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IFAC PapersOnLine 55-10 (2022) 2902–2907

Agent-based simulation for vaccination networks design and analysis: preliminary gaps

Piffari, C.*, Lagorio, A.*, Pinto, R.*

* *Department of Management, Information and Production Engineering, University of Bergamo, Italy (e-mail: claudia.piffari@unibg.it; alexandra.lagorio@unibg.it; roberto.pinto@unibg.it)*

Abstract: During an epidemic or a pandemic emergency, various approaches are undertaken to contain the infectious disease spread. Some of the most common interventions are lockdowns, social distancing, contact tracing and the use of personal protective equipment. However, whenever available, the most helpful intervention is the administration of vaccinations. Countermeasures need to be taken as quickly as possible in emergencies, but predicting their full consequences and effects is often difficult, mainly because there is no room for trial-and-error approaches. Simulation – in its different implementations – represents a useful approach for modelling and analysing reality and predicting the evolution of a real-world system. Agent-based models could be particularly beneficial as they allow for modelling each individual as a distinct entity, thereby enabling the evaluation of the effects of public policies in the field of interest. This paper reviews the existing literature on agent-based simulation for vaccine distribution and administration. This work highlights areas where agent-based simulation has been most utilised and areas that could be explored further. Specifically, the most significant gaps are the lack of application of agent-based simulations to vaccine distribution networks and the lack of consideration given to resources requirements and costs associated with alternative vaccine administration methods to citizenship.

Keywords: Vaccination network, Pandemic, Epidemic, Emergency, Activity-Based Modelling, Simulation.

1. INTRODUCTION

As the world is experiencing, the risk of epidemics and pandemics is extremely high (Batistela et al., 2021). In a few months, the Sars-Cov-2 spread from the epicentre in the Hubei region to the whole world, forcing governments to adopt drastic containment solutions. Various approaches were undertaken during the early stages of the pandemic: lockdowns, social distancing, contact tracing and the use of personal protective equipment (PPE). These measures were aimed at limiting the spread of the virus until the arrival of effective vaccines that would mitigate virus transmission without the necessity of restriction on the social and economic life of individuals. As the months passed, interest and studies on the effectiveness of pharmacological and non-pharmacological interventions undertaken to combat the pandemic multiplied. One of the most widely used methodologies to this scope is the simulation. Simulation has been researched and applied successfully to model real-world processes. The results gathered from the simulation indicate how the real system behaves (Sulistio et al., 2004). When it comes to simulation, there are four main methods in use: (1) Discrete Event Simulation (DES), which models the process of interest as a series of discrete events, namely state changes at precise points in simulated time (Rashidi, 2017); (2) System Dynamics (SD), which focuses more on flows around networks (Borshchev et al., 2004); (3) Agent-Based Modelling (ABM) consisting of autonomous agents which follow a series of predefined rules to achieve their objectives whilst interacting with each other and their environment (Rondini et al., 2017);(4) Hybrid systems, which combine the features and the advantages of two or more of these approaches, integrating the specific features from the different techniques (Cimini et al., 2021). In the healthcare context, simulation can be used to analyse interventions' effects on diseases outbreaks, and many studies have been conducted in this respect (Bissett et al., 2021). In ABM, in particular, each entity of a population (i.e. humans) is represented as a distinct agent, allowing to model complex, heterogeneous, and distributed environments in a realistic way (Isern et al., 2010). The global system behaviour emerges as a result of the simulation of the behaviour of many individuals (i.e. agents), each following its own rules (Borshchev et al., 2004). This type of model allows performing studies at an individual level to evaluate the effects of public policy during an emerging infectious disease (Barrett et al., 2011). This paper aims to analyse the application of ABM to simulate the distribution chain of vaccines. This pharmacological measure is essential for infectious diseases management; therefore, the management of the distribution chain is a key factor for the success of pandemic control measures. In an effort to fully understand the effects of vaccinations, it is important to consider that vaccines not only provide individual protection for those people who are vaccinated: they can also provide community protection by reducing the spread of disease within a population (Orenstein et al., 2017). Indeed, agent-based models allow for a more complete representation of the social contact network in which contagion occurs, allowing a deeper understanding of the effect of vaccination on the considered disease diffusion

10.1016/j.ifacol.2022.10.172

(Chang et al., 2020). Secondly, by focusing on the relationship between an entity in the real world and its corresponding entity in the "electronic world" (Daknou et al., 2009), the design and analysis of the vaccination network can become easier and quicker. Finally, agents, which usually represent individuals, can contain information about their preferences and take them into account to provide vaccination procedures and networks tailored to them (Isern et al., 2010).

1.1 Goal and structure of the paper

In consideration of the complex – and somehow volatile and uncertainty-based – decision-making processes that are required during a pandemic, we deem interesting to investigate the use of ABM to support decision-makers. ABM can be useful for the design and management of various types of processes. The advantage is that it makes it possible to map the preferences and choices of each of the relevant actors involved. ABM can thus simplify decision-making by comparing alternative scenarios. The relevance of simulation in the healthcare sector, in particular agent-based simulation, led us to perform a literature review inherent the themes of ABM applied to the process of distribution and administration of vaccines. This paper aims to highlight gaps in the existing literature that need further investigation where analysis is less thorough. Based on any gaps identified, suggestions for future research will be made. For example, fields or issues that could be investigated using ABM. In this way, it will be possible to understand in which areas there is a greater need to focus research and should be investigated more to support public health decisions. Such suggestions will be mainly focused on the vaccine distribution chain, but the same kind of approach could be applied to the design and management of other logistic networks. The manuscript is organized as follows: the criteria used for the definition of the corpus for the literature review are reported in section 2; the analysis of the results is highlighted in section 3. Section 4 outlines gaps derived from the literature review and directions for future research. Conclusion and future work are addressed in the last section.

2. CORPUS DEFINITION FOR THE LITERATURE REVIEW

We analysed the literature on agent-based simulation applied to the vaccination process (including the distribution of the vaccines on the territory) to evaluate the current state of research. The query formulated for the search was as follows: ((simulation OR model*) AND "agent based" AND vaccin*), with the aim of including as many papers as possible on this topic. We restricted the search to papers of the last 10 years (from 2012 to 2021) to include research prior to the Sars-Cov-2 pandemic, and capture the evolution of this type of simulations in recent years. We selected only scientific papers, conference papers, and reviews in English language. The search was launched on the Scopus database, which is one of the most complete scientific papers' database (Araújo et al., 2020), and produced 279 results. Reading the title and abstract of each paper, we excluded 225 papers because they were not related to vaccination from an operational point of view: many papers were focused on the medical aspect of vaccination effects and consequently were removed as they were not within the topic of this article. Finally, some articles include agent-based simulation focusing mainly on the effect of the non-pharmaceutical intervention and were consequently excluded since vaccines had a marginal consideration. The remaining 54 articles were read and categorized according to the objective of the agent-based simulation used within them (see Table 1). For space constraints, in Table 1 are reported only the ID of the papers. The complete list of papers included in the study with the corresponding ID is available at the following link. The interest in this subject has progressively increased. The most relevant increase occurred in the year 2021, with 31 papers published.

3. RESULTS OF THE ANALYSIS

3.1 Infectious diseases containment strategies

As reported in Table 1, most papers concern the analysis through agent-based simulation of the effects of various strategies to contain an epidemic. The models used by researchers differ according to inputs and outputs considered. However, their functioning can be summarized as follows (see Figure 1): the agents in the model represent individuals with their own personal characteristics (i.e., age, gender) and preferences. During simulation period individuals carry out activities interacting with other agents. Agents' behaviour is influenced by the external environment: environmental, epidemiological, demographic factors. ABM makes it

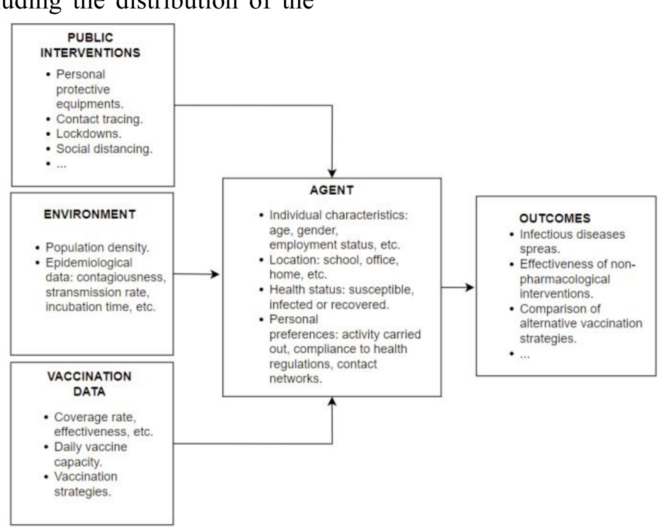

Figure 1: general scheme of the ABM used in the selected papers.

Table 1: Topic of the selected papers

Topic	Sub-topic	Papers (codes)
Infectious diseases containment strategies	Multiple interventions (i.e., face mask, social distancing, positive quarantine, contact tracing, closure)	• Country level: 12, 11, 30, 27, 22, 51 • City level: 19, 42, 48, 17 • School level: 5 • Long-term facility care level: 43 • Public indoor venue: 50
	School closure	23
	Testing	10, 16, 41, 39
	Contact tracing	8
	Individual protective behaviour	15
	Long-term strategies	45, 40
Vaccination strategies	Vaccination effects	• Vaccination campaign effect on virus spread: 44, 46, 1, 47, 35, 7, 53, 54, 13, 28, 20 • Human interaction effect: 52
	Vaccine scheduling	26, 34, 32, 33
	Population prioritization	• Risk prioritization: 29, 25, 9, 31, 14, 6, 39, 18, 38, 36 • Spatial prioritization: 21, 49, 28, 37, 24
	Vaccinal hubs	• Single hub layout design and management: 2, 3 • Vaccination in traditional location vs. pharmacies: 4

possible to realistically simulate the social contact network in which contagion occurs and to detect valuable outputs of interest (i.e., virus spread, public interventions efficacy, cost-effectiveness of alternative scenarios). Only five articles were conducted prior to Sars-Cov-2 pandemic while all the others are inherent to the pandemic. The cause of this could be that previous epidemics have mainly occurred in third world countries with fewer resources available for research activities. Covid has led to an explosion of these topics even in more developed countries with higher resources. This does not reduce the importance of this topic to the narrow case of the Sars-Cov-2 pandemic: the results obtained could be applied to improve countermeasures in case of new epidemics or to support healthcare decision-making in developing countries. Regarding the papers carried out after the spread of the Sars-Cov-2 pandemic, thus from 2020 onwards, most concern the combined analysis of the effects of pharmacological and multiple non-pharmacological strategies (i.e., face masks, social distancing, positive quarantine, contact tracing, closure) on virus containment. Of these, ten papers carried out the analysis at country or city level. Only three at smaller-setting level, in detail at school level (Bilinski et al., 2021), at long-term care facility level (Vilches et al., 2021) and at public indoor venue (Zhou S. et al., 2021). Other papers focus instead on the analysis of the effects of vaccines combined with a single non-pharmacological strategy. This second approach does not consider the interaction between alternative interventions even though the effectiveness of a public health intervention may be contingent on the other interventions being implemented (Beeler et al., 2012). Only two papers address the return to normality, evaluating not only how to contain possible Sars-Cov-2 outbreaks in the short term, as most papers do, but examining long-term strategies to coexist with a possible pandemic (Truszkowska, et al., 2021b). In the considered papers concerning pharmaceutical and non-pharmaceutical strategies to contain an epidemic, the goodness of the different scenarios was evaluated mainly based on epidemiological indicators (i.e., number of infected, number of hospitalizations, number of deaths); only one also considers the economic aspects associated with the different strategies (Moosavi et al., 2014). In addition, in the previous papers, vaccination was introduced into the models as a method of reducing virus spread added to non-pharmaceutical control strategies; the single value of vaccination was little investigated.

3.1 Vaccination effects

In the remaining thirty-three articles, the individual effect of vaccinations on the infectious disease under investigation is analysed. The vaccine is evaluated as the predominant intervention. The ABM models used in this second group can be schematised in a similar way to the previous paragraph (Figure 1). Instead of focusing on the effect of non-pharmaceutical strategies, the scenarios carried out aim to compare different vaccination strategies (i.e., risk prioritisation vs. spatial prioritisation, alternative vaccination schedule). In twelve papers, the isolated effect of vaccine administration on virus spread was investigated so that non-pharmaceutical restrictions could be reduced and relaxed. These papers compare different rates of population vaccination, different levels of efficacy (Alagoz et al., 2021) and different speeds of whole population vaccination (Sah et al., 2021). Some papers focus on the optimal vaccination scheduling in order to achieve the maximum benefit from population immunization point of view (Moghadas et al., 2021). Most papers deal with the development of agent-based models to identify optimal vaccination prioritization strategies in case of an epidemic. Of these, some suggest that vaccinating youth and students first has a greater effect on reducing infection (Markovič et al., 2021). Two articles report instead that to reduce hospitalizations and deaths from Covid-19, the best strategy is to vaccinate the elderly and frail people first (Jahn et al., 2021). Truszkowska, et al. (2021a) performed a comparative analysis of different vaccination strategies.

Specifically, evaluating the effect of vaccinating only high-risk groups of individuals, hospital, school, or retirement home employees or residents and compare the results to a random immunization across the entire population. Lee et al. (2015) studied the effect of vaccination prioritization versus a random strategy concluding that the more transmissible the virus is, the lower the threshold for switching to nonprioritized vaccination. Tatapudi et al. (2021) suggested that instead of adhering strictly to a sequential prioritizing strategy, the focus should perhaps be on distributing the vaccines among all eligible as quickly as possible, after providing for the most vulnerable. Li et al., (2018) also incorporated considerations of inventory levels in vaccinal hubs. Few of them have also considered the spatial prioritization strategy. Zhou Y. et al. (2021) showed that space-age strategy requires 30%-40% vaccine coverage to control the epidemic, comparatively that for a random strategy is 60%-70%. A paper (Nadini et al., 2020) evaluated vaccination's spatial prioritization, supporting the intuition that vaccination in central and dense areas should be prioritized. Sill regarding vaccination, some agent-based models have focused on analysing the optimal layout of vaccination hubs in order to reduce queues, maximize throughput, and optimize resource utilization (Asgary et al., 2020, 2021). To the best of our knowledge, there are currently no agent-based simulations regarding vaccinal-hub-network design and management in a territory of interest. Only one (Bartsch et al., 2018) performed a comparison of in-hospital versus in-pharmacy administration of vaccines, comparing different scenarios using the incremental cost-effectiveness ratio (ICER). Even in this second group of papers dealing with vaccination as a single intervention, the goodness of the different scenarios was evaluated mainly based on epidemiological indicators. Studies also considering the economic aspects or resource requirements are limited.

4. IDENTIFIED GAPS AND RESEARCH AGENDA

As observed in the literature, most papers focus on the vaccination effects on Sars-Cov-2 spread and diffusion, evaluating the impact of vaccination and different vaccination strategies on the virus spread or evaluating simultaneously pharmaceutical and non-pharmaceutical interventions. This section outlines the main research gaps that emerged from the literature review.

4.1 Vaccination distribution network

One of the main gaps in the analysed literature is that there is only a limited consideration of alternative vaccine distribution methods. Most of the papers considering this aspect focus on the population prioritization for the access to vaccination, while the evaluation of the network for vaccine delivery to citizens is often neglected. Currently, such analysis has only been performed regarding a single vaccine centre (Asgary et al., 2020, 2021). Only Bartsch et al. (2018) conducted a cost-effectiveness comparison between administering vaccines only in hospitals or also in pharmacies. Regardless of the type of hub, appropriate planning and process design are essential to success. Vaccination hubs planning efforts should address the numerous complex design features, possible logistical entanglements, and anticipate challenges inherent to large-scale vaccine delivery, even more considering the vaccine distribution network consisting of multiple centres. Consequently, other alternative scenarios (i.e., general practitioner offices, clinic ambulatory, massive hubs) can be modelled and evaluated with an agent-based simulation too, in order to capture the individual preferences and to assess the costs, resource requirements and effectiveness of each method. In addition, a limited number of large hubs could lead to a higher contact rate and consequently higher virus spread, while small capillary ambulatory could reduce this possibility (Morawska et al., 2020). Additionally, large hubs opened specifically during a pandemic scenario are short-term solutions. For example, in the Italian region of Lombardy, anti-Sars-Cov-2 vaccinations were largely carried out in hubs built inside sports halls and consequently disrupting the regular activity of those places. Therefore, assessing the effectiveness of alternative delivery methods could be helpful to reduce these limitations. Additionally, the application of ABM simulation could provide great support not only for the design of the vaccine distribution network but also in other logistic fields. Using ABM allows evaluating alternative logistic scenarios taking also into account the preferences of all agents involved. Accordingly, ABM provides decision-makers with robust and accurate "what-if" scenarios of the dynamic interplay among several business functions. These scenarios can guide managers in the process of moving from policy space to performance space (Nilsson et al., 2006).

4.2 Emergency preparedness

Comparing solutions applied during the Covid-19 pandemic phase with alternatives could strengthen existing systems, which can be used as a basis for intervention during possible pandemics. Indeed, preparedness should aim to strengthen existing systems rather than develop new ones (European Centre for Disease Prevention and Control). Most of the papers on agent-based simulation do not evaluate the interventions with the objective of a return to normality. Only two (Truszkowska, et al., 2021b) actually consider that such interventions should provide a restriction reduction for long-term coexistence with the virus. This is an area of research that could be further investigated to respond to any pandemic with robust and flexible solutions that can be used in the inter-pandemic period and strengthen the health system. Another important element for effective pandemic preparedness is access to adequate funding. The cost of a pandemic can be extremely far-reaching. To ensure the success of pandemic financing preparedness, countries should engage in dialogue on the importance of investing in such preparedness (Osewe, 2017). However, the majority of papers compare alternative scenarios of interventions to control the spread of epidemics primarily with epidemiological indicators: virus diffusion, stringency of non-pharmaceutical intervention (Zachreson et al., 2021), date after which the number of cases is under a threshold (Alagoz et al., 2021), number of hospitalization and deaths (Sah et al., 2021). One paper also considers direct and societal costs associated with infections (Bartsch et al., 2018) and Ozaltin et al., (2015) consider the cost reduction of alternative strategies. To the best of our knowledge, there are no other agent-based simulations considering human and material resources required in alternative administration scenarios that could impact the system's sustainability and efficiency and influence the funds allocated to pandemic preparedness.

4.3 Research agenda: a first attempt

In light of the results obtained from the literature review, we propose possible future developments to fill the gaps highlighted. This could be helpful to improve the decision-making process regarding vaccination but could be applied to other sectors as well. Indeed, ABM models are particularly suited to model complex systems: agents can adapt their behaviour based on their own characteristics, on the characteristics of other agents, and on the environments capturing the complexity of real systems. This explains why further research with such models could be useful. In conclusion, possible goals of future research on agent-based simulation for vaccine administration should focus on the following research opportunities: (1) comparing alternative vaccine delivery scenarios which could also be used in ordinary situations without disrupting the activities of large facilities built with other purposes, strengthening at the same time pre-existing vaccinal system (i.e. general practitioner ambulatory, pharmacies); (2) reviewing and evaluating decisions made throughout the pandemic period not only from the epidemiological point of view: resources requirements, costs and patient flows should also be considered; (3) testing new systems implemented during a pandemic during the inter-pandemic period (European Centre for Disease Prevention and Control); (4) studying the vaccination and non-pharmaceutical intervention with a view to return to normality and long-term solution helpful in strengthening the preparedness for other epidemic or pandemic situation instead of short-term intervention. In conclusion, to bridge the gap uncovered by the literature review, we propose the following research questions that summarise the main gaps highlighted and that could be investigated through the application of ABM, such as: what is the optimal vaccine distribution network that can be used both in emergencies (i.e., pandemics) and in routine situations and that could strengthen the pandemic preparedness?; what is the impact of different methods of vaccine distribution in terms of resources needed, costs, patient flow and epidemiological consequences?. Further research could also focus on the application of ABM in other fields. In fact, ABM, taking into account the choices and preferences of various actors involved, allows to analyse and compare alternative scenarios useful for the design and management of logistics networks in various sectors, not only healthcare.

5. CONCLUSIONS

Simulations and modelling acquired more and more importance in the epidemiological sector, particularly after Sars-Cov-2 advent. Agent-based simulations are one of the most widely used methods since they allow modelling of behaviour and preferences at an individual level. This paper reviewed the existing literature on agent-based simulation for vaccine distribution, particularly during a pandemic scenario. This work highlighted areas where simulation has been most utilized and areas that could be explored further. The results presented in this paper do have some limitations: the selected papers refer only to the last ten years, and consequently, there might be papers in previous years with relevant analyses on vaccine distribution, particularly following the H1N1 influenza outbreak of 2009. In addition, this paper favoured agent-based simulations; it might be helpful to compare the suitability of other types of simulation models as well. In conclusion, future research should extend the analysis of the current literature, and build models to fill the gaps highlighted in the previous paragraph on agent-based simulation applied to the vaccine distribution process.

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