APPLICATIONS OF OPERATIONS RESEARCH/STATISTICS IN INFECTION OUTBREAK MANAGEMENT.

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ABSTRACT.

Operations Research (OR) can be identified as the discipline that uses statistics, mathematics, computer-modelling and similar science methodology for decision making [10]. Surprisingly, very little OR/statistics research has been aimed at infection outbreak management: usually, other general epidemiology issues were tackled in models. However, OR/statistics models for that exist. The present paper aimed at filling that gap and providing two benefits contributions: first, developing awareness on the use and benefits of OR/statistics models for the infection outbreak management decision making, and second for plotting the current state of affairs to highlight research opportunities.

INTRODUCTION TO OR/STATISTICS USE IN INFECTION OUTBREAKS.

Operations Research (OR) can be identified as the discipline that uses statistics, mathematics, computer-modelling and similar science methodology for decision making [10]. According to consensual views, OR was born during World War II to support military operations. Applications of those days were radar defence systems, anti-submarine systems, bombing strategies etc. Upon the end of the war, OR was employed by leading industrial organizations to re-engineer and improve efficiency of business and manufacturing processes [10].

There is little done to provide a review of OR/MS applied research for use in epidemics control. That review will be welcome by both OR/MS community and the epidemics control and management authority. OR can address a number of problems facing epidemics management: how to allocate resources among options to better control outbreak or spread of a disease within population(s), what resources needed to control a disease within population(s), which resources to employ for disease control interventions etc.[4].

Conceptually, tackling the resource allocation for epidemics control and management involves several directions of research. Relatively simple and general analytical and computer epidemic models are used to plot and forecast epidemics. Quantitative analysis of advanced models is used for quantifying exposure and forecasting resources needed. Decision making techniques are used to help decision and policy makers in setting up policies and making decisions [4].

The basic model [4] used in epidemics modelling is

$$dx(t)/dt = -\beta(t)x(t)y(t) - u(t);\ dy(t)/dt = \beta(t)x(t)y(t) - \gamma(t)y(t);\ dz(t)/dt = \gamma(t)y(t) - u(t).$$

Here $x(t)$ is the number of persons not infected at t time; $y(t)$ is the number of infected persons at t time; $z(t)$ is the number of persons taken away from infection outbreak; $\beta(t)$ is the rate of getting infected at t time; $u(t)$ is the immunization rate among susceptible persons at t time; $\gamma(t)$ is the removal from

population rate at t time. The most important aspect in the model is the non-linear growth rate as a product of healthy and infected subpopulations.

On the basis of that model, many other ones were developed, breaking down elements on smaller variables to address in details various aspects of disease outbreaks.

Those methods and models help develop understanding of the epidemics dynamics and outcomes. The rest of the paper will be organized as following: a specific and detailed review of research questions, existing models and results will be presented in the following section. Then, future research opportunities to develop the field will be outlined and embedded in the last section, followed by references to source publications.

REVIEW OF CURRENTLY EMPLOYED MODELS AND RESULTS.

The epidemics control service deals with a number of issues addressing different stages and elements of the epidemics control. Preparation and planning constitute first service's activities. Monitoring and identifying the epidemic compliment those early stages. When an epidemic is detected, treatment and quarantine are in focus. That includes managing affected, vaccinating still healthy population, monitoring the outbreak development. Managing resources and addressing specific issues (such as the vector eradication, overlapping diseases, special population groups affected etc.) are more examples of healthcare authority's challenges. Minimizing consequences and off-setting losses of epidemics are other tasks of the authority. In that sequence, the review of OR/MS research is organized. Highlights of research questions, methodology and results are given in a more detailed presentation than in the review section.

For public, epidemics start when the actual germ spreads out and infects population. For epidemic control authorities, the work starts much earlier – in the preparation stage. OR can address in its research important planning issues confronting healthcare authorities.

[9] argued for wider spread of scientific knowledge on disease prevention, planning and management. They provided examples of 1997 Nile virus outbreak in New York City and built up an argument that a better competence in disease control preparation and management would be of asset to many instances, from specialized public authorities to municipal entities.

The preparation/planning application of OR/MS was illustrated by [2]. They researched into preparing for viral epidemics. The scope of the paper was to test what anti-viral treatment/prophylactic approaches had produced better results for both treatment and prevention. Limited stockpile of anti-viral agents was under assumption to make the research more applicable to real life. Also, specific risk groups' management strategy was researched. Specifically, the authors studied a scenario of response to a flu infection in UK, where 25% of population could be treated with anti-viral stockpile. The compartmental model of homogeneous population was used first and then it was modified by inclusion of high risk groups in population studied. The finding of the paper was leading to better effects of aggressive treatment/prophylactic even if that exhausts the medicine stockpile early. In general, early and massive anti-viral treatment cut disease length in people and saved both finance and lives.

The healthcare authority's responsibility is to monitor infectious disease prevalence to recognize in time eruption of epidemics and commence appropriate actions. Delay of time for starting anti-epidemic actions can cost lives and substantial expenditures. An automated system can be used for recognizing arrival of

epidemics. The appropriate model should power that system. An approach to construct such a model was proposed by [16]. They developed a method for automatic, human-free, decision-making upon start of an influenza outbreak. Their model is powered by Hidden Markov Models technique coupled with "an Exponential-Gaussian mixture to characterize the non-epidemic and epidemic dynamics in a time series of influenza-like" cases incidence rates. The validation of the method on actual data suggested reducing the incidence of wrong detections of epidemics comparing to the currently used approaches. According to [16], the model proposed delivered better accuracy then previous ones and can function in automatic mode.

Another research and practical question OR can address is the way emerging epidemics will evolve: Will it die out or explode? The issue can be addressed through partially observed branching processes for stochastic epidemics [14]. Branching processes are, for instance, death/birth or die-out/epidemic explosion. The author assumed that quite often, observation of the epidemics had differed from reality (the measurement error). If so, the model developed could be wrong. Thus, deployment of controls and initialization of action plans could be or missed or triggered at no actual reason. The model worked through analyzing the conditional probability of extinction of epidemics and the conditional time for that extinction, from the point of knowing existing parameters of epidemics. Stochastic processes were used to model the construct. The author concluded that the use of randomness in partial observation for a given branching process could result in better stochastic models of epidemics. The technique used in the model was binomial thinning for introducing partial observations. The core of the model was making the infected and observed patients a Markov chain process. Transitional probabilities and conditional distributions were developed for and by the model, too. The model described the probabilistic behaviour of the epidemics, and could be modified by the course of obtaining new data for initial stages.

[13] researched into out-breaking infections across complex population networks with acquired immunity. The authors discovered, that scale-free networks with diverging connectivity fluctuations with a large number of nodes limit, produced lower epidemic threshold and exhibited a finite portion of affected persons. That issue resulted in a high variance of response from systems upon introduction of infected individuals with various connectivity. The model added to understanding the spread of epidemics across complex heterogeneous networks.

[17] added to studies of scale-free weighted networks with asymmetric infection, while focusing on both the epidemic threshold and critical behaviours. The study demonstrated that asymmetry could be redistributed across parameters influencing spread-out of the infection, and the threshold could be recovered to make the infection more manageable.

[5] addressed outbreaks of diseases transmitted by mosquitoes. They developed a non-autonomous dynamic model, which incorporated seasonal fluctuations in mosquito population. That model aimed at explaining Dengue fever seasonal pattern. The authors introduced a time-dependant threshold R(t). The model assumed the Dengue outbreak when the mean R(t) was more than 1, and no outbreak if below 1. The model explained the gap between the peak in mosquito population and the Dengue fever outbreak. The Dengue fever re-appeared worldwide as a major healthcare challenge in 1990s after decades of relatively local episodes of disease. The pattern of Dengue is its peak in wet season (3-4 months after rains start) and drop to almost nothing in dry season – due to the mosquito population fluctuation. An interesting research question, surprisingly the model provided insight on, was how the virus survived the dry season. According to the model, the virus survived in some mosquitoes alive and their eggs – the pattern of mosquito population matched mosquito number and the hatching time. Eggs reservoir seemed to be more plausible. The model in itself consisted of three components to incorporate all major locations of virus – people, mosquito, and their eggs. The model differed from previously used time-independent

threshold for vector-dependant epidemics, developed by [11]. The model stipulated that the delay of epidemics peak versus peak in mosquito population was due to two factors – immunity of population and increase in number of infected mosquito/bites (it takes time to get mosquito infected from infected individuals). The extinction of disease outbreak was explained through the immunity parameter growth by the course of epidemics, and a seasonal decrease in mosquito population.

[8] investigated bluetongue virus basic reproduction number. The vector for that agent could be a number of Europe resident mosquito species. The basic reproduction number (R_0) was the expected number of secondary infection cases due to the single infected person who entered a healthy population. The study developed maps of (R_0) for better utility in healthcare and epidemics control practice. Such maps help identify areas of higher epidemics risk and pre-plan for epidemics outbreaks. The novelty of their paper and approach was in combining the mathematical modeling with GIS (Geographic Information System). The value of GIS for epidemics control in case of vector-related infections (transmitted by mosquito and other biological species) was in incorporating climate parameters, geographic details, human-influenced land use parameters, other anti-epidemics and industrial factors into the method then available to epidemic control authorities.

[7] addressed the issue of infections overlap. SIR linear model type was used. An influenza epidemic often provoked outbreak of complementary viral and bacterial infections. That inflated morbidity and mortality during the epidemics. The authors developed a model to estimate consequences and management strategies for those superposition outbreaks. Dimensions of the infections interaction were spread-out of the epidemics, morbidity/mortality rates. The finding from the model showed that antibacterial interventions during viral epidemics could decrease the number of cases (incidence) and mortality.

[3] advanced the use of SEIR (susceptible – exposed – infected – removed) stochastic compartmental models for forecasting epidemics outbreaks dynamics with only partially known data (if only removal time is available). The model worked in the following way: those compartments (or stages) were common for population members in many epidemics. The statistical and modelling component was included through probabilities of transfer from one compartment to another. Those probabilities were usually derived from rates of contact, getting infected etc. The authors stipulated that constant removal parameters were not applicable to many outbreaks. Thus, they developed a model with time-dependent function for the removal time/rate. The technique used was the reversible jump MCMC (Markov Chain Monte Carlo) algorithm. Gamma distribution was used. It allowed incorporate Bayesian inference in the model through the use of model parameters associated with the step function. The validation of the model was performed on a small pox outbreak and a respiratory infection epidemic. According to the authors, an important finding was the need to introduce time dependence by contrasting the predictive distributions of removal times. Then, they might be compared to actual times. Should those estimated parameters be derived accurately enough, that would enable the model to predict epidemics course and plan accordingly epidemics control and health management strategies. An interesting solution was to use MCMC model and the reversible jump MCMC algorithm jointly to fit the model to actual data and make it more precise and applicable. Interestingly, that only one parameter available – the removal times of the infective individuals – enabled the model to develop posterior distributions for both the number and the position for removal rate changes.

[6] addressed another important issue in modelling disease outbreak and dynamics. They focus on consequences of decision making in planning for and combating epidemics: how to flexibly keep those expenditures minimal. Early models were based on decision trees to address screening decision. Then, Markovian models were developed. The authors developed their own discrete event simulation model and

came out with results different from previous models. In that model, individuals with attributes (entities) progress from event to another in a timely manner [6]. Those attributes could be diverse in nature to reflect features of individuals. Time transition intervals and passes were developed from sampling data. The attributes affected distribution parameters and brought flexibility into the model. Assumptions of the model dealt with the cohort and incidence patients (a single fixed incidence cohort was used), the base scenario (usually assuming no management measures taken), system boundaries (what population and environment to include tec.), data compatibility. Results included lives saved, life years saved, quality adjusted life years, costs, NPV of savings, efficiency etc. The main advantage of their technique was the ability to incorporate various patient type parameters (co-morbidities etc.) into the model without exponentially enlarging the number of states (contrary to that, previous models had some 5,400 states).

[1] described an applied software (WINPEPI) developed to help epidemiologists in researching and planning epidemic control measures. That software was a good example of building a user-friendly application based on both statistics (mainly) and OR techniques (some of them included). WINPEPI consists of DESCRIBE (used in descriptive epidemiology); COMPARE2 (used for comparing independent two groups or samples in epidemiology, including an option to compare odds ratios for two samples); PAIRSetc (to compare paired and other matched observations); WHATIS (a utility program for modelling epidemiologic challenges). Those programs all together have 75 modules and can be used for alleviating epidemiology practitioners' life in regard to statistical and modelling issues.

FUTURE RESEARCH OPPORTUNITIES.

(i) the multidisciplinary approach to the epidemics modelling/forecasting research. The OR/Statistics researchers will get complimentary benefit from teaming up with epidemiologists, managers, physicians etc. (ii) the customization of OR/Statistics research for use in epidemiology. Developing disease-customized models will help epidemics control practitioners withstand and better manage outbreaks. (iii) the use of innovative methods in the epidemics outbreak management research. (iv) the resource management in the epidemics outbreak management research. (v) the involvement of public sector in the epidemics outbreak management research. Those models would help public administrators better understand epidemics complexity and better communicate importance of proper proactive measures. Developments in those research areas will boost OR/Statistics reputation in the society.

CONCLUSION.

Operations Research (OR), powered with statistics and models, is a high potential engine for use in many areas that require evidence-based or model-based decision making. One of the most promising areas is specifically the infection outbreak management. Given the complexity of and high value at stake in that field, a number of stakeholders and interested participants, such as academia, public policy makers and practitioners might be interested in obtaining a review of literature on OR-backed methods and techniques to manage the epidemics outbreak. The paper aimed to contribute the OR in three ways: (1) provide the contemporary literature review along with summary of methods/techniques/models used in the epidemics outbreak management; (2) improve awareness among the specialist community of OR/statistics use and benefits in their decision making for the epidemics outbreak management; (3) highlight research opportunities for developing the field by academics and epidemics outbreak management professionals.

Key findings indicated that there was a number of instruments OR could offer to the epidemics control field. The models/techniques could be deployed by practitioners and contribute to the healthcare. The review of the field would also help OR academics identify prospective research streams and projects to pursue.

REFERENCES:

1. Abramson, J., 2004. WINPEPI (PEPI-for-Windows): computer programs for epidemiologists. Epidemiologic Perspectives and Innovations. 1(6), pp.1-10.
2. Arinaminpathy, N., McLean, A., 2009. Logistics of control for an influenza pandemic. Epidemics, 1, pp.83-88.
3. Boys, R., Giles, P., 2007. Bayesian inference for stochastic epidemic models with time-inhomogeneous removal rates. Journal of Mathematical Biology, 55, pp.223-247.
4. Brandeau, M., 2008. Resource allocation for epidemic control. In: Encyclopedia of Optimization, Second edition. Springer Verlag, 2008.
5. Coutinho, F., Burattinia, M., Lopeza, L., and Massada, E., 2006. Threshold conditions for a non-autonomous epidemic system describing the population dynamics of Dengue. Bulletin of Mathematical Biology, 68, pp.2263-2282.
6. Davies, R., Roderick, P., Raftery, J., 2003. The evolution of disease prevention and treatment using simulation models. European Journal of Operational Research. 150, pp.53-66.
7. Handel, A., Longini, I., Anitia, R., 2009. Intervention strategies for an influenza pandemic taking into account secondary bacterial infections. Epidemics, 1, pp.185-195.
8. Hartemink, N., Purse, B., Meiswinkel, R., 2009. Mapping the basic reproduction number (R0) for vector-borne diseases: A case study on bluetongue virus. Epidemics, 1, pp.153-161.
9. Khan, A., Ashford, D., 2001. Ready or not – preparedness for bioterrorism. New England journal of medicine. Vol. 345, 4, pp.287-289.
10. Luss, H., Rosenwein, M., 1997. Operations Research applications: Opportunities and accomplishments. European Journal of Operational Research 97, pp.220 – 244.
11. Macdonald, G., 1952. The analysis of equilibrium in malaria. Tropical Disease Bulletin, 49, 813-828.
12. May, R., Anderson, R., 1984. Spatial heterogeneity and design of immunization programs. Mathematical Bioscience, 72, pp.83-111.
13. Moreno, Y., Pastor-Satorras, R., Vespigniani, A., 2002. Epidemic outbreaks in complex heterogeneous networks. The European Physical Journal B. 26, pp.521-529.
14. Panaretos, V., 2007. Partially observed branching processes for stochastic epidemics. Journal of Mathematical Biology, 54, pp.645-668.
15. Richter, A., Brandeau, M., Owens, D., 2000. Optimal resource allocation for epidemic control in multiple independent populations. Technical Report, Department of Industrial Engineering and Engineering Management, Stanford University, Stanford.
16. Rath, T., Carreras, M., Sebastiani, P., 2003. Automated detection of influenza epidemics with Hidden Markov Models. In: IDA 2003, LNCS 2810, pp.521-532, 2003. Springer Verlag, Heidelberg, Germany.
17. Yan, G., Fu, Z., Chen, G., 2008. Epidemic threshold and phase transition in scale-free networks with asymmetric infection. The European Physical Journal B, 65, pp.591-594.