

**REFLECTION ON CONTEXTUAL FACTORS ASSOCIATED
WITH BURDEN OF INFECTIOUS DISEASES IN MULTI-COUNTRY
MODELLING APPROACH ON THE EXAMPLE
OF EASTERN EUROPE**

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Abstract

Thesis. The use of mathematical models to nowcast and forecast allows to improve predictive understanding of epidemiological targets and indexes among various populations during infectious disease epidemics. Such models enable trend predictions of various scenarios of the pandemic and guiding epidemic prevention and control.

Concept. In order to avoid the influence of low-quality studies (for a given region) on the interpretation and decision making, a critical analysis based on experience in field epidemiology should be carried out. For the sake of transparency and quality of scientific discourse, such observations should indeed be collected and discussed by the scientific and medical community. Selected global modelling studies have been assessed according to their epidemiological outcomes such as cases and deaths.

Results and Conclusions: I show that the discrepancy between reported and predicted epidemiological features varies more significantly than the order of magnitude between the countries in selected models. My findings highlight that models' results; readers should prefer locally developed models over multi-country models, even those being published in prestigious journals. Thus, agent based models should be prioritised against system dynamics or machine learning models. I suggest that future epidemiological models should adopt health-care access as a factor of so-called dark figure of infections, especially in Eastern Europe.

Keywords: COVID-19, mathematical modelling, e-health, methodology

EPIDEMIOLOGICAL INTRODUCTION

Mathematical modelling offers a theoretical and practical framework to simulate the spread of infectious diseases in populations by providing trajectories that may guide decision-makers to formulate policy measures to limit the epidemic (Squazzoni et al., 2020). One can incorporate pharmacological and behavioural techniques into the models for COVID-19 mitigation strategies, such as those suggested by Jarynowski, Wójta-Kempa & Krzowski (2020):

- reducing contacts (e.g., isolation, physical distancing and restrictions on mobility, i.e., “physical distancing” and “lockdown”);
- reducing the probability of infection (e.g., vaccinations, standard isolation such as hygiene and use of personal protective equipment as masks, and immunomodulation as well as promotion of a healthy lifestyle);
- reducing the duration of effective infectivity (e.g., vaccinations, treatment, contact tracing and isolating, and testing).

The results of the modelling studies have always had a huge impact on public health decision-making in some countries (and only to a lesser extent in Eastern Europe). Models allow to conduct epidemiological analyses of disease burden, health economic and to derive estimates for the effectiveness of pharmacological approach (e.g., vaccination or treatment) as well as non-pharmaceutical interventions (NPIs). In particular, these models can estimate the number of subjects who are: latent (during incubation period), infectious symptomatic (severe/not severe), infectious non-symptomatic, hospitalised, occupying ICU bed, partly recovered/immunised, and dead. Nowcasting can be used to adjust reported infection/death cases daily to the real burden of the disease. Infection control decisions may be based on an empirical or prognostic foundation (thus mathematical models could help), but in Eastern Europe too often political interests were more important than medical knowledge (Duszyński, et al., 2020). Due to uncertainty of what type of variant would next emerge (i.e., waning immunity, different infectivity, virulence), models must remain vigilant for better adjustment to the next phase of the COVID-19 pandemic (Shankar et al., 2021). Thus, in this paper I discuss the performance of ensembles in nowcasting and forecasting COVID-19 cases and deaths across Eastern European countries.

MATHEMATICAL INTRODUCTION

Various mathematical models were applied to predict the epidemiological consequences of the COVID-19 pandemic (Shankar et al., 2021). There are three main categories of models (ECDC, 2022; Jarynowski et al., 2019):

System dynamics (SD). Differential equations (used by system dynamics) were applied to describe and predict those phenomena first (one can solve some epidemic equations analytically, numerically or by simulations). These simple models (can be stochastic or deterministic) often assume homogeneous mixing within a population, i.e., that individuals mix randomly and uniformly with each

other and that everyone is equally likely to infect everyone else in the given sub-population. Worth mentioning here are the analysed models (Barber et al., 2022; Bollyky et al., 2022; Watson et al., 2022) as well as other famous COVID-19 models from Institute for Health Metrics and Evaluation WA, USA (Jr Reiner et al., 2022) or London School of Hygiene & Tropical Medicine/Imperial College (Ferguson et al., 2020). They usually have poor short- and medium-term predictability (lack of adaptability to non-smooth changes in non-stationary parameters), but may be satisfactory in the long-term (ECDC, 2022).

Agent-based models. ABM is a computational technique used for experiments with artificial systems populated by agents that interact in non-trivial ways. In reality, individuals behave heterogeneously and mix with other individuals based on their own contact patterns depending on age, geography, social settings, and also severity of symptoms of potential infectious agents or fear of acquiring infection. Additionally, human contact patterns as well as aetiology of infections (with changing variants or immunity status) are often dynamic over time. Recently, in the COVID-19 era, agent-based models have been appearing even more often. Models which describe the transmission of the pathogen among hosts rely on a correct model formulation and parametrisation of the patterns of contact between infectious and susceptible individuals with proper estimation of infection upon given contact time (Rakowski, 2020). ABMs are usually the best in the medium-term and are also satisfactory in short and long-term windows (ECDC, 2022).

Machine/deep learning models (ML). Alongside efficient computational algorithms, the data-driven analytical approaches allow for prediction of epidemiological outcomes based on labelled historical data (not only epidemiological, but multiple sources such as medical procedures count, economic indexes, weather conditions, opinion poll etc.). ML models are almost always the best in forecasting outcome variables in short-term and some-times in medium-term, but do not work at all in long-term (ECDC, 2022).

Sometimes the same epidemiological problem could be solved in multiple ways. Because computer simulation has changed the world of mathematical modelling, agent-based models usually give better predictions and some hints for decision-makers, even parallel to the development of numerical methods for differential equations. On the other hand, differential equations allow us to understand the core process, which could be missing in the agent-based approach. Machine learning approaches are usually black-boxes and could lead to overfitting. Thus, SD and ABM perspectives are common among specialists and depending on the theoretical or applied aspects, their percentage representations differ (Jarynowski et al., 2019).

OBJECTIVES

The primary goal of this article is a critical analysis of selected mathematical multi-country models prepared for decision-making during pandemics, specially tailored to the Eastern European population. Understanding socio-epidemiolo-

logical background of infection disease dynamics is an extremely difficult task and this problem was professionally approached in several latest Lancet papers (Barber et al., 2022; Bollyky et al., 2022; Watson et al., 2022). However, some concerns in interpretation and limitation need additional discussion. As authors used fit-all-size methodology, they could lose precision due to heterogeneity of given regions. Thus, estimated variation in the COVID-19 outcomes in geography on global scale could be far from reality on the local scale. The cumulative effect of simplifications made in multi-country models is quite noticeable. Reader should be aware that the models which use real data in whatever aspects and process inputs could become a base for medical guidelines (Squazzoni et al., 2020). Thus, I call to improve the methodology of models' verification with the field experience and epidemiological knowledge.

RESULTS

Many scientists attempt to reveal the "epidemiological mystery" of COVID-19: why the coronavirus hit some regions so much harder than others and how it corresponds with measurable epidemiological indexes. This and a few other modeling and epidemiological paradoxes (in which different regions are compared on populational level) such as effectiveness of pharmaceutical intervention (e.g. vaccination) or NPIs (e.g. lockdowns) need to be carefully assessed if they are interpreted correctly according to epidemiological knowledge. There were plenty attempts to assess the impact of government-induced interventions such as mandatory mask wearing, school closures, contact tracing, banning of public events and "lockdowns" in early phases of the pandemic. Moreover, an increasing number of studies incorporate vaccinations with multiple available vaccines or treatment (i.e. Paxlovid, Molnupiravir). Unfortunately, even with a correct statistical model (without understanding underlying socio-epidemiological variables), by comparing incidences in different regions one could easily underestimate effectiveness of NPI (Herby et al., 2022) or vaccination (Subramanian & Kumar, 2021) (even unintentionally) or it could also lead to manipulation (for instance one could pick up only these indices which support a given thesis). This is a well discussed tactic of selectivity with mechanism of cherry-picking of data for statistical significance (Ioannidis, 2005).

I have decided to share my opinion because:

- it is easy to provide an example of mismatch between model prediction in the Lancet papers and what we are observing in Eastern Europe on geographical scale (Bollyky et al., 2022; Jarynowski & Belik, 2021; Watson et al., 2022);
- of own experience and research on the role of social capital on infection dynamics in Europe (Jarynowski, 2021; Jarynowski, Wójta-Kempa, Krzowski, 2020; Jarynowski et al., 2020; Jarynowski, Semenov, Wójta-Kempa et al., 2021; Jarynowski & Skawina, 2021), which cannot be simplified into few variables chosen by Lancet authors;
- of focus on Eastern Europe sharing similar patterns in the way in which the societies function and how people seek healthcare services and trust in medi-

cal authorities (Jarynowski, Semenov, Kamiński et al., 2021; Jarynowski & Wójta-Kempa, 2021), where models proposed by scientists from CDC (Centre for Disease Control, USA)/Imperial College (London, UK) do not need to work;

- wanting to stress the need for regional and local research (Stochmal et al., 2021) to really understand epidemic processes in European countries.

I would like to closely examine the post-communist, Slavic majority Eastern Europe countries as an example since their public health systems, political transformations, alternative social capitals and second demographic transitions follow similar patterns (Jarynowski, 2021). One should certainly be alarmed if they were to compare the reported case notifications (Our World in data, 2022) with infection standardised estimates (Bollyky et al., 2022) per 1000 inhabitants for the same time period for Slovakia 147 (166), Poland 76 (469) and Russia 50 (1165). Thus, cumulative cases till the end of the so-called European 3rd wave (so called “dark figure”) were estimated to be from 1.13-fold to 23.3-fold greater than the confirmed cases for Slovakia and Russia respectively. Even having in mind that Slovakia performed all country cross-sectional studies on COVID-19 prevalence and Russia has been accused of manipulating infection registries since the times of the HIV epidemic according to some studies (Rechel, 2010), such a difference is rather impossible to be true. Moreover, death toll (if no vaccination is applied) based on crude death registry as well as expected death estimation (in bracket) per 1000 inhabitants for the first year of vaccination roll-out were calculated (Watson et al., 2022) for Poland 7.9 (9.0), Russia 5.2 (12.8), Czechia 9.9 (10.0). Thus, the corrected death tolls using expected deaths were estimated from 1.01-fold to 2.46-fold greater than the crude deaths for Czechia and Russia respectively. Once again, death registries in Russia are known to be flawed (Danilova et al., 2016), yet the Czech mortality registry is working relatively well (Kossarova et al., 2013). All this being said, such a variation is extremely unlikely.

CONCLUSIONS

This could lead to the conclusion that even a well performing estimation method on a global scale may be really poor in some particular regions. I guess that possibly Healthcare Access (*sensu lato* with affective and behavioural components (Jarynowski & Belik, 2021)), which was found not to be associated with epidemiological outcomes (Bollyky et al., 2022) should be revisited. Therefore, published models have a great advantage of modelling from a global perspective, but on the other hand, due limitations raised here, together with those already indicated by authors (Barber et al., 2022; Bollyky et al., 2022; Watson et al., 2022), more emphasis should be placed on regional research, especially on intra-country variability. It makes it impossible for taking anything practical from these models to Eastern European countries to the satisfactory scientific level of discussion. To support the governing bodies in their decision-making process, models must allow for fine-

grained geographical resolution (for instance LAU-2 level). A special focus should be put on the conceptualisation of the model, incorporating expertise from different disciplines and a realistic model structure that takes into account heterogeneities in the population structure, intra- and inter-individual contacts, mobility, access to healthcare with individual sociological and psychological characteristics and epidemiological measures with a framework for decision-making linked to public health. The core message of this study is that there are significant biases in the commented Lancet (Bollyky et al., 2022; Watson et al., 2022) articles and estimated variation in the COVID-19 outcomes in geography on global scale could be far from reality on local scale (Niedzielewski et al., 2022).

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