if restricted measures were in place until 01 September 2020. This model would probably not be sustainable, as it would have large impact on the mental health of the population as well as on economic situation.

The third model indicated current, realistic situation, without restrictive measures in Bosnia. The question of the health capacities of Bosnia, as well as the number of beds in intensive care units is a big problem for this scenario. Model showed that we could expect a larger number of infected individuals, which will ultimately present a problem for healthcare institutions and society in general.

The fourth model indicated what would happen in case a new set of restrictive measures was introduced. The analysis shows the measures can slow down the spread of disease and decrease the number of infected and deceased.

The question is what to do, but the fact is that the overburdening of the health care system should be avoided, which is very vulnerable because of the decentralization in Federation of Bosnia and Herzegovina. Nevertheless, regardless of the consequences in the social spheres, the health of the population should be in the first place, and this should be a guide to the directions of action regarding the pandemic. It should be noted approximately that 77 to 89 percent of infected individuals remained asymptomatic over time (34, 35, 36, 37, 38, 39, 40).

As for severe cases, in 81% of cases pneumonia was recorded, of which 14% had severe clinical picture (dyspnea, hypoxia, or more than 50% of lung involvement on imaging within 24 to 48 hours), critical disease was in the area of 5%, while fatality rate was in 2.3% of monitored patients (41). Given these percentages, prevention also leads to the preservation of the health system in terms of avoiding overload in intensive care units.

Person-to-person contact needs to be reduced and education of population about the importance of distancing and avoiding contact is imperative (34). Protective facemasks should be worn at all times (35). Personal protective measures refer to hand and respiratory hygiene, along with use of respirator face masks or facemasks (36). Appropriate indoor ventilation, where a large population resides, is very important (36). The reorganization of the places where business activities are performed, while respecting the distance, should be carried out in all companies (36). Medical staff should be adequately protected, regularly tested and thus reduce the possibility to have lower number of available staff, but also to prevent consequences for the health of medical staff (36, 37, 38). All potentially infected should keep in mind that mean incubation period is on average 5.2 days, and all infected should be followed up for at least 14 days (37, 38).

The fact is that for the first time in the recorded human history, the treatment of a disease is based on everyday knowledge from the scientific community. Therefore, the medical staff should be regularly updated with the latest information, and the treatment should be in accordance with the evidence-based medicine instructions. The future of SARS-CoV-2 infection is unclear, and waiting for the appearance of vaccines, which again brings certain problems, if we know the characteristics of viruses, the only help to humanity is self-discipline and respect for the instructions of experts. A clear aim for everyone should be to protect the health of the population (39).

6. Conclusion

The introduction of the suggested measures would again lead to a decrease in the number of infected people, with the implementation of active testing, and controlled self-isolation of the infected. Self-discipline, adherence to measures, while trying to avoid restrictive binding measures should be the way to fight the COVID-19 pandemic. Whatever the consequences, the inclusion of restrictive measures to preserve the health of the population should be imperative. The mathematical model gives an overview of the importance of preventive measures and their application brings benefit in health status of the population.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms.

Author's contribution: SB, RK, EB and FV gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. SB, NB and AI had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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