

Editorial / Uvodnik

## The role of epidemiological modeling of COVID-19 in the health system Vloga epidemiološkega modeliranja COVID-19 v zdravstvenem sistemu

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A new infectious virus, dubbed SARS-CoV-2 by the World Health Organization and causing COVID-19 coronavirus disease (World Health Organization, 2020), first occurred in Wuhan, China, in December 2019. The virus spread around the world fairly quickly and was confirmed in Slovenia for the first time on 4 March 2020, with the case of a Slovenian tourist who was infected on his way back from Morocco via Italy (Portal gov.si, 2020).

With a higher number of confirmed cases worldwide and their detailed study, it has been found that the new SARS-CoV-2 coronavirus is transmitted between humans by droplets, through direct contact and with continuous exposure to high indoor aerosol concentrations (Li, Liu, Yu, Tang, & Tang, 2020). The spread of the epidemic among the world's population has increased the number of measures taken to curb the epidemic, as well as the interest of experts in various fields to understand the course of the epidemic, and predict its development and consequences. Mathematical models of epidemic development are an important tool for limiting and managing an epidemic. With appropriate epidemiological models, simulations and prediction of different scenarios can be performed. However, appropriate methodology and epidemiological models must be applied (Eržen, Kamenšek, Fošnarič, & Žibert, 2020). Epidemiological models are divided into phenomenological, departmental and agent. Phenomenological models are statistical models that are based on data, use regression analysis, and often adapt epidemiological data to the exponential growth, which is observed in the early stages of an epidemic. Their essential disadvantage is that they do not include the mechanics of the spread dynamics of an infectious disease. Departmental models are

standard epidemiological models and are also widely used during the COVID-19 epidemic. They include the mechanics of the dynamics of the epidemic spread process and have a relatively simple structure, where individual population groups (or departments) in the epidemic are defined and the transitions between them are modelled. The third group of models is represented by agent models. Here, instead of groups in the population, the individual in the epidemic and their interactions with other individuals (or agents) are defined and in this way, the dynamics of the spread of the epidemic are predicted. Individuals or groups of individuals in such models are represented by vertices in the network, where connections between vertices define their interactions. Therefore, such models are also called network models. They can be used to model the heterogeneous spread of the disease, but as a rule, a lot of data are needed to determine the parameters of the model. Therefore, in the absence of these data, the results of the agent model can be highly inaccurate (Keeling & Rohani, 2008).

The minimum requirements for epidemiological modeling must take into account the dynamics of the epidemic spread process and the model parameters must be appropriately estimated or determined, so that the model projections match the previous epidemic state, as this is the only way to use the epidemiological model to predict and simulate the spread of the epidemic. However, we must be very precise in interpreting the results. The dynamics of the spread of an epidemic is highly dependent on the behavior of individuals in an epidemic, such as how many contacts an individual is exposed to, how they behave protectively, or how they follow other government measures to prevent the spread of the COVID-19 infection. However, this cannot be fully

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predicted by models. Therefore, certain assumptions in epidemiological models must be included and can thus only be used to simulate different scenarios of possible epidemic courses with fulfilled or unfulfilled assumptions. Nevertheless, or precisely because of this, epidemiological models can be very useful.

With epidemiological models, it can be showed promptly that the flattening of the curve of infected and consequently hospital treatments depends on the reproductive number  $R$ . This is the number that reveals how many people on average are infected by one infected person in an epidemic. If the number of  $R$  is greater than 1, the epidemic increases exponentially; if  $R$  is around 1, the epidemic spreads constantly (on the average just as many people fall ill as recover); and if  $R$  is less than 1, the epidemic declines. The higher  $R$  is, the more infected people there will be at a given time, which in turn, results in a greater burden on the health system. The lower the  $R$  is (but still greater than 1), the more the curve of the infected is flattened and the epidemic lasts longer, but the health system is consequently less burdened although for a longer period of time. The models can also show that it is necessary to implement measures as restrictively as possible to reduce  $R$  as much as possible and as early as possible in the epidemic. In this way, the course of the epidemic can be controlled or completely limited. The finding that the decline of an epidemic takes longer than its increase is also significant. In other words, more time to get back to the baseline than from the baseline to the peak of the epidemic is needed.

Furthermore, by adding new groups to departmental models, the impact of more or less risk groups on the dynamics of the epidemic can be studied. Here, it is important to note that a relatively small group of individuals behaving more risky and thus spreading infection more, can significantly affect the overall spread of the epidemic. For example, we have found that already 10% of the population with 3 times riskier contacts, can cause a 40% higher maximum value of the number of the infected in the population. Similarly, the emergence of new virus strains, which are more virulent, for example, can also significantly alter the dynamics of the virus spread and can critically change the course of the epidemic despite measures. By adding new groups to epidemiological models, the impact of vaccination on the course of the epidemic can also be simulated, illustrating that vaccination is necessary to achieve herd immunity. Stopping the spread of the epidemic depends on the reproductive number  $R$  and is achieved with the proportion of vaccinated population being at least  $1-1/R$ .

With more complex epidemiological modeling, the course of the epidemic with the inclusion of various measures that are more targeted to individual population groups can also be simulated. For example, the release of measures in education (primary and secondary schools) in combination with vaccination of the elderly population in the presence of new

variants of the virus. Such simulation for Slovenia, for example, is made with the SEIR C19 SI model and is available at the Rpubs webpage (Žibert, 2021).

Similarly, models can be used to plan hospital capacities during the epidemic. It can be shown that, for example, the patient treatment time in a hospital or in an intensive care unit can significantly affect the load on hospital capacities with the rapid spread of the epidemic. Just one day of shorter treatment of patients on average in intensive care units or in general wards of hospitals can significantly reduce the burden on the hospital system as a whole with the rapid spread of the epidemic. Therefore, the integration of epidemiological models into the planning, analysis and management of an epidemic in extreme situations, such as the COVID-19 pandemic, is urgently needed.

Healthcare professionals also play an important role in this. They are an example in following government measures to control the epidemic, understanding the measures and helping to make the lay public aware of their importance (Prosen, 2020). It should be noted that without quality input data it is not possible to make a good predictive model, so it is important to keep treatment protocols and COVID-19 patient registers, accurate and consistent data collection, which is anonymously accessible to developers of predictive epidemiological models. It is also important that healthcare professionals know how to use predictive models in their work, especially in terms of planning the influx of patients, lighter and heavier forms, occupancy of beds in individual departments and units, work process planning and staffing.

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### *Slovenian translation / Prevod v slovenščino*

Decembra 2019 je v mestu Vuhan na Kitajskem prišlo do izbruha novega nalezljivega virusa, ki ga je Svetovna zdravstvena organizacija poimenovala SARS-CoV-2 in povzročila koronavirusno bolezen COVID-19 (World Health Organization, 2020). Virus se je zelo hitro razširil po svetu in 4. marca 2020 je bil prvič potrjen tudi v Sloveniji s primerom slovenskega turista, ki se je okužil med vračanjem iz Maroka skozi Italijo (Portal gov.si). Z večjim številom potrjenih primerov po svetu in njihovim podrobnim preučevanjem je bilo ugotovljeno, da se novi koronavirus SARS-CoV-2 med ljudmi prenaša kapljično, s tesnimi stiki in z neprekinjeno izpostavljenostjo visokim koncentracijam aerosola v zaprtem prostoru (Li, Liu, Yu, Tang, & Tang, 2020). Širjenje epidemije med svetovnim prebivalstvom je povečevalo število sprejetih ukrepov za zaježitev epidemije in tudi interes strokovnjakov različnih področij za razumevanje poteka epidemije, napoved njenega razvoja in posledic.

Pri zamejevanju in upravljanju z epidemijo so pomembno orodje matematični modeli razvoja epidemije. Z ustreznimi epidemiološkimi modeli

lahko izvajamo simulacije in predvidimo različne scenarije, vendar moramo pri tem uporabljati ustrezno metodologijo in ustrezne epidemiološke modele (Eržen, Kamenšek, Fošnarič, & Žibert, 2020). Slednje v osnovi delimo na fenomenološke, oddelčne in agentne. Fenomenološki modeli so statistični modeli, ki nastanejo na podlagi podatkov, uporabljajo regresijsko analizo ter pogosto prilagajajo epidemiološke podatke eksponentni rasti, ki je opažena v zgodnjih fazah epidemije. Njihova bistvena slabost je, da ne vključujejo mehanizmov dinamike širjenja nalezljive bolezni. Oddelčni modeli so standardni epidemiološki modeli in jih veliko uporabljamo tudi v času epidemije COVID-19. Vključujejo mehanizme dinamike procesa širjenja epidemije in imajo sorazmerno enostavno strukturo, pri čemer definiramo posamezne skupine populacije (ali oddelke) v epidemiji in modeliramo prehode med njimi. Tretjo skupino modelov predstavljajo agentni modeli, pri katerih namesto skupin v populaciji definiramo posameznika v epidemiji in njegove interakcije z drugimi posamezniki (ali agenti) ter na ta način poskušamo napovedovati dinamiko širjenja epidemije. Posamezniki ali skupine posameznikov v takšnih modelih so predstavljeni kot točke v mreži, kjer s povezavami definiramo interakcije med njimi. Zato takim modelom pravimo tudi mrežni modeli. Z njimi lahko modeliramo heterogeno širjenje bolezni, vendar praviloma potrebujemo mnogo podatkov za določanje parametrov modela. Zato so lahko ob pomanjkanju teh podatkov rezultati agentnega modela zelo nenatančni (Keeling & Rohani, 2008).

Minimalne zahteve pri epidemiološkem modeliranju morajo upoštevati dinamiko procesa širjenja epidemije, pri čemer morajo biti parametri modelov ocenjeni ali določeni tako, da se projekcije modela ujemajo s predhodnim stanjem epidemije, saj le tako epidemiološki model lahko uporabljamo za napovedi in simulacije širjenja epidemije v prihodnosti. Vendar moramo biti tudi pri tem pozorni na interpretacijo rezultatov. Dinamika širjenja epidemije je namreč zelo odvisna od obnašanja posameznikov v epidemiji, npr. koliko stikom z okuženimi osebami je izpostavljen posameznik, kako se varovalno obnaša ali kako upošteva druge vladne ukrepe za preprečevanje širjenja okužbe COVID-19. Tega z modeli ne moremo v celoti predvideti. Zato moramo v epidemiološke modele vključevati določene predpostavke, ki jih lahko uporabljamo predvsem za simulacije različnih scenarijev možnih potekov epidemije ob izpolnjenih ali neizpolnjenih predpostavkah. Kljub temu oziroma ravno zaradi tega pa so epidemiološki modeli lahko zelo uporabni.

Z epidemiološkimi modeli lahko hitro pokažemo, da je sploščevanje krivulje okuženih in posledično bolnišničnih obravnjav odvisno od  $t$ , i. e. reprodukcijskega števila  $R$ . To je število, ki pove, koliko ljudi v poprečju okuži ena okužena oseba v epidemiji. Če je število  $R$  večje od 1, epidemija eksponentno narašča; če je  $R$  okoli 1, se epidemija širi konstantno (v povprečju zbolji in ozdravi

enako število ljudi); če je  $R$  manjši kot 1, epidemija upada. Večji kot je  $R$ , več okuženih bomo v nekem trenutku imeli, kar posledično pomeni večjo obremenitev zdravstvenega sistema. Nižji kot je  $R$  (še vedno večji od 1), bolj je krivulja okuženih sploščena in epidemija traja dlje časa, zdravstveni sistem pa je posledično manj, a dlje obremenjen. Z modeli lahko pokažemo tudi, da je treba ukrepe izvajati čim bolj restriktivno, s čimer v procesu širjenja epidemije, kolikor se da in čim prej, znižamo  $R$ . Na ta način lahko bolj nadziramo potek epidemije oziroma jo popolnoma omejimo. Pomembna ugotovitev je tudi, da upadanje epidemije traja dlje časa kot naraščanje oziroma da potrebujemo več časa za vzpostavitev izhodiščnega stanja kot za prehod od izhodiščnega stanja do vrha epidemije.

Nadalje lahko z dodajanjem novih skupin v oddelčne modele preučujemo vpliv bolj in manj rizičnih skupin na dinamiko širjenja epidemije. Ob tem je pomembna ugotovitev, da lahko že številčno razmeroma majhna skupina posameznikov, ki se obnašajo bolj rizično in s tem bolj širijo okužbo, znatno vpliva na celoten potek širjenja epidemije v neki populaciji. Tako lahko na primer ugotovimo, da že 10 % populacije, ki ima trikrat več rizičnih stikov, povzroči za 40 % višje maksimalne vrednosti števila okuženih v populaciji. Podobno lahko ugotovimo, da pojav novih sevov virusa v epidemiji, ki so na primer bolj virulentni, znatno spremeni dinamiko širjenja virusa in s tem tudi potek epidemije ukrepom navkljub. Z dodajanjem novih skupin v epidemiološke modele lahko simuliramo tudi vpliv cepljenja na potek epidemije. S tem lahko pokažemo, da je treba s cepljenjem doseči čredno imunost za zaustavitev širjenja epidemije, ki je odvisna od reprodukcijskega števila  $R$  in jo dosežemo ob precepljenosti populacije najmanj v deležu  $1-1/R$ .

Z bolj kompleksnim epidemiološkim modeliranjem lahko simuliramo tudi poteke epidemije z vključenimi različnimi ukrepi, ki so bolj usmerjeni v posamezne skupine populacije: na primer sproščanje ukrepov v šolstvu v kombinaciji s cepljenjem starejše populacije ob prisotnosti novih različic virusa. Takšna simulacija je npr. za Slovenijo narejena s pomočjo modela SEIR C19 SI in dostopna na spletni strani Rpubs (Žibert, 2021).

Podobno lahko uporabimo modele za načrtovanje bolnišničnih kapacitet v epidemiji. Tako se na primer pokaže, da čas obravnave pacienta v bolnišnici ali na intenzivnem oddelku lahko znatno vpliva na obremenjenost bolnišničnih kapacitet ob hitrem širjenju epidemije. V povprečju lahko že dan krajša obravnava pacientov na intenzivnih ali splošnih oddelkih bolnišnic pomembno zniža celotno obremenjenost bolnišničnega sistema ob hitrem širjenju epidemije. Zato je vključevanje epidemioloških modelov v načrtovanje, analiziranje in upravljanje z epidemijo v ekstremnih razmerah, kot je pandemija COVID-19, izjemno pomembno.

Pri tem imajo pomembno vlogo tudi zdravstveni delavci, ki so zgled upoštevanja vladnih ukrepov

za obvladovanje epidemije, razumejo ukrepe in pomagajo ozaveščati laično javnost o njihovem pomenu (Prosen, 2020). Opozoriti je treba, da brez dobrih vhodnih podatkov ni mogoče narediti dobrega napovednega modela, zato je pomembno, da se vodijo protokoli obravnave in registri bolnikov s COVID-19, da so podatki zbrani natančno in dosledno ter da so v anonimizirani obliki dostopni razvijalcem napovednih epidemioloških modelov. Pomembno je tudi, da znajo zdravstveni delavci napovedne modele uporabljati pri svojem delu, predvsem z vidika načrtovanja priliva bolnikov, lažjih in težjih oblik, zasedenosti postelj na posameznih oddelkih in enotah, načrtovanja delovnega procesa in kadrovske obremenitve.

## Conflict of interest / Nasprotje interesov

Avtorji izjavljajo, da ni nasprotja interesov. / The authors confirm that there are no known conflict of interest.

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