SIMULATION OPTIMIZATION FOR AN AGE-BASED VACCINES DISTRIBUTION STRATEGY AGAINST THE SPREAD OF INFLUENZA EPIDEMIC

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ABSTRACT

Through a small world complex network simulation epidemic lifespan of the influenza virus outbreak is analyzed considering an age-based vaccines distribution preference. Mexico´s City population was divided in three different groups:

- all children aged 4-12 years;
- persons aged 2-64 with underlying chronic medical conditions;
- adults aged 65 years and older;

The simulation model is based in the vaccines distribution to this three groups in a differential way, exploring which proportion would show the shortest epidemic duration, therefore being that one the more efficient distribution strategy. The results obtained through the simulation, would help to minimize epidemic damage as in 2009 with the A(H1N1) strain. Also any other influenza strain should be considered in order to develop a containment strategy. To set up the simulation model a homogeneous social contact network was considered, where every population group presents its own social behavior forming small clusters and also presenting a probability of being in contact with an agent of a different cluster, as happens in social groups. Based on Mexico's city population, estimations show that the 28% presents underlying chronic medical conditions, health care institutions consider only the most acute disease such as diabetes mellitus, heart problems and some kinds of cancer. The population group aged between 4-12 years represents approximately also the 28% of the entire population, while adults aged 65 years and older represents hardly a 6.6%. These three considered groups represents the more vulnerable population to be infected by a respiratory transmission disease during an epidemic threshold situation. The agent based simulation was set up in the NetLogo software and was run under a full randomized factorial experiments design, results were analyzed by an analysis of variance. Final results show that epidemic duration lasts less when the schoolchildren population received the biggest proportion of vaccination rather than giving priority to persons with underlying chronic medical conditions as done now by the actual containment strategies. These results are consistent with the knowledge that an epidemic outbreak starts between the household population, and due to the higher social interactions that occur at schools, it is more probable that this population affects more in the epidemic propagation.

The 2009 new AH1N1 influenza virus strain showed the weakness of the public health authorities in for planning a pandemic containment strategy. The outbreak of the new strain had expanded rapidly around the world by the current connectivity conditions. An optimal strategy was needed to design an adequate containment policy at the proper outbreaks moment. The most common ways to control an outbreak are vaccination and isolation, the first one represents public investments in acquiring enough amounts of doses, the decision of social isolation involves less expenses as much as promoting, but imply stopping many productive activities. One of the more affected sectors, as an example, would the touristic sector, which in Mexico has represented the third economical income in the past years (Mexico´s National Institute for Statistics Geography and Information, INEGI 2014 report). This means that before such a critical arrangement could be implemented, other containment strategies should be carry out. While influenza vaccine is the most effective tool for preventing

Keywords: complex network, epidemiology, spreading models, small world networks, vaccination strategies.

INTRODUCTION

health complications, the distribution and use of pandemic influenza vaccine will differ from that of the annual vaccine in several ways. Pandemic influenza vaccine would not be available due to production lags for at least 4-6 months after the pandemic virus had been identified and the supply of vaccine from manufacturers would be insufficient for some time after that. Another critical issue in planning pandemic influenza mitigation strategies is the delay between the arrival of the pandemic in a community and the availability of an effective vaccine. The likely scenario, born out in the 2009 pandemic, is that a newly emerged influenza pandemic will have spread to most parts of the world before a vaccine matched to the pandemic strain is produced. It is likely that even after a vaccine is invented against a new pandemic, its near-term availability would be highly limited until its mass production. For a severe pandemic, additional rapidly activated intervention measures will be required if high mortality rates are to be avoided. It is also of considerable concern that government strategies of recommending that vaccine be

concentrated primarily in high-risk groups and distributed to those people who keep the health system and social infrastructure operating. Because of A(H1N1) influenza vaccine shortage, a plan was enacted to distribute the limited vaccine stock to these groups first. This vaccination strategy, based on direct protection of those most at risk, has not been very effective in reducing influenza morbidity and mortality (Donghyun, et al. 2015). The present research plan, supported by agent based simulation models, would be to concentrate vaccine in schoolchildren, the population group most responsible for transmission, while also covering the reachable high-risk groups, who would also receive considerable indirect protection. In conjunction with a plan to ensure an adequate vaccine supply, this alternative influenza vaccination strategy would help control interpandemic influenza and be instrumental in preparing for pandemic influenza as the case of the A(H1N1) virus presented in 2009. The main objective of the present research is to find an optimal age-based vaccine distribution strategy considering three priority groups by means of an agent model simulation. To achieve this objective, a propagation model should be designed. Therefore an epidemiological SIR model in order to evaluate their parameters of contagious conditions has been explored. Also a model for A(H1N1) spread can be estimated by a small-world-like network. Interactions within a population are studied by means of different kinds of social networks, mathematically based on the structure of the population, which in a SIR model presents three different subpopulations (Susceptible, Infected and Recovered) that interact in proportion to their sizes. With these zero dimensional models, it has been possible to study the epidemic features, the asymptotic solution for the density of infected people, the effect on stochastic fluctuations on the modulation of an epidemic situation as well as the thresholds values. (Lara & De la Mota, 2014). Another classical approach to the epidemic spread describes spatially extended subpopulations, such as elements on a lattice. We consider a population rarely falls into either of these categories, being neither well mixed nor lattices. Recently Watts and Strogratz (Watts & Strogratz, 1998) introduced the small world network in order to study many social processes such as disease spreading, formation of public opinion, distribution of wealth, transmission of cultural traits, etc. In the case of epidemiological models, it has been shown that small world networks present a much faster epidemic propagation than other studied epidemic models, such as reaction-diffusion models, or discrete models based on regular lattices of a social network (Vázquez 2006). In this study the epidemiological SIR model is used to acquire the epidemic features and with these parameters the pandemic spread was simulated by means of a small-world network which, as mentioned before, presents a much faster epidemic propagation. Therefore the epidemic propagation model considers a SIR model set up on a small-world-network, and another subgroup is added to the interacting population which is the vaccinated group. As the three vaccinated groups present a different social dynamic and different respiratory disease resistance as well, a simulation of different vaccination distribution strategies would show an optimal scenario in order to reduce the pandemic propagation time.

2. METHODOLOGY

The first part of the project consists in defining a complex system where interactions between agents represent the dynamical in a complex small world social network where three kinds of nodes are set up in the network. One kind of nodes are Susceptible, other Infected and the third kind represent the Recovered as epidemiological SIR model which considers homogeneous contacts between an specific deterministic population within a one-dimensional lattice. The random network was built upon a topological ring with N vertices and coordination number 2K. Each link connecting a vertex to a neighbor, considering clockwise sense, is then rewired at random, with probability ***p,*** to any vertex of the system. It is assumed any self-connection and multiple connection as prohibited, obtaining a regular lattice at p=0 and progressively random graphs for p>0. The system model was programmed in NetLogo5.1.0. Once the system was established, the pandemic evolution takes part as any infected node contacts any other susceptible node and with a defined probability of getting sick the susceptible node gets infected, and after some steps with a defined resistance gain chance this node turns into a recovered node. Basic reproduction number R_0 is being read at every timestep, and once it becomes R_0=1.4, the containment vaccination strategy is triggered, and susceptible subroup is then divided in three other different subgroups based on an age-based division to whom vaccines will be suplied. The shortest duration time of the epidemical propagation is being seeked bay means of simulation. Finding the optimal vaccine distribution strategy based on three target age groups is seeked by means of the epidemic length considering three different levels of vaccines doses distribution to each age group. And through a design of experiments and its later results ANOVA for three factors, which are represented by the target groups, the optimal influenza vaccine distribution plan is obtained.

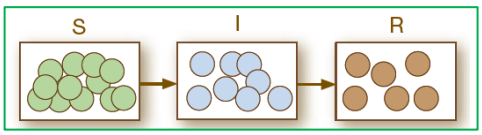


Figure1. SIR model used to establish the system

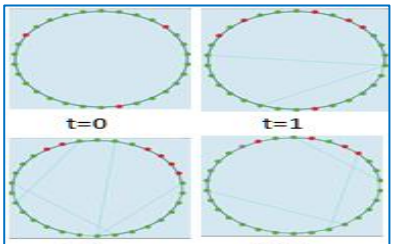


Figure 2. Small world network where social contacts were carried out

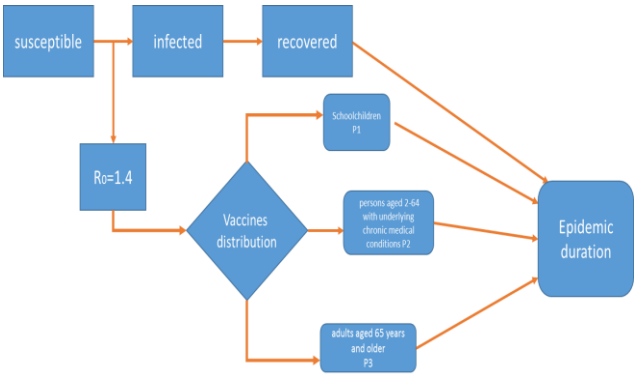


Figure 3. Methodology

2.1. The model

To establish the model it is considered that target aged subgroups, (school aged, elderly and population with underlying chronical medical conditions), have its own social affairs patterns. As an elder individual, having more than 64 years old, its more common to have a more isolated and sedentary way of life, interacting with persons of the same age range, having less participation in labour force and also present less outdoor activities. Hence in a social contact network topology this age group as nodes present less probability to interact with other social cluster nodes. This age group will be represented in the small-world network with a lower rewiring probability than stablished in the network. The considered range is between 0.6-0.4 of the general rewiring probability.

About school aged group, its social dynamic is considered opposite to the previous mentioned age group, as school aged population have a lot of social affairs within its educational centers and between their household related. These interactions causes a highly dynamic social contact network, which can trigger a more harmful disease propagation. Therefore, in the model, a higher rewiring probability level is assigned to this subgroup ranging between 1.2-1.3 times the assigned rewiring probability.

Population which presents chronic medical conditions, concerning this conditions as diabetes mellitus, heart illnesses and some other kind of cancer, interact the same way as the general population does, in most of the cases, so its rewiring probability is the one used for the entire small-world network. About the illness susceptibility, an assumption done for building the model is that these three targets population subgroups present most likely the same probability of being infected by an influenza contagion, young children don´t have their immunity system well developed and elderlies have also a weak immune system due to natural causes, as well as chronical disease subjects which have an affected immune system due to medication. This characteristic is represented in the model by the gain resistance chance.

Table 1. Rewiring probabilities and corresponding percentages for each target age group used to set up the model. Source INEGI 2015 and Mexico´s Public Health Care System.

Age population subgroup	Rewiring probability parameter	Population proportion
School aged (4-12 years old)	1.2 - 1.3	27 %
Elderlies (65 years and older)	0.4 – 0.6	7.2 %
Persons aged 2-64 with chronic medical conditions	For this group it is consider the same rewiring probability of the whole population	28 %

Once the population dynamic was included in the model through the rewiring probability, epidemiological parameters for an influenza epidemic were also considered. These parameters indicate the disease propagation not the individual risk of being infected, therefore weakness or strength of the different immunity systems of each objective group could not be represented by the epidemical parameters. The three age subgroups are also distinguished as Susceptible, Infected or Recovered individuals, as in a SIR model, and each one with a corresponding probability of becoming infected, or recovered. If vaccination strategy is assigned to an age group, some members of that group will become recovered with the corresponding probability established by the vaccination plan. Every individual is represented by a node in a complex small-world network and at every time step a node has a probability of getting infected by another adjacent infected node and after some time steps and based in a recovery chance this infected node would become recovered. Also through every tick some network links are rewired with a rewiring probability ***P*** which represent the social dynamic in the contact network resulting in different epidemic lengths. Considering that every age group has different social dynamic besides the general one, epidemic duration would vary if a vaccination strategy is established.

2.2. Model parameters

Simulation was set up with a design of experiments where vaccination distribution proportion among the three target groups took three levels for each group, L1=30%, L2=60% and L3=90%. After running simulation based on a complete randomized factorial design an ANOVA was studied in order to determine which level combination could show significantly less epidemic duration. Other considered parameters were about the target groups behavior as the school aged population presents more mobility, but it is expected that population portion which present chronic medical conditions behaves with normal social interactions, different as the older group (65<) whose social affairs are lower. It is assumed that epidemical conditions are

the same for the three groups The transmissibility, parameters are considered in the gain resistance chance, recovery chance, and mobility by the rewiring probability due to the kind of network it is used.
In the following chart the mentioned parameters are shown:

Table 2. Epidemiological parameters and their corresponding values used in the model for an influenza disease. (Fraser, 2009),(Wu,JT et al, 2006)

Parameters	Definition	Estimated value
$1/\gamma$	Infectious period	1.5 days
$1/\kappa$	Latency period	1.9 days
Average recovery time	Total time since the contagious moment	3.4 days (84 hours)
Recovery chance	Inverse of mortality rate	98%
Attack Rate Transmission ART	Is the infection chance	7.5%
Transmission risk	Corresponds to the infection chance. This parameter affects directly the transmission rate β	is adjusted during the simulation process to acquire the corresponding R_0 threshold value

2.3. Simulation

Once we established the parameters, NetLogo 5.1.0 software was used to perform the simulation for different scenarios of propagations disease. Also the versatility of this software was proven given that it contains several libraries in which it is possible to develop different kinds of models with remarkable simplicity without losing generality. Besides, it has not been enough employed in the epidemic spread simulation field. Thereby we were able to perform our simulation, to obtain the needed scenarios for a later searching of the optimal epidemical mitigation strategy.

The model was programed in NetLogo 5.1.0. Epidemic and vaccine distribution controls were set up. Population and age subgroups were represented in a ring network shape, each group with different radius, and each with different rewiring probability. Although every subpopulation had the same node degree K=4.

First performed simulation were run with vaccine settings = 0 and other model controls set as shown below:

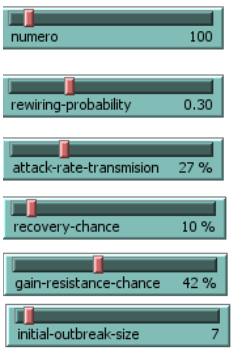


Figure 3. Epidemiological model settings.

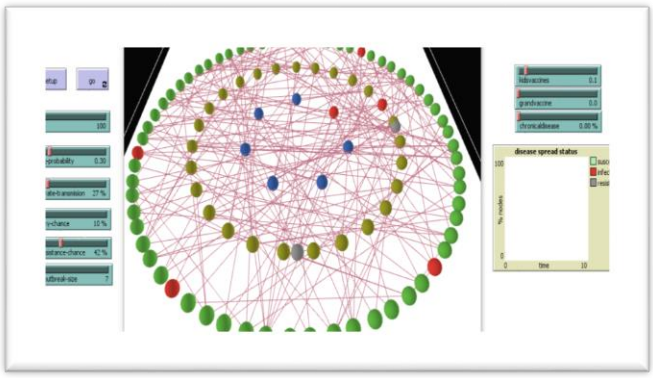


Figure 5. Model interface developed with NetLogo5.1.0. At the right side epidemiological controls are stablished. In the center part population is represented as circle nodes. Green nodes represent Susceptible population including subjects with chronic medical conditions. Yellow circles represent school-aged population and blue circles are elderlies subjects. Infected nodes are red colored and gray nodes represent Recovered as well as vaccinated subjects.

Rewiring probability ***P*** was varied in order to find system stability. Four different values were used (0.20, 0.40, 0.60 and 0.80) the rewiring probability with the less variation would be considered as a steady state. For each ***P*** value 60 run were performed.

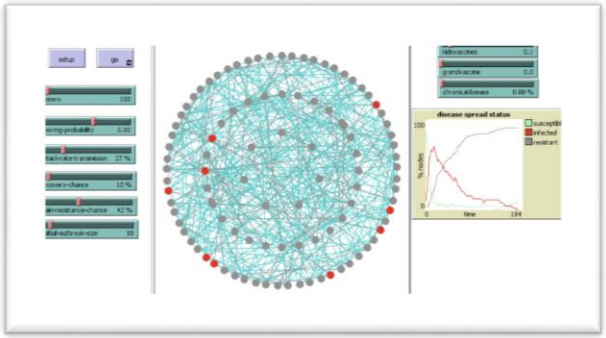


Figure 6. Simulations run for a rewiring probability P = 0.60. Four different adjustments were stablished P to find steady state of the system (0.20, 0.40., 0.60 and 0.80). 60 runs were performed in every case.

The simulations outgoing results were first analyzed through an ANOVA in order to find the lowest variation

in the epidemic duration. The results and its analysis are presented in section 3.

Once the stability was found model validation was considered by the literature (Tuite, et al. 2010). Moreover simulations implementing vaccine distribution strategy were performed. As the main objective of the present project is to establish an optimal vaccine distribution strategy among the target age groups simulations of the model were run according to a full factorial design of experiment with three factors corresponding to the mentioned age groups and each factor with three levels, which correspond to vaccine coverage in each group. The chosen levels were 30%, 60% and 90% of vaccine coverage. Next the corresponding statistical analysis of variance showed the optimal vaccine distribution levels for each population target age group.

The DOE implemented is shown below:

Table 3. Multilevel factorial design of experiment with 3 factor and 3 levels for each factor.

Multilevel Factorial Design			
Factors	3	Replicates	3
Base Runs	27	Total runs	81
Blocks	1	Total blocks	1
Number of levels	3, 3, 3		

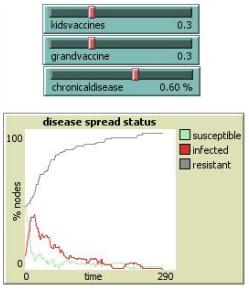


Figure 7. Vaccination strategy settings.

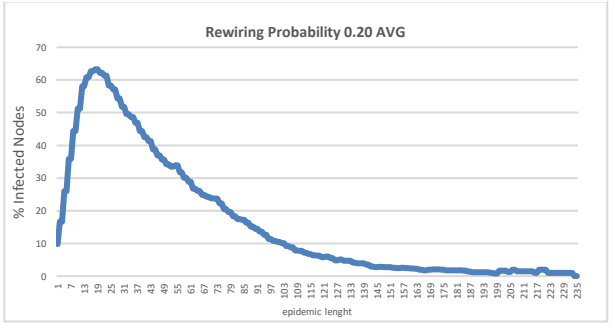
Corresponding results are discussed in next section as well.

3. RESULTS AND ANALYSIS

3.1 Simulation setup results

Results for the first simulation designed for system steady state are showed below for every chosen ***P*** level with 60 replicates for each run.

A



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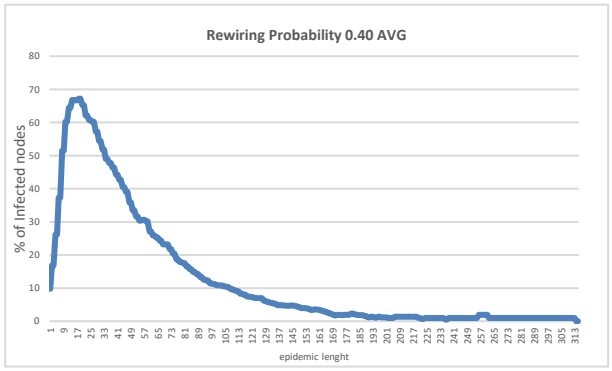

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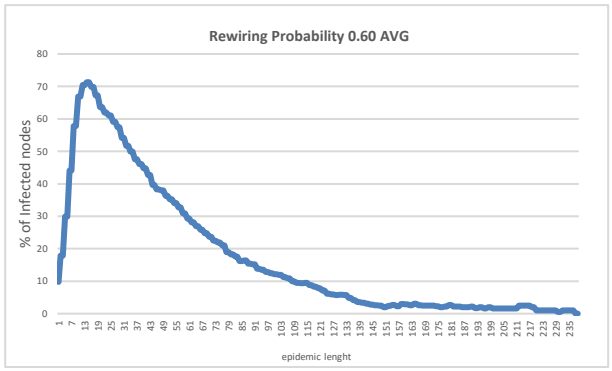

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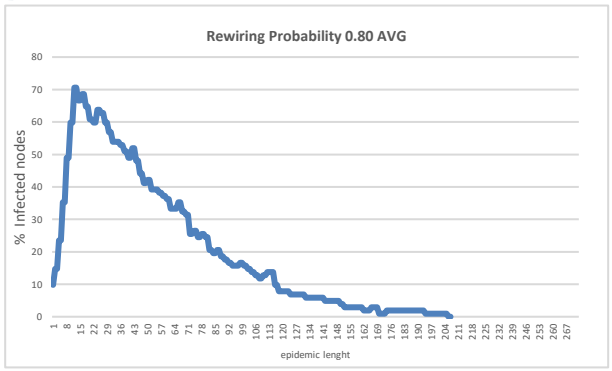


Plots A-D ***¡Error! No hay texto con el estilo especificado en el documento.*** *Epidemic duration corresponds to the horizontal axe and Infected population dynamic is plotted in vertical axe.*

Plots A-D show epidemic status through the percentage of infected nodes including the targets groups. These results were obtained with no vaccine strategy in order to obtain permformance characteristics of the model. The system behaves normaly respect to an epidemic outbreak with an asymptotic infected population grow and a slow decay. As social contact dynamic grows it is expressedby rewiring probability, epidemic length last more, hence fo a level P = 0.80 a longer epidemic duration should be observed it verificated through the following ANOVA's.

About the media and variance analysis an one-way media ANOVA test was permformed in order to find if there exist significant differences bewtween the chosen levels, and as mentioned the scope of the lower variability. Results are discussed next.

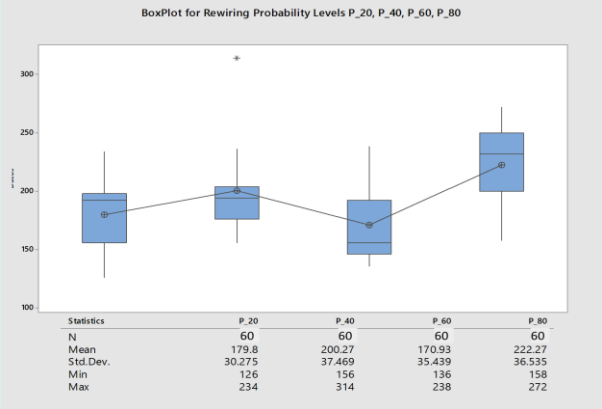


Figure 8. Boxplot Graph for each P level with corresponding statistical summary.

With figure 8 Boxplot graph is shown and statistical summary is added. It can be seen that level presenting lower standard deviation corresponds to P = 0.20, additional information should be analyzed to assert a significant media and variability difference.

With a significant level α =0.05 difference meaning test is performed

Table 4. Means differences using Tukey Method

#	Sample	Differs from
1	P_60	4
2	P_20	4
3	P_40	
4	P_80	1, 2

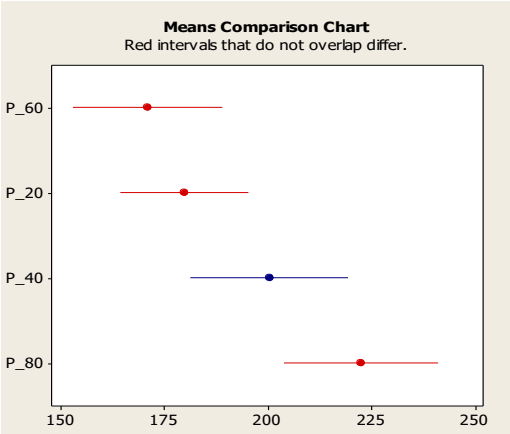


Figure 9. Mean comparison chart. Confidence intervals are drawn in different colors to show significant difference between means for P selected levels

Table 5. Descriptive summary for each P level.

Sample	N	Mean	Std.Dev.	Mean 95% CI
P_20	60	179.8	30.275	(22.975,45.983)
P_40	60	200.27	37.469	(17.404,92.792)
P_60	60	170.93	35.439	(23.698,60.963)
P_80	60	222.27	36.535	(28.232,54.384)

In figure 9 one can observe that there are difference among the mean at the 0.05 level of significance. Also none of the red intervals overlap which indicates difference among each other. About information showed in table 5 about Confidence Intervals it can´t be asserted that there is a significant difference in variability for each sample.

3.2 Optimization Results

The spread model is then used to determine an optimal vaccine strategy. The corresponding DOE was performed using a rewiring probability P = 0.20, due to a better performance in the simulation and also by literature considerations (Lara & De la Mota 2014, Jiahao 2005), although there they consider a random wire probability of 0.30 for a social contact small world network.

For the ANOVA design the corresponding results as shown as follows:

Table 6. ANOVA results from the DOE.

Source	DF	Seq SS	Adj MS	F	P
Chronicalmedical affected	2	24132	12066	11.65	0.00
elderlies	2	548	274	0.26	0.768
Scholar age	2	25114	12557	12.13	0.000
Error	74	76632	1036		
total	80	126425			

S = 32.1803 R-Sq = 39.39% R-Sq(adj) = 34.47%

For a significant level 0.05, vaccination school aged population is significant as well as population underlying chronic medical conditions, different to vaccination to elderlies which is not significant. It would be confirmed through the main effects Plot for the epidemic duration.

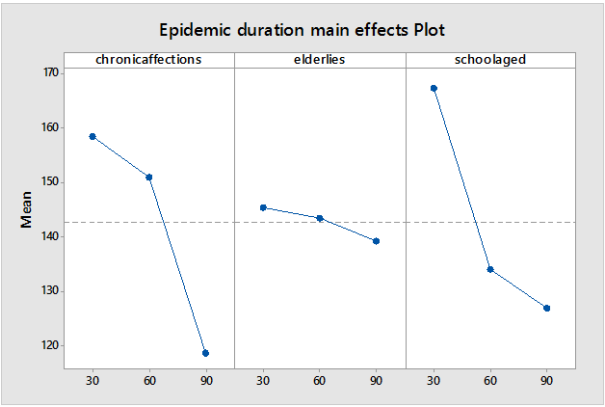


Figure 10. Main effect Plot for epidemic duration based on three level vaccination strategies.

For chronic medical affected population significant difference in the vaccine coverage is observed, same as a school aged population vaccine policy it is shown that there would be considerable difference in vaccine

coverage. For the third age group corresponding to elderlies, there´s no significant effect on epidemic duration.

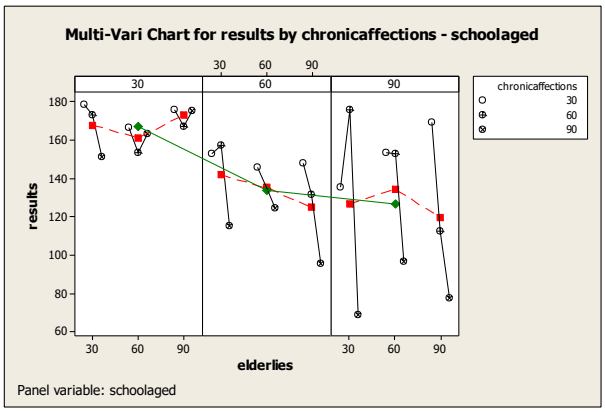
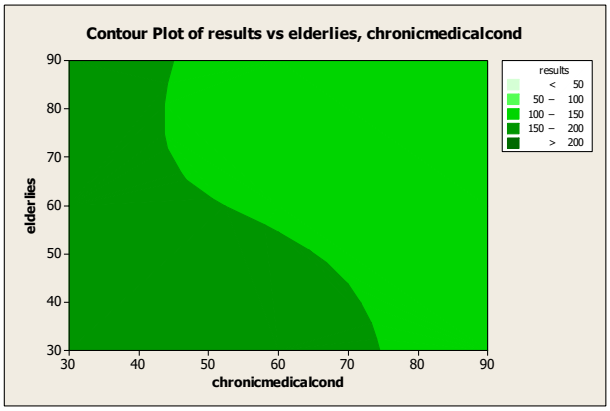


Figure 11. Multi-Vari Chart for epidemic length by chronic medical condition population group – school aged and elderlies. Green line represent school aged dynamic for three different vaccination levels. Red line represents elderlies infection behave under the same vaccination policy. Third group is represented by three different marks for each level. (reference is placed in the plot).

The above graph shows effects each factor has for the corresponding vaccination strategy. Red line indicates effect that elderlies vaccination strategy has in epidemic duration when the others groups are in the corresponding level. For instance if school ages group vaccine coverage is about 30% (green line in the firs block). With this plot an optimal vaccine distribution strategy could be implemented. Also through a contour graph analysis it would be able to assert corresponding policy.

A



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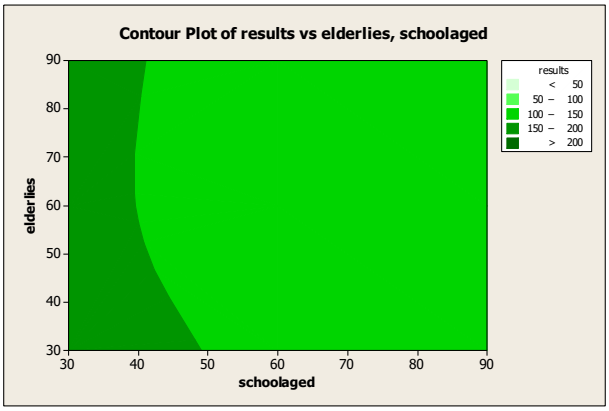

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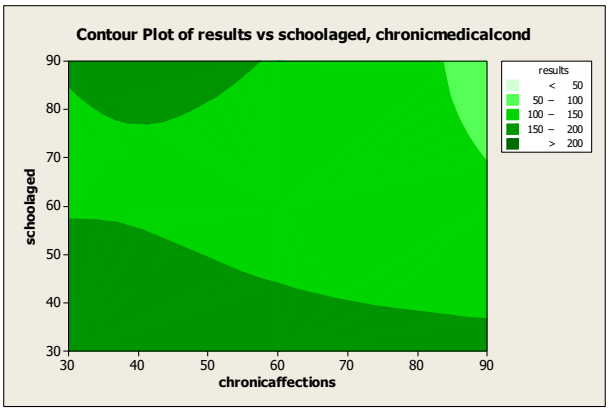

Figure 12. Three-dimensional Contour Plots for effects vs epidemic duration. Plot A represents interaction between elderlies and population underlying chronic medical conditions vaccine distribution policies. Plot B represents interaction between elderlies and school aged vaccine distribution policies. Plot C represents interaction between school aged and population underlying chronic medical conditions vaccine distribution policies.

By the scope of contour plots it is possible to determine for which vaccine distribution coverage an optimal policy should be implemented. In plot A epidemic duration is more affected would last less with a 40% coverage of population with chronic medical conditions but with a coverage of 70 to 80 % of elderlies. And comparing with plot B in the same coverage range for elderlies (70-80 %), school aged population could have an enough coverage of the 40-50 %. Comparison with other scenarios would show good policies.

CONCLUSIONS

A influenza strain propagation model was developed based on complex interactions between social groups, structuring the system in a complex small world network, considering three different social groups (children aged 4-12 years; persons aged 2-64 with underlying chronic medical conditions; adults aged 65 years and older) with the assumption that these three population groups present same contagion risk but different number of social interactions, represented in the small world network as the probability of having contact with other cluster far from their educational centers. The model present good approximation to previous works

done by authors (Lara & De la Mota 2014) and presented an according behavior to an epidemic spread (Fraser 2010), although an numerical goodness of fit could not be done because the lack of information but nevertheless the model is adequate for simulating different epidemic scenarios, and moreover to design an optimal vaccine distribution policy among these population subgroups using statistical technics being that the simulation showed what was expected that due to school aged population dynamics prioritizing this population group in a vaccine coverage would diminish epidemic risk more than if an elderlies population vaccine distribution policy is implemented. The present research would support stakeholders during an influenza epidemic outbreak, in order to help decision making. As further works it is suggested to explore a linear program model using the outgoing information of the simulation of the presented system, considering costs of vaccination.

REFERENCES

Ashleigh R. Tuite, Amy L. Greer, Michael Whelan, Anne-Luise Winter, Brenda Lee, Ping Yan, Jianhong Wu, Seyed Moghadas, David Buckeridge, Babak Pourbohloul and David N. Fisman, Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza, CMAJ. 2010 Feb 9; 182(2): 131–136.

Chen Jiahao, Epidemics on small-world networks. Unpublished term paper for PHYS, 2005.

D. Watts and S. Strogatz. "Collective dynamics of 'small world' networks", Nature 393, 440-442 (1998).

Donghyun Kim, Hao Guo, Wei Wang, Joong-Lyul Lee, Sung-Sik Kwon, Alade O. Tokuta, “On efficient vaccine distribution strategy to suppress pandemic using social relation”. *Discrete Math. Algorithm. Appl.* 08, 1650010 (2016).

Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science. 2009;324:1557–61.

Public Mexico´s Health Care System (Secretaria de Salud), 2014 influenza vaccination report.

INEGI, 2014 annual report.

Joel K Kelso, Nilimesh Halder and George J Milne, Vaccination strategies for future influenza pandemics: a severity-based cost effectiveness analysis, BMC Infectious Diseases, 2013, **13**:81.

Lara Javier, De la Mota Idalia, Simulation optimization for a vaccine distribution strategy against the spread of A(H1N1) epidemic, Proceedings EMSS 2014.

Longini Ira, Jr. and M. Elizabeth Halloran, Strategy for Distribution of Influenza Vaccine to High-Risk Groups and Children, American Journal of Epidemiology, Volume 161, Number 4, p 303-306, 2005.

Moore C. and Newman M. E. J., Phys. Rev. E 61, 5678(2000).

Vazquez A., Spreading dynamics on small-world networks with connectivity fluctuations and correlations, Physical Review E 74, 056101 2006.

Terry White; Suzanne Lavoie, and Mary D. Nettleman, Potential Cost Savings Attributable to Influenza Vaccination of School-aged Children. Pediatrics Journal, V 103,6, e73, 1999.

Wilensky,U.(1999).NetLogo. http://ccl.northwestern.edu/netlogo/. Center for Connected Learning and Computer-Based Modeling, Northwestern Institute on Complex Systems, Northwestern University, Evanston, IL.

Wu JT, Riley S, Fraser C, et al. Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med. 2006;3:e361.

Xiao Fan Wang, Guanrong Chen, Complex Networks: Small-World, Scale-Free and Beyond, IEEE circuits and systems magazine, First Quarter 2003.

Yang, C. and Wilensky, U. (2011). NetLogo epiDEM Basic model.http://ccl.northwestern.edu/netlogo/models/epiDEMBasic. Center for Connected Learning and Computer-Based Modeling, Northwestern Institute on Complex Systems, Northwestern University, Evanston, IL.

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