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CONTENTS

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APPLICATION OF SPATIO-TEMPORAL EPIDEMIOLOGICAL MODELER (STEM) TO AN ANTHROPIC SMALLPOX DIFFUSION SCENARIO

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ABSTRACT

The use of mathematical models to simulate the diffusion of biological agents represents an essential tool to understand the dynamics of epidemic spread. In particular, mathematical models can be applied to scenarios of deliberate release of biological warfare agents, e.g., during simulations of a terrorist attack, to evaluate their potential effects and to study possible strategies to implement effective countermeasures. In this paper, an open-source software named Spatio-Temporal Epidemiological Modeler (STEM) has been applied to a possible scenario of deliberate release of smallpox virus by an unknown terrorist group in Italy. By providing boundary conditions derived from the literature, and making conservative preliminary assumptions, it was possible to recreate a reference scenario for the voluntary diffusion of smallpox, while providing an insight into the application of user-friendly tools for the implementation of epidemiological models as a support for decision makers in the field of biosecurity.

Keywords: *Epidemiological modelling; smallpox; bioterrorism; countermeasures; Susceptible / Exposed / Infectious / Recovered (SEIR) model.*

1. INTRODUCTION

According to current opinions, the devastating effects of the spread of genetically modified microorganisms can be potentially more dangerous for the population than an attack with a nuclear fission weapon (Henderson, 1999; Olson & Shchelkunov, 2017). In addition, while nuclear weapons (as well as conventional ones) cause damage to both physical infrastructure and people, the use of a biological weapon would only have effects on the population, animals and even materials. The biological warfare agents (BWA), microorganisms used for warfare or terrorism purposes, are defined as organisms or substances derived directly from living organisms, whose use can result in deaths or serious injuries to people, animals and plants (Dudley & Woodford, 2002a). To be effective as a BWA, a biological agent must possess several characteristics, including high mortality and transmissibility rates, ability to survive for a long period in the environment, as well as resistance to methods of air, water and food purification (Cenciarelli *et al*., 2014). In order to carry out an effective bioterrorist attack, it is crucial that the attackers possess the means (e.g. vaccines and other tools for prophylaxes) not available for the victims. Moreover, modern bioengineering and molecular biology techniques can potentially improve the virulence and resistance to treatments for selected microorganism (Utgoff, 1993; Olson & Shchelkunov, 2017; Meyer *et al.*, 2020).

Mathematical models constitute an essential tool to assess the potential spread of epidemics. In the event of a deliberate release of biological agents, early estimation of potentially affected areas and individuals is essential. The risk assessment that can be implemented through these tools is therefore a valuable help to the emergency management. In this paper, we used the Spatio-Temporal Epidemiological Modeler (STEM) to understand and evaluate how a smallpox outbreak caused by a bioterrorist attack would spread, and also evaluate the application of specific physical countermeasures. We built a deterministic Susceptible / Exposed / Infectious / Recovered (SEIR) model to simulate the course of the epidemic, and evaluate the effectiveness of social distancing, shutting down air travel and preventing mixing of infected individuals across borders.

Assuming a reference scenario with 1,000 index cases and considering the implementation of the intervention 25 days after the attack, the model forecasts an epidemic of thousands of cases with an outbreak duration of 180 days.

STEM is an open source tool is designed to provide support to decision makers in the evaluation of how many people will be involved in an epidemic and in the visualization of the dynamics of the spread of infectious diseases, independently on whether they are the result of a natural epidemic or non-conventional human activity (Baldassi *et al*., 2015). In particular, STEM uses mathematical models of diseases (based on differential equations) to simulate the development or evolution of a disease in space and time.

2. POXVIRUS AS A BWA

Consciously or unconsciously, mankind has been using biological agents as lethal weapons for centuries. Microorganisms and biological toxins have been used from ancient times for direct attacks against the people. Among the several episodes recalled by history, the use of smallpox virus as a biological weapon was among the most sensational. In the 18th century, during the French-Indian war (1754-1767), the British colonial army used smallpox-contaminated blankets to disseminate the disease among native American tribes (Dudley & Woodford, 2002b); the smallpox outbreak killed more than 50% of the affected people and the recrudescence of the virus among the indigenous lasted for more than 200 years (Riedel, 2005; Cenciarelli *et al.*, 2013). More recently, it was reported (although not officially confirmed) that during the Cold War, several attempts for the genetic modification of the smallpox virus were carried out by Soviet scientists to create a new and more destructive BWA (Henderson, 2009).

Humans are the only known hosts of the smallpox virus; this aspect has allowed, through two global vaccination campaigns carried out by the World Health Organization (WHO), the total eradication of the pathogen (Wolfe *et al.*, 2007). The last natural case in the world was in Somalia in 1977, and at this date, the vaccination campaign was already stopped (Henderson, 2009).

The poxviruses (*Poxviridae*) comprise a family of enveloped DNA viruses that replicate within the cytoplasm of vertebrates and invertebrates' cells. Only members of the genus Orthopoxvirus, which includes smallpox, can infect humans. Smallpox is readily transmitted from person to person via saliva or nasal secretion droplets and contaminated objects (Moss, 2007; Sulaiman *et al.*, 2007; Cenciarelli *et al.*, 2013; Meyer *et al.*, 2020). The virus is highly infective and the mortality rate can reach 40%. During the infection, the smallpox virus enters the respiratory tract and spreads between mucous membranes, moving quickly into local lymph nodes (Breman & Henderson, 2002). An incubation period that lasts from seven to 17 days follows the infection of the host. The early symptoms are common to other diseases (e.g., cold and flu); this period is called the prodromal phase. During this stage, the mucous membranes in the throat and mouth are infected. The virus then invades the capillary epithelium of the dermis in the skin, leading to the development of lesions (Breman & Henderson, 2002). Currently, no treatments for smallpox infection are known; the therapy approach involves supportive care using antipyretic and anti-inflammatory treatments (Esposito & Fenner, 2001; Bhalla & Warheit, 2004; Cenciarelli *et al.*, 2013; Meyer *et al.*, 2020).

According to the severity of the disease, and to the possibility to be used as a bioterrorism agent, the U.S. Centers for Disease Control and Prevention (CDC) classified *Variola major* as a "Category A" biological agent (CDC, 2015); posing a global threat for biosafety and biosecurity (Henderson, 1999; Whitley, 2003). Due to the stop of the vaccination campaigns, a large part of the world population is no longer immune. Therefore, smallpox is once again an ideal candidate to be used as a biological weapon (Mahy, 2003). Following the official eradication, the remaining stocks of smallpox were collected by two WHO approved Biosafety Level 4 (BSL-4) laboratories. Particularly, 451 smallpox virus stocks are located at the CDC in Atlanta (USA) and 120 stocks in State Research Center of Virology and Biotechnology (SRCVB) in Koltsovo (RUS) (DHHS, 2009). Furthermore, the possibility that samples containing the DNA of the smallpox virus have been left, even unintentionally in remote parts of some laboratories cannot be completely ruled out, posing the risk that one or more of these samples might be recovered with malevolent intentions. The recent discovery of Variola virus in old specimens at the National Institutes of Health (NIH) in Bethesda, Maryland highlights this risk (CDC, 2014; Kaiser, 2014; Reardon, 2014).

3. METHODOLOGY

3.1 Spatio-Temporal Epidemiological Modeler (STEM)

STEM is an open-source software built on JAVA™ platform that allows to create spatial and temporal patterns of the spread of infectious diseases. The software comes with some existing compartment models, as Susceptible / Infectious (SI), Susceptible / Infectious / Recovered (SIR) and Susceptible / Exposed / Infectious / Recovered (SEIR) models pre-coded with both deterministic and stochastic engines, as well as a new model building framework that allows users to rapidly extend existing models or create entirely new models (Eclipse Foundation, 2020).

The STEM software integrates data from geographical information systems (GIS) from across the world, including information about national borders, populations, shared borders, highways, airports, etc. STEM organizes the world as a graph into a modular and hierarchical modeling structure; from bottom to top, this structure has three basic levels: graphs, models and scenarios. In particular, graphs represent spatial entities with defined shape and geospatial location, or carries information relevant for the scenario to be modeled (e.g., population, area). Models consist of at least one graph and a combination of other information regarding the population and disease states (compartments). In the end, scenarios may contain a variety of additional components, but they consist at least of a model and a time sequencer to easily create, run, and visualize the experiments (Eclipse Foundation, 2020).

3.2 Scenario

As described in Section 2, smallpox is among the most dangerous organisms that might be used by bioterrorists and is not widely available. An attack using this virus would involve relatively sophisticated strategies and would deliberately seek to sow public panic, social disruption, discredit official institutions, and shake public confidence in government.

In this paper, the authors created a possible scenario that considers a release of aerosolized smallpox agent in a public building placed in a big city in central Italy. The number people initially involved and heavily infected is 1,000. The airborne nature of smallpox allows the disease to spread quickly (O'Toole, 1999; Bozzette *et al.*, 2003; Olson & Shchelkunov, 2017).

The scenario designed in this work intends to provide food for thoughts and elements for discussion in the field of mathematical models as decision support tools not only for classical epidemiology, but also for planning and response in the framework of bioterrorism and biological related threats.

3.3 SEIR Epidemic Model

Several mathematical models can be used to fit epidemic data (Lavine *et al.*, 2008; Bachinsky & Nizolenko, 2013; Ndanguza *et al.*, 2013; Eclipse Foundation, 2020). In this work, smallpox epidemiological data was analyzed through a simple deterministic (continuous time) SEIR epidemic model (Hethcote, 2000). Almost all existing literature (Chowell *et al.*, 2004; Lekone & Finkenstädt, 2006; Legrand *et al.*, 2007) on smallpox epidemic prediction is based on this model. Typically, these types of models of the behavior of an infectious disease in a large population of people consider each individual as being in a particular epidemiological state. These states are often called compartments, and the corresponding models are called compartment models. The analyzed population (N) is classified into four epidemiological states: Susceptible (S), Exposed (E), Infectious (I) and Recovered (R). These compartments are described in Table 1, while the model flowchart is represented in Figure 1.

Table 1: Epidemiological states of the population considered for the SEIR epidemic model and compartments of $S(t)$, $E(t)$, $I(t)$ and $R(t)$ of the whole population size (N).

EPIDEMIOLOGICAL STATES	POPULATION (N)	DESCRIPTION
Susceptible (S)	$S(t)$	Susceptible individuals at the time t
Exposed (E)	$E(t)$	Exposed individuals at the time t, not yet infectious; incubation period of $\mathbf{1}/\varepsilon$ days
Infectious (I)	$I(t)$	Infected and infectious individuals at the time t; they move to the R class at the per-capita rate $\mathbf{1}/\gamma$
Recovered (R)	$R(t)$	Individuals who recovers from the disease or die as consequence of the disease at the time t

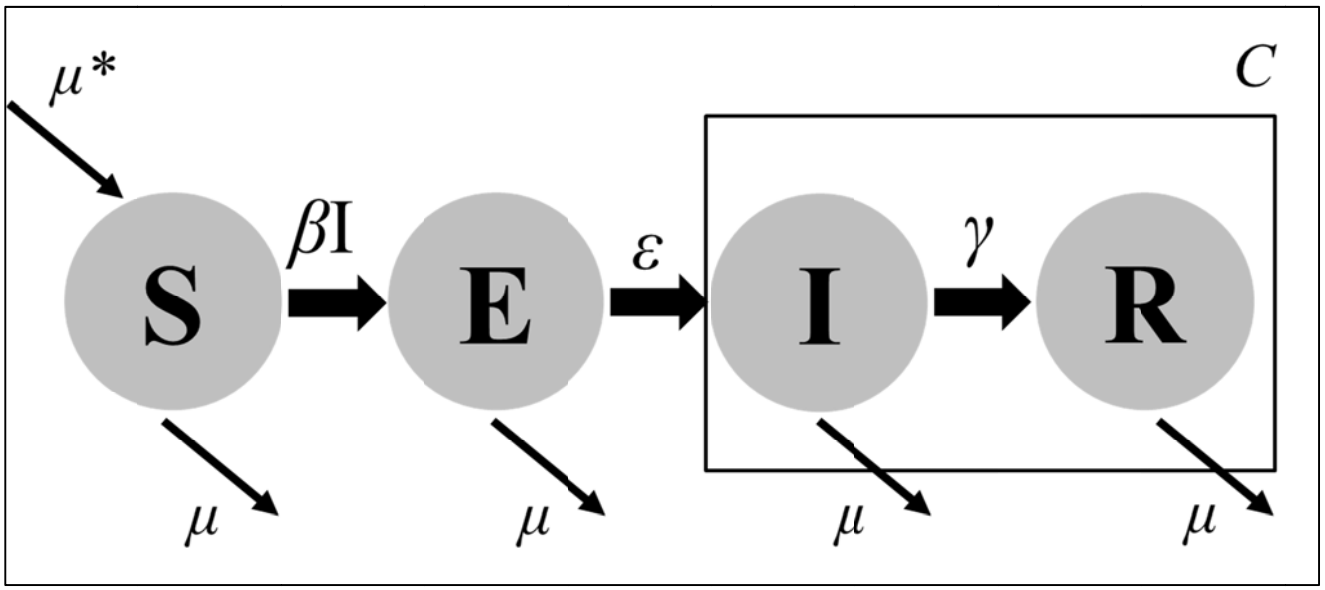

Figure 1: SEIR compartment model. This model shows the SEIR epidemiological states, the transmission rate (β), the incubation rate (ε) , the recovery rate (γ), the population birth rate (μ*), and the population death rate (μ). C is not a compartment but is a cumulative number of disease cases occurred ($I + R$).

The transmission process is modeled by the system of the following nonlinear ordinary differential equations (Lavine *et al*., 2008; Eclipse Foundation, 2020): Susceptible individuals at time t (1); exposed individuals at time t (2); infected and infectious individuals at time t (3); and individuals who recover from the disease or die as consequence of the disease at time t (4).

$$\frac{dS(t)}{dt} = -\frac{\beta S(t)I(t)}{N}\,\alpha R(t) + \mu\big(N - S(t)\big) \tag{1}$$

$$\frac{dE(t)}{dt} = \frac{\beta S(t)I(t)}{N - \varepsilon E(t)} - \mu E(t) \tag{2}$$

$$\frac{dI(t)}{dt} = \varepsilon E(t) - \gamma I(t) - \mu I(t) \tag{3}$$

$$\frac{dR(t)}{dt} = \gamma \boldsymbol{I}(t) - \alpha R(t) - \mu R(t) \tag{4}$$

The model takes into account both the people infected by direct contact with an infected person, and the people infected by indirect contact with the equation $\beta S(t)I(t)/N$. Individuals who pass on to the infectious stage and show the symptoms of the disease are denoted by εE, where ε is the per-capita infectious rate. $1/\varepsilon$ represents the average time for a latent individual to become infectious. It will be denoted by γI, where γ is the per-capita recovered rate.

The first assumption to apply the SEIR model in this work considers the population as closed; meaning that the effects of demographic changes are theoretically minimized during the epidemic. Both birth rate and death rate are taken to be zero, and thus, the compartment model is said to be closed, i.e., the population is static with no new individuals coming or going.

When the population is approximately constant over the time of the epidemic and the disease has a high mortality rate (such as smallpox), a new parameter called infectious mortality rate (δ) can be assigned to track the deaths caused by the disease. In this case, the total mortality rate for the infectious state is represented by δ. Consequently, $1/\delta$ is the average time it takes for an individual to die once having entered the infectious stage.

Without medical treatment, the *R*-class is removed because the outcome of the disease will surely be death (*D*) (Lekone & Finkenstädt, 2006; Ndanguza *et al.*, 2013). *C* is not an epidemiological parameter and does not represent a compartment, rather it is used to keep track of the cumulative number of smallpox cases at the onset of symptoms (sum of *I* and *R*).

The smallpox virus epidemiological data obtained from a deep review of the scientific literature available is reported in Table 2.

Table 2: **Smallpox virus epidemiological data provided by scientific literature.**

EPIDEMIOLOGICAL FEATURES	VALUE	REFERENCES
Incubation rate ($\mathcal{E}$)	0.0667 day^{-1}	Gani & Leach (2001), Legrand *et al*. (2004), Del Valle *et al*. (2005) and Adivar & Selen (2011)
Recovery rate (γ)	0.0625 day^{-1}	
Infectious mortality rate (δ)	0.0268 day^{-1}	
Transmission rate (β)	0.1 day^{-1}	
Size of the population (N)	57.756.988	Eclipse Foundation (2020)
Number of index cases	1,000	Section 3.2
Population density	206/km^2	Worldometer (2020)

3.4 Interventions - Physical Countermeasures

The physical countermeasures are intended three different type of interventions: social distancing, shutting down air travel (for a county, state or the whole country), and preventing mixing of infected individuals across borders. These kinds of interventions are used, together with a vaccination program and isolation of infected individuals (medical countermeasures), to control an outbreak (Olson & Shchelkunov, 2017; Meyer *et al.*, 2020). STEM uses triggers, predicates and modifiers to implement interventions. A trigger contains a predicate which, when satisfied, invokes one or more modifiers that change some aspect of a running simulation.

3.4.1 Social Distancing

Social distancing (e.g., distributing face masks, closing public buildings) reduces the transmissibility of the pathogen, so changing the transmission rate in the disease makes sense. In this work, the control of the outbreak by implementing social distancing was applied 26 days after the attack; consequently, the transmission rate (β), according to previous studies (Ahmed *et al.*, 2018), was reduced by 50% from 0.1 day^{-1} to 0.05 day^{-1}.

3.4.2 Shutting Down Air Travel

Shutting down the air transportation in a region is one of the options that can be carried out to control an outbreak. To model this in STEM, modifiers that change the total number of passengers traveling to / from the major Italian regions (Lazio, Tuscany, Lombardy, Piemonte, Emilia-Romagna, Sicily and Sardinia) were applied. In particular, the air traffic was blocked in these regions after 26 days from the attack by bringing the air travel rate value to 0.

3.4.3 Preventing Mixing of Infected Individuals Across Borders

The contacts of infected and healthy individuals across borders can either be shut down globally, or for a particular border only. The common borders (Figure 2) were modified in the simulated scenario. In particular, the common boundaries between the main Italian regions (Lazio, Tuscany, Lombardy, Piemonte, Emilia-Romagna) were closed 26 days after the attack.

3.5 Assumptions

To run the simulations, the following assumptions were considered:

i) The whole population was considered susceptible at t=0; at the start of the outbreak $N = S(t)$.
ii) During the epidemic simulation, the population was considered as constant. In a constant population, no deaths due to outside factors are taken into account. Moreover, the number of births that occurred is so small that is negligible. For this reason, in the simulation the parameters μ^* and μ were unconsidered.
iii) All the observed cases (expect index cases) were assumed to be related to human-to-human transmission only.
iv) The time from the bioterrorist attack to the intervention of the authorities was considered 25 days. If an attack with smallpox occurred, the first case would develop the first symptoms around 12–14 (7–17) days (mean and range of the duration of the latency period) after the attack (Legrand *et al*., 2003). Since smallpox was eradicated in 1979, lack of experience could lead physicians to misdiagnose smallpox initially, delaying intervention (O'Toole, 1999; Legrand *et al.*, 2003; Madeley, 2003). Thus, we assumed that the time to intervention ranged between 7 and 45 days, and was fixed at 25 days (half).
v) The three types of interventions were applied together in the simulation; the time of intervention was fixed at 26 days after the attack.
vi) The duration of the outbreak was considered as 180 days (about 25 weeks); at that simulated time, the number of exposed (E) and infectious (I) was near to zero, and the number of disease deaths and recovered (R) remained constant.
vii) The prodromal phase was combined with the incubation phase. Thus, the mean time in the non-infectious stages denoted by E, here corresponding to the incubation period plus the prodromal phase, was assumed to be 15 days. The incubation rate ($\mathcal{E}$) was consequently 1/15.
viii) Since smallpox vaccination programs ended about 30 years ago, and the effectiveness of a smallpox vaccine is assumed to last for 10 to 30 years (Kaplan, 2003), it was assumed that the population has no immunity.

Figure 2: The schematic representation of the Italian common borders in STEM.

4. RESULTS & DISCUSSION

In this work, the authors aimed to demonstrate, considering a hypothetical scenario in Italy, the consequences of a bioterrorist attack carried out using smallpox virus in three different situations. In the first case, the consequences of the epidemic were studied and evaluated at 25 days after the attack and before the application of any intervention, applying to STEM the estimated parameters shown in Table 2. In this case, 25 days after the start of the simulated outbreak, 1,851 affected people were identified (Table 3). The STEM analysis of the simulated outbreak (Figure 3A) shows the evolution of the population in different epidemiological states during the time. Moreover, the geographical distribution of the involved population (Figure 4A) in different epidemiological states (*E*, *I* and *R*) after 25 days of simulation was obtained using STEM. The intensity of the colors in the different Italian regions is proportional to the number of people involved in one of the four epidemiological states.

In the second case, the consequences of the epidemic were studied and evaluated at 180 days after the attack and without the application of any intervention. As expected, a considerable number of affected people was identified, reaching the value of 14,943 (Table 3). As in the previous case, the STEM analysis of the

simulated outbreak (Figure 3B) shows the evolution of the population in different epidemiological states during the time and geographical distribution of the involved population (Figure 4B).

In the third and last case studied the consequences of the outbreak 180 days after its start and considering the application of physical countermeasures (starting the 26th day after the attack). The obtained data were compared with the second case and, as expected, a strong difference between the second and third simulation results was identified (Table 3): the involved people were reduced by four times when physical countermeasures were applied. The STEM analysis and related geographic distribution of the involved population are showed in Figures 3C and 4C respectively.

All the simulations were adjusted using a logarithmic intensity scale and a specific gain factor (x 10^5), and the fourth-order Runge-Kutta algorithm to solve it numerically, written in JavaScript™.

Table 3: Results of the simulated scenario for 25 days and 180 days after the outbreak started, as well as 180 days after the outbreak started with the application of physical countermeasures.

	After 25 days	After 180 days	After 180 days with physical interventions applied
Index cases	1,000	1,000	1,000
Exposed (*E*)	666$^{(*)}$	1,476$^{(*)}$	23$^{(*)}$
Infectious (*I*)	489$^{(*)}$	1,049$^{(*)}$	22$^{(*)}$
Recovered (*R*)	953$^{(*)}$	8,695$^{(*)}$	2,557$^{(*)}$
Disease deaths (*D*)	409$^{(*)}$	3,723$^{(*)}$	1,093$^{(*)}$
People involved (*C*)	1,851	14,943	3,695

* Rounded off to the nearest whole number

5. CONCLUSION

Although smallpox has been declared eradicated, the possibility of releasing smallpox or smallpox like organisms brings the potential for a catastrophic scenario as it is for deadly emerging pathogens (Olson & Shchelkunov, 2017). In order to predict and prevent, or at least to reduce this kind of threat, or an epidemic outbreak or infection from spreading, decision makers and policymakers can benefit from simulation tools such as STEM.

In this paper, STEM was applied to a hypothetical bioterrorist scenario using historical epidemiological data from the literature, considering three different cases. The obtained data, starting from 1,000 index cases, were achieved by applying the deterministic SEIR compartmental model to a STEM using standard population and integrating the input data with real smallpox outbreak data from the literature (e.g., transmission, incubation, and recovery rates). The project was designed as the starting point for scenario evolution simulations. The final results obtained from STEM analysis allowed, with some preliminary assumptions, an easy and complete assessment of how the population size changes in the three cases considered as a whole during the simulations as well as in the different spatial disease compartments. The STEM simulations analyze the effects of epidemic behavior change alone and in combination with specific control measures. As a result, the provided information can suggest to decision makers, with a high level of accuracy, how the outbreak would spread and develop in space and time in different phases: in the early, during, and in the last phases of the epidemic, as well as in combination with control measures.

Thus, STEM can significantly improve preparedness and response in the field of bioterrorism. In fact, being able to estimate the spatial distribution and spread of an agent and the temporal disease outbreak patterns reflects a more effective emergency planning and response. As a result, this tool could help to develop (and test) control strategies based on computer simulations. Additionally, it would address the most important information gaps for the creation of faster and more specific exposure assessments and risk characterization.

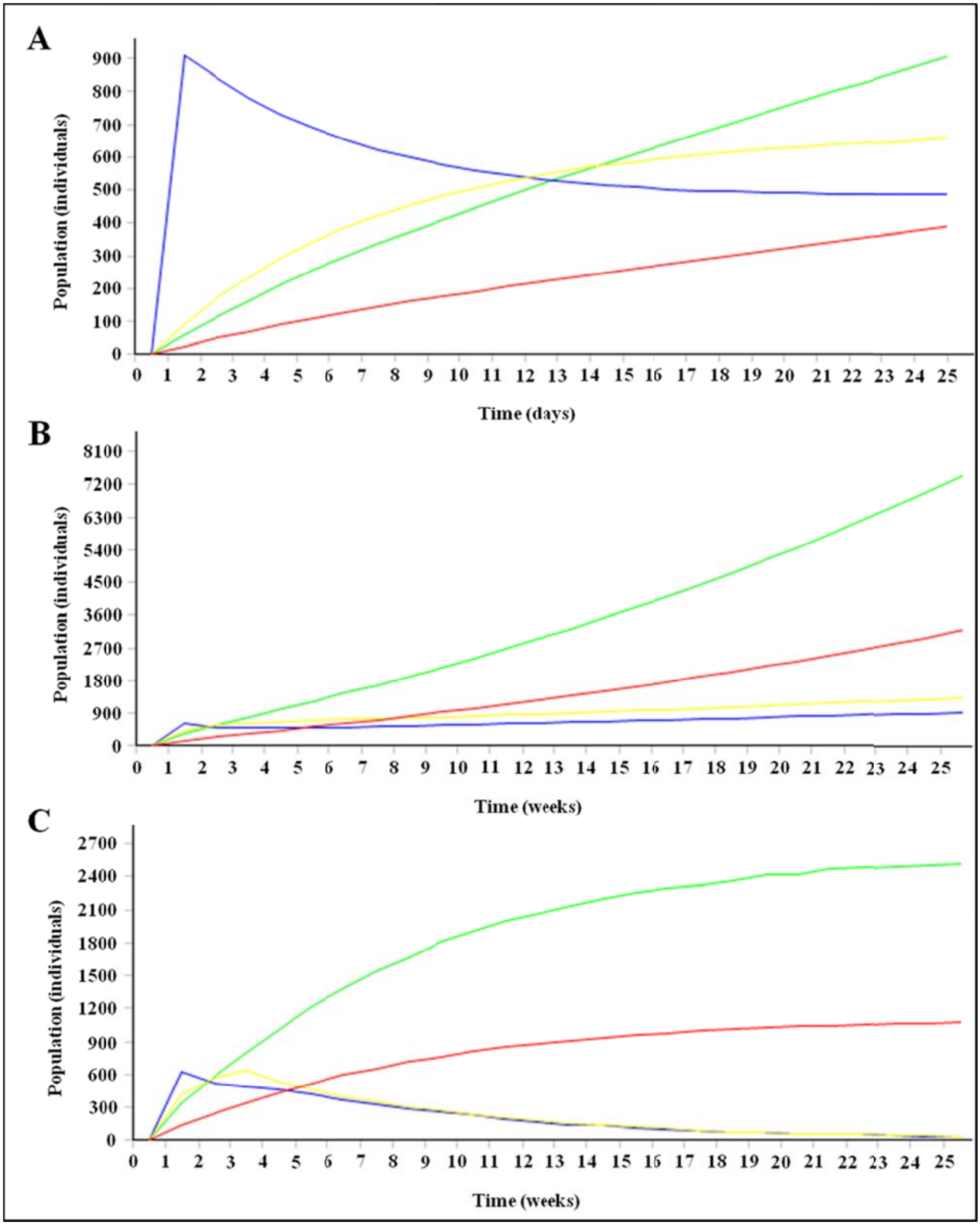

Figure 3. STEM analysis of the scenario in the different considered situations. The evolution of people compartmented in different states with respect to time is represented. Each state is reported in a specific color; exposed (yellow line), infected (blue line), recovered (green line), and dead (red line) individuals. A) First case: 25 days after the outbreak start. B) Second case: 180 days after the outbreak start. C) Third case: 180 days after the outbreak start with the application of physical countermeasures after the 26th day from the outbreak start.

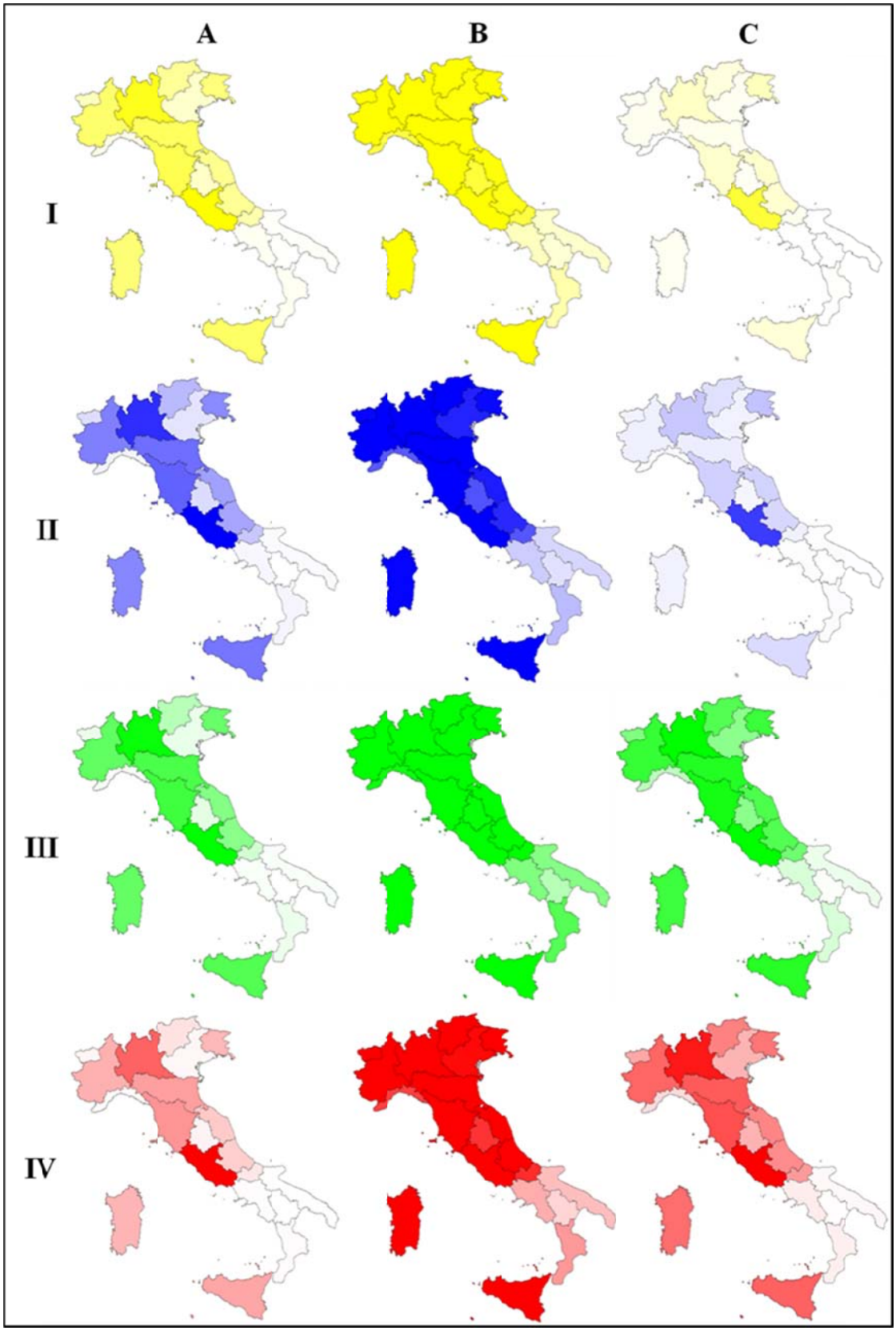

Figure 4. STEM analysis of the scenario in the different considered situations. The geographical distribution of people compartmented in the different states is represented. Each state is reported in a specific color; I) Exposed (*E*), yellow; II) Infected (*I*), blue; III) Recovered (*R*), green; IV) Disease Deaths (*D*), red. The color intensity is proportional to the number of involved people in the four different epidemiological states. A) First case: 25 days after the outbreak start; B) Second case: 180 days after the outbreak start. C) Third case: 180 days after the outbreak start with the application of physical countermeasures from the 26th day from the outbreak start.

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