Available online at www.sciencedirect.com

SciVerse ScienceDirect

Procedia Computer Science 18 (2013) 2492 – 2495

Procedia Computer Science

International Conference on Computational Science, ICCS 2013

A mathematical model to study the meningococcal meningitis

M.J. Fresnadillo Martínez[a], E. García Merino[b], E. García Sánchez[a], J.E. García Sánchez[a], A. Martín del Rey[c], G. Rodríguez Sánchez[d]

[a]*Department of Preventive Medicine, Public Health and Clinic Microbiology, Faculty of Medicine, University of Salamanca, C/Alfonso X "El Sabio" sn, 37007-Salamanca, Spain*
[b]*Department of Health, IES Ramón y Cajal, Valladolid, Spain*
[c]*Department of Applied Mathematics, E.P.S. de Ávila, Universidad de Salamanca, C/ Hornos Caleros 50, 05003 Ávila, Spain*
[d]*Department of Applied Mathematics, E.P.S. de Zamora, Universidad de Salamanca, Avda Requejo 33, 49022 Zamora, Spain*

Abstract

The main goal of this work is to introduce a novel mathematical model to study the spreading of meningococcal meningitis. Specifically, it is a discrete mathematical model based on cellular automata where the population is divided in five classes: susceptible, asymptomatic infected, infected with symptoms, carriers, recovered and died. It catches the individual characteristics of people in order to give a prediction of both the individual behavior, and whole evolution of population.

Keywords: Meningococcal meningitis, Mathematical modeling, Cellular automata, Infectious diseases.

1. Introduction

Meningococcal meningitis is a contagious and severe bacterial disease caused by the meningococcus (*Neisseria meningitidis*). It is spread by a close and prolongated contact with an infectious person through the air via respiratory secretions or sharing of personal items contamitated with this secretions. *Neisseria meningitidis* causes the infection of the bloodstream or meninges and has several and varied symptoms: high fever, headache, vomiting, stiff neck, rash,... If meningitis is not early treated, can lead to swelling of the fluid surrounding the brain and spinal column as well as severe and permanent disabilities, and even death (it is fatal in the 50%-80% of untreated cases). Even with an early diagnosis and an adequate treatment, 5% to 10% patients die usually within 24 to 48 hours after the onset of symptoms (see, for example, [1]).

The main characteristic of *N. meningitidis* is that it is possible to harbor such bacteria in the nose and throat without any symptoms. Susceptible individuals acquire *N. meningitidis* through a contact with an infected or a carrier (asymptomatic) individual; the probability to be colonized in developed countries is estimated to be 0.0009-0.00146. Carriers play a decisive role in spreading of meningococcal disease since the most of infected cases are acquired through exposure to them. WHO (World Health Organization) estimates that 11% to 25% of the population carries the bacteria in their throat at any given time (this carriage rate may be higher in epidemic situations). Once the host is reached by the bacteria, they bond to the cells at the back of the throat and nasal passage. Infected individual are those in which the bacteria can overwhelm the body's defenses allowing infection

[c]Corresponding author. Tel.: +34-920-353-500 ; fax: +34-920-353-501.
E-mail address: delrey@usal.es.

Selection and peer review under responsibility of the organizers of the 2013 International Conference on Computational Science
doi:10.1016/j.procs.2013.05.426

to spread through the bloodstream to the meninges (in approximately the 10%-20% of cases). The symptoms may appear 2-10 days after exposure (usually within 5 days)

Once a successfully diagnosis is made, the antibiotic treatment must be started as soon as possible. Empirical therapy includes ceftriaxone or cefotaxime, and vancomycin for *Streptococcus pneumoniae*. There is a vaccine against meningococcal disease which is 85%-100% effective in preventing four kinds of bacteria (the serogroups A, C, Y, W-135) that cause about the 70% of the disease in the United States. Efficient vaccines against universal group B are in late states of development (see [3]). After vaccination, immunity develops within 7-10 days and remains effective for approximately 3-5 years.

Meningococcal disease is more common in children and young adults. There is also an increased risk of this disease in some communities that live in closed quarters (college students, military staff, etc.) Other groups at increased risk include household contacts of an infected person, immuno-compromised persons, etc.

Due to the seriousness of meningococcal disease, it is necessary to develop tools that help the health authorities to make decisions when an outbreak occurs. In this sense computational tools based on mathematical models play an important role when simulations and predictions about the future behavior of the disease are required. Unfortunately there are few works dealing with the design of mathematical models to study the spreading of meningococcal meningitis. All of them are based on differential equations ([2, 4, 5, 6]) and they exhibit some drawbacks: they do not take into account the individual characteristics of population, it is not possible to simulate the behavior of each individual, they are not suitable for computational implementation, etc.

The main goal of this work is to propose a discrete mathematical model in order to design an efficient computational tool. This model is based on simple models of computation called cellular automata which can simulate complex phenomena ([7, 8]). This new model can catch the individual characteristics of people giving a prediction not only of the global dynamics but also of the individual behavior of the disease.

Cellular automata were introduced by J. Von Neumann and S. Ulam in the 50's and their motivation was to obtain a better formal understanding of biological systems. A cellular automaton on the (undirected) graph $G = (V, E)$ is a particular type of finite state machine formed by a set of n memory units called cells which are the nodes of the graph G. These states change synchronously in discrete time steps accordingly to the local transition function f. The function f computes the state of every node v at time $t + 1$, $s_v^{t+1} \in S$, from the states of the its neighbors (adjacent nodes) at the previous time step t, that is: $s_v^{t+1} = f\left(\mathcal{SN}_i^t\right) \in S$, where $\mathcal{SN}_i^t$ is the collection of states of neighbor cells of the node v at time t, and S is the finite state set.

The rest of the paper is organized as follows: In section 2 the mathematical model to simulate the spreading of meningococcal disease is shown, and the conclusions are presented in section 3.

2. The proposed model to simulate the meningoccocal disease

2.1. The mathematical formulation of the model

The following assumptions will be taken into account in the proposed model: (i) The proposed model is a compartmental one: people are divided into different classes attending to the status in relation with the disease: susceptible (individuals which are susceptible to the disease); infected -with or without symptoms- (individuals which have been infected by the disease becoming ill); carriers (healthy people which carry the meningococcus and are infectious); recovered (individuals which have been vaccinated acquiring temporal immunity or which are free of bacteria), and died (those individual died as a consequence of the disease). (ii) We will focus our attention on the simulation of meningococcal disease in only one age-group: that one given by children and teenagers. The carriage rate of this group is higher than other age-group. (iii) The infectious status is acquired immediately after the infection. (iv) As the period of time passed from the moment of the infection to the moment of the recovery or decease is a few days, we will suppose the following: (1) The total population is constant (that is, no births are considered); (2) The carrier status is permanent; and (3) The recovered status is permanent.

The model is based on a probabilistic cellular automaton on graph. In this sense, each individual of the population stands for a node of the graph and there is an edge between to nodes if the associated individuals are in contact. The state of the i-th node at time t, s_i^t, can be S (susceptible), I_A (infected without symptoms), I_S (infected with symptoms), C (carrier), R (recovered) or D (died).The local transition rule is defined by the following considerations: (1) A susceptible individual moves to the carrier (*resp.* asymptomatic infected) state

with probability α (*resp.* β) per contact with an infectious. (2) An asymptomatic infected individual remains in the same state during the incubation period (T_{inc}). When the incubation period is finished, the symptoms appear and the individual becomes symptomatic infected. (3) Let γ be the probability of a symptomatic infected to be succesfully diagnosed. If an infected individual is treated then he/she recovers with probability 0.9-0.95 in one day, otherwise (when any treatment is not applied) the recovery rate probability is about 0.5-0.8. Consequently, the mathematical expression of the local transition function is as follows:

$$s_i^{t+1} = \begin{cases} S, & \text{if } s_i^t = S \text{ AND } F\left(\mathcal{SN}_i^t\right) = 0 \\ I_A, & \text{if } \left[s_i^t = S \text{ AND } F\left(\mathcal{SN}_i^t\right) = 1 \text{ AND } G\left(\mathcal{SN}_i^t\right) = 1\right] \text{OR} \left[s_i^t = I_A \text{ AND } T_i^t \leq T_i^{inc}\right] \\ I_S, & \text{if } \left[s_i^t = I_A \text{ AND } T_i^t = T_i^{inc}\right] \text{ OR } \left[s_i^t = I_S \text{ AND } H\left(\mathcal{SN}_i^t\right) = 0 \text{ AND } \bar{T}_i^t \leq T_i^{inf}\right] \\ C, & \text{if } \left[s_i^t = S \text{ AND } F\left(\mathcal{SN}_i^t\right) = 1 \text{ AND } G\left(\mathcal{SN}_i^t\right) = 0\right] \text{ OR } s_i^t = C \\ R, & \text{if } s_i^t = R \text{ OR } \left[s_i^t = I_S \text{ AND } H\left(\mathcal{SN}_i^t\right) = 1\right] \\ D, & \text{if } \left[s_i^t = I_S \text{ AND } H\left(\mathcal{SN}_i^t\right) = 0 \text{ AND } \bar{T}_i^t > T_i^{inf}\right] \text{ OR } s_i^t = D \end{cases} \tag{1}$$

where F, G and H are boolean functions determining the appearance of an (asymptomatic) infected individual, a carrier, or a recovered one, respectively. Specifically, their explicit expressions are the following:

$$F\left(\mathcal{SN}_i^t\right) = \bigvee_{\substack{j \in \mathcal{N}_i \\ j \text{ infected}}} X_i \vee \bigvee_{\substack{k \in \mathcal{N}_i \\ k \text{ carrier}}} Y_k, \quad G\left(\mathcal{SN}_i^t\right) = U_i, \quad H\left(\mathcal{SN}_i^t\right) = Z, \tag{2}$$

where X_i, Y_i, Z and U_i are random variables following Bernoulli distributions with parameters $\beta, \alpha, \gamma \cdot \epsilon + 0.5 \cdot (1-\gamma)$ and δ_i respectively, where γ is the probability to be treated, $0.9 \leq \epsilon \leq 0.95$, and $0.1 \leq \delta_i \leq 0.2$ is the probability of a colonized individual to get infected ($1 - \delta_i$ is the probability to become a carrier). Furthermore, T_i^{inc} and T_i^{inf} are the individual incubation period and infective period respectively, and $T_i^t, \bar{T}_i^t$ is the time steps from the start of symptomatic infected status to time t.

The proposed model has been computationally implemented using *Mathematica* (version number 8). The parameters of the model are chosen taking into account the characteristics of meningococcal meningitis, that is: (1) The percentage of carriers will be considered 11%-25%. (2) For every i, set $2 \leq T_i^{inc} \leq 10$ and $1 \leq T_i^{inf} \leq 2$. (3) If an infected individual is treated, the probability to recover is $0.9 \leq \epsilon \leq 0.95$. (4) If an infected individual is not treated, the probability to recover, r, is 0.5-0.8 depending on the country. (5) *N. meningitidis* enters bloodstream with probability $0.1 \leq \delta_i \leq 0.2$. In all simulations the population is constant and equal to $n = 1000$, and we will assume that the probabilities to be colonized by both, the carriers and the infected individuals, are the same: $\alpha = \beta = 0.0009 - 0.00146$. The probability to be treated (once there is a diagnosis) could be considered $\gamma \simeq 1$.

An illustrative simulation is shown in Figure 1. In this example, we consider the case with more similarities to those studied in the models based on differential equations: the topology of the cellular automata is defined by means of a complete graph (that is, each individual is in contact with the rest $n - 1$ individuals of the population). The evolution of the different classes of population is shown in Figure 1-(a) and they are computed using the following parameters: $\gamma = 0.75, \epsilon = 0.94, \alpha = \beta = 0.00135$ and $r = 0.5$.

The simulations obtained allows us to assert the following: (1) If no vaccination procedure is stablished then: (1) The number of susceptible individuals tend to zero, *i.e.* all individuals become infected or carriers; and (2) The number of carriers grows up to the total of population. (2) With an adequate vaccination protocol, the disease could be controlled as is shown in Figure 1-(b). (3) The carriers play a decisive role in the dynamic of the disease; in fact, the evolution of the different compartments depend on the evolution of the carrier class: The number of infected grows and the number of infected decreases as the number of carriers grows. Moreover, if the carriers could be satisfactorily treated, the disease could be controlled and eradicated as is shown in Figure 1-(c). (4) In non-developed countries the force of disease is greater than in developed ones. (5) With a suitable treatment, the deceased rate is small: 2 (*resp.* 51) died individuals in a population of 1000 in developed countries (*resp.* non-developed countries). (6) The last mentioned features are boosted when random contact networks are considered.

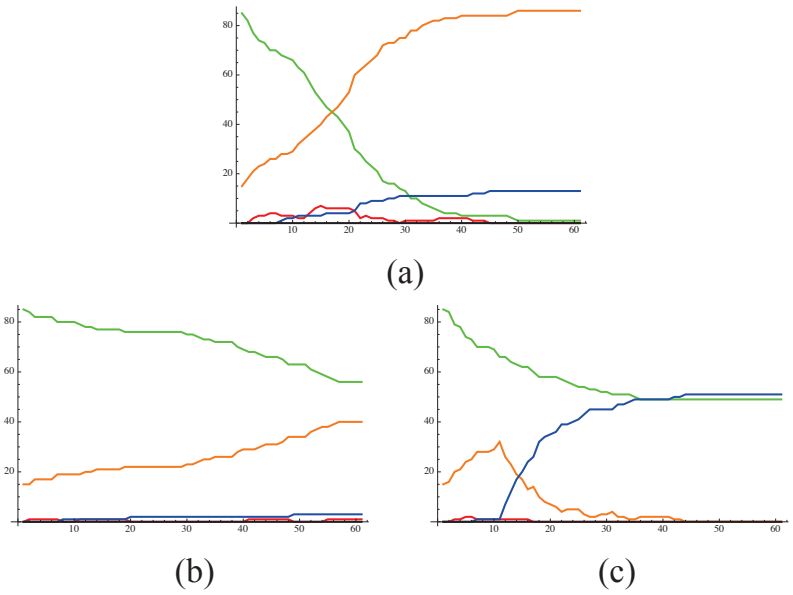

Fig. 1. Simulations of the evolution of a meningococcal disease: Susceptible (green), Infected (orange), Carrier (red), Recovered (blue) and Died (black). (a) Evolution of the different classes of population; (b) Evolution of the disease when there is a successfully vaccination protocol of 25% of susceptible individuals from $t = 0$. (c) Evolution of the disease when the 25% of carriers are successfully treated for $t > 10$.

3. Conclusions

In this work a novel mathematical model to simulate the spreading of meningococcal meningitis is introduced. It is based on the use of cellular automata on graphs. The most important characteristics of this model are the following: (1) Due to the discrete nature of the mathematical objects involved in the algorithm, the computational implementation of the model is simple and efficient. (2) Both the global and the individual behavior of the disease can be predict. (3) The simulations obtained agree with empirical predictions regarding with the basic role played by the carriers.

Acknowledgments

This work has been supported by Fundación “Memoria D. Samuel Solórzano Barruso” (University of Salamanca, Spain).

References

[1] H. Christensen, M. May, L. Bowen, M. Hickman, C.L. Trotter, Meningococcal carriage by age: a systematic review and meta-analysis, Lancet Infect Dis. 10(12) (2010) 853–861.
[2] P.G. Coen, K. Cartwright, J. Stuart, Mathematical modelling of infection and disease due to *Neisseria meningitidis* and *Neisseria lactamica*, Int. J. Epid. 29 (2000) 180–188.
[3] J.P. Cramer, A. Wilder-Smith, Meningococcal disease in travelers: update on vaccine options, Curr Opin Infect Dis. 25 (5) (2012) 507–517.
[4] M. Martcheva, G. Crispino-O’Connell, The transmission of meningococcal infection: a mathematical study, J. Math. Anal. Appl. 283 (2003) 251–275.
[5] C.L. Trotter, N.J. Gay, W.J. Edmunds, Dynamic Models of Meningococcal Carriage, Disease, and the Impact of Serogroup C Conjugate Vaccination, Am. J. Epidemiol. 162 (1) (2005) 89–100.
[6] E.N. Wiah, I.A. Adetunde, A Mathematical Model of Cerebrospinal Meningitis Epidemic: A Case Study for Jirapa District, Ghana, KMITL Sci. Tech. J. 10 (2) (2010) 63–73.
[7] J.R. Weimar, Simulation with Cellular Automata, Logos-Verlag, Berlin (1998).
[8] S. Wolfram, A New Kind of Science, Wolfram Media Inc., Champaign, IL (2002).