A Network-Based Compartmental Model For The Spread Of Whooping Cough In Nebraska

Kimia Ameri, MS[1], Kathryn D. Cooper, Ph.D.[2]
[1,2]College of Information Science and Technology, University of Nebraska at Omaha, Omaha, Nebraska, United States

Abstract

Outbreaks of pertussis have increased over the past few years, drawing the attention of health care providers. Understanding the transmission mechanisms of contagious disease is critically important, but depends on many intricate factors including pathogen and host environment, exposed population, and their activities. In this work, we try to improve upon the prediction model for the exposed population. The number of whooping cough reported cases in Nebraska between 2000-2017 was gathered. The standard Susceptible-Exposed-Infected-Recovered (SEIR) model is used to predict the infected numbers. The results show that the SEIR model prediction for the number of infected individuals is much higher than the actual number. To overcome this problem, the Network Based-SEIR model is proposed, and is able to estimate the number of infected more accurately than the classic SEIR model.

Introduction

Bordetella pertussis is a highly epidemic bacterium that lives in the mouth, nose, and throat. It is life-threatening specially in infants. Also known as whooping cough, or simply pertussis, it can easily spread via air by cough and sneeze of an infected individual. The disease is infectious to others on average for a period of three weeks; the cough itself can last on average around 10 weeks. According to the Centers for Disease Control and Prevention (CDC)[1] vaccination can reduce transmission of whooping cough. Although the disease is largely preventable by vaccination, it remains a challenge to control. Vaccination against whooping cough started in the 1940s, when the number of reported cases exceeded 100,000 per year[1]. The number of reported cases decreased dramatically to fewer than 1,000 in 1965 after the introduction of the Global Vaccination Program from the World Health Organization. During the 1980s, the number of whooping cough reported cases increased gradually despite more than 90% vaccination coverage[1]. According to Americas Health Ranking Annual Report in 2017, Nebraska had the highest number of infections for pertussis in the United States at 27.2 cases per 100,000 population[2]. Figure 1 shows the number of infected in Nebraska from 1937-2017 (Per data retrieved and aggregated from CDC, HealthMap.org, and the TYCHO project by the University of Pittsburg)[1,3,4].

The increase in the number of infected individuals may be the result of multiple factors, including, incomplete vaccination, bacterial evolution, or other issues affecting infection rates. The Tdap vaccine provides protection from potentially serious diseases caused by three types of bacteria: tetanus (lockjaw), diphtheria, and pertussis (whooping cough). The Tdap booster is recommended for adolescents, preferably starting at age 11 or 12, who have completed the recommended childhood diphtheria, tetanus, and acellular pertussis (DTaP) vaccine series[1,2].There are several studies which consider the influence of incomplete vaccination on the resurgence of pertussis, duration of pertussis, vaccine resistance, and its effects on epidemiology[5–7]. These studies examine three different factors in the resurgence of whopping cough: (1) loss of vaccine efficiency due to evolution of *B. pertussis* strains (2) diminished vaccine-induced immunity, and (3) low immunization rates. Besides the incomplete vaccination, spread of contagious disease depends on various other factors. Riolo *et al.* proposed a mathematical model to explain the resurgence of pertussis without referral to complex hypotheses about pathogen evolution, subclinical infections, or trends in surveillance efficiency. They claimed that the alarming revitalization of pertussis among adults in UK is a result of the incomplete immunization of children[6]. In 2017, Nebraska reported an 86.8% immunization rate for the Tdap vaccine, ranking 34th out of all 50 states[2].

A major global threat to public health is communicable disease. Understanding and predicting the short- and long-term impacts of communicable diseases depends on many complicated factors including pathogen and host environment, the exposed population, and their activities. Preventing and predicting the spread of contagious diseases involves understanding the relationships between social structure, pathogenicity, and environmental factors of transmission.

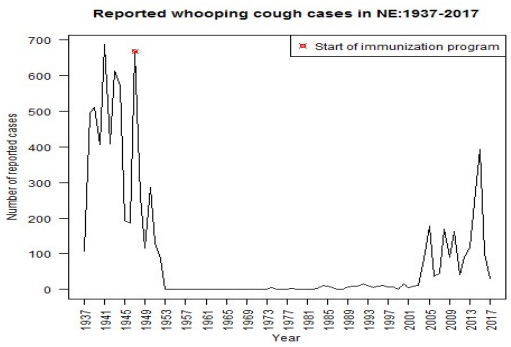

Figure 1: Weekly case notifications of whooping cough in Nebraska from 1937 to 2017, Data retrieved from CDC, HealthMap.org, and the TYCHO project by the University of Pittsburg. Red point shows starting time of vaccination program.

A broad category of contagion processes can be modeled by a network-based approach. In the proposed network model, nodes represent individuals and edges represent close physical contacts between individuals. Using network science as a framework to understand the role of contact patterns in epidemiological disease is known as the social structure of transmission. Scale-free networks seem to be a best-fit description for real-world networks[8,9]. Zhou *et al.* claim that the spread of contagious diseases follows the scale-free network model[10]. Some studies[5–7,11–13] have discerned that the spread and arise of whooping cough is random. Preferential attachment is a structural principle used to simulate and generate networks with a scale-free structure[8]. Diffusion and communication processes in scale-free networks are not random. Several studies[9,14] discussed that the neglecting of connectivity changes in finite scale-free networks leads to a higher estimate for the epidemic threshold. Therefore, to model the transmission of disease, we propose a Network-Based SEIR (NB-SEIR) model to simulate random transmission through social contact on scale-free networks generated using preferential attachment (PA). The aim of this paper is to demonstrate that the proposed NB-SEIR model increases the accuracy of prediction of infected individuals. Specifically, this information can be used to quickly inform public health preparedness and prevention in states with low adherence to recommended vaccine schedules. In this paper, we present a methodology to improve the accuracy of standard SEIR model. In this methodology, we use scale free network to find the number of infected individuals for SEIR to improve its accuracy. We utilize whooping cough case reports in Nebraska from 2000 to 2017 to measure accuracy. In the Methodology section, we present our approach for data collection, SEIR prediction, and our novel approach, the Network-based SEIR (NB-SEIR) model. The Results section will compare the two models and the strengths and limitations of NB-SEIR.

Methodology

Standard Compartmental Models in Epidemiology

Understanding the spreading mechanisms of contagious disease is very important and timely. One can simulate the spread of pathogens using compartmental epidemiological models, which investigate the transmission dynamics of contagious disease in a host population. Standard epidemiological models are usually compartmental, where a population is divided into different compartments[15–17], and then predictions are made to see how these compartments will change over time using fractional calculus. The mathematical model underpinning the description of these diseases starts with the classic SEIR model, which groups individuals within a set population into different epidemiological classes[18]:

- *S(t)* defines the class (compartment) of susceptible individuals. Initially, an individual/host is susceptible to infection. The disease can be transmitted from any infected individual to any susceptible individual.Equation 1 shows the differential equation which govern the standard deterministic SEIR compartmental model.

$$\frac{dS}{dt} = \mu(N - S)\beta\frac{SI}{N} - \upsilon S \tag{1}$$

- *E(t)* defines the class of exposed individuals. In early stages, the host or infected person may not exhibit obvious signs of infection or abundance of pathogen may be too low to allow further transmission. An exposed individual is any individual who is directly exposed to the infected disease but is not infectious.Equation 2 shows the fractional calculus for exposed population in standard SEIR model.

$$\frac{dE}{dt} = \beta \frac{SI}{N} - (\mu + \sigma)E \tag{2}$$

- *I(t)* defines the class of infected/infectious individuals. Any infected person can transmit the disease to a susceptible or exposed individual. Equation 3 shows the fractional calculus for the *I* population in the SEIR model.

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I \tag{3}$$

- *R(t)* defines the class of recovered individuals. In the SEIR model, an individual in the recovered compartment (1) was at one point infectious/infected and (2) is either no longer infectious (recovered) or removed (dead). In the case of this application of the pertussis approach, anyone who is in the recovered class from the disease will be immune re-infection (i.e., once an individual has moved from Infected to Recovered, they will not return to the Susceptible, Exposed, or Infected compartments). Equation 4 shows the fractional calculus for Recovered and resistant population in the standard SEIR model. Resistant phase refers to the phase in which individuals become immune to an infectious agent in response to an antigen (i.e, vaccine) or being being exposed to a big portion of the vaccinated population.

$$\frac{dR}{dt} = \gamma I - \mu R + \upsilon S \tag{4}$$

The population size, defined by *N*, is defined as *S(t) + E(t) + I(t) + R(t) = N*. Based on the disease nature and its spread pattern, the compartmental models are divided into different classes:

1. *Susceptible-Infected-Recovered (SIR)*: This model divides the population of size *N* into three subpopulations of epidemiological overview; Susceptible, Infected and Recovered represented by variables *S,I* and *R*, respectively. Birth , mortality and vaccination rate also can be add to this model. Individuals are born into the susceptible class. Infected individuals spread the disease to susceptible,and remain in the infected class (the infected period) and Individuals in the recovered class are assumed to be immune for life[19].

2. *Susceptible-Exposed-Infected-Recovered (SEIR)*: This model divides the population of size *N* into four subpopulations of epidemiological overview; Susceptible, Exposed, Infected, and Recovered, represented by variables *S,E,I* and *R* respectively. Birth rate, mortality rate, and vaccination rate can also be considered in this model if known/applicable. This is an appropriate model for a disease where there is a considerable post-infection incubation period in which an exposed individual is not infectious yet[20].

3. *Susceptible-Infected-Susceptible (SIS)*: Some infections, for example those from the common cold, do not confer any long lasting immunity. Such infections do not give immunization upon recovery from infection, and individuals become susceptible again. This model is appropriate for this scenario[21].

4. *Susceptible-Exposed-Infected-Susceptible (SEIS)*: This model can be used when there is no immunity to the pathogen (implying that R class will be zero). One example for this model can be tuberculosis[22].

Compartmental models in epidemiology have been successfully used in different studies to model the spread of numerous contagious disease over time such as Ebola[23,24] and Chikungunya[25,26].A number of different studies have used compartmental models to simulate the spread of pathogens using compartmental epidemiological models such as SIR[7,11,12] and SEIR[13,27]. These studies discuss the effects of asymmetric transmission rate mainly based on vaccinated and non-vaccinated populations. For example, Althouse *et al.* used wavelet analyses of whooping cough occurrence in the United States and United Kingdom to explain the transmission of whooping cough. The SIR model shows bias based on evaluation on the effect of vaccination[7]. In the same year, Dottori, M.,and Fabricius, G. proposed a SIR

model on dynamic networks to analyze the influence of the network structural properties on parameters corresponding to pertussis in the pre-vaccine era. Their results showed that network structure has strong influence on disease dynamics, and disease transmission decreases if locality of the network increased[12].

Data Collection

In this work, we retrieved the number of reported whooping cough cases (the number of infected persons per week in Nebraska) from the Centers for Disease Control and Prevention (CDC), HealthMap.org, and the TYCHO project by the University of Pittsburg for the period of January 1, 2000 through December 31, 2017[1,3,4] (shown in Figure 1). Weekly CDC reports were used as the number of reported infected. If any data was discovered as missing (not 0-valued, but missing) for any week in 2016 to 2017, the number of infected was determined by HealthMap query (using a search for alerts for whooping cough in Nebraska as the location). Data for the years 2000 to 2015 are not freely accessible via HealthMap. For missing CDC from 2000 to 2016, the TYCHO database was used.

SEIR Model Implementation

Compartmental mathematical models of contagious disease are standard tools in public health. These models can help our understanding of specific aspects of infectious disease dynamics. The simplicity of this model facilitates the clarity of interpretation, but makes extreme conclusions unavoidable. Thus, the proposed SEIR model describes the transmission of the disease and the death rate of individuals depend on the population density[28]. For this work, we define the following parameters:

1. Beta(β): The transition rate from susceptible to exposed.
2. Gamma(γ): The transition rate from infected to recovered/ resistant phase.
3. Sigma(σ): The transition rate from exposed to infected.
4. Mu(μ): The natural mortality rate; this may or may not be used to imply a population of a constant size.
5. Nu (ν): The vaccination rate, which moves people directly from susceptible to resistant.

Figure 2 exemplifies transmission between each group. We simulate the spread of whooping cough in Nebraska based on the SEIR model as described and calculate the accuracy of the model. Several studies are used to find the most accurate number for each of these parameters. Table 1 includes the value used for each parameter and their reference from which it was derived.

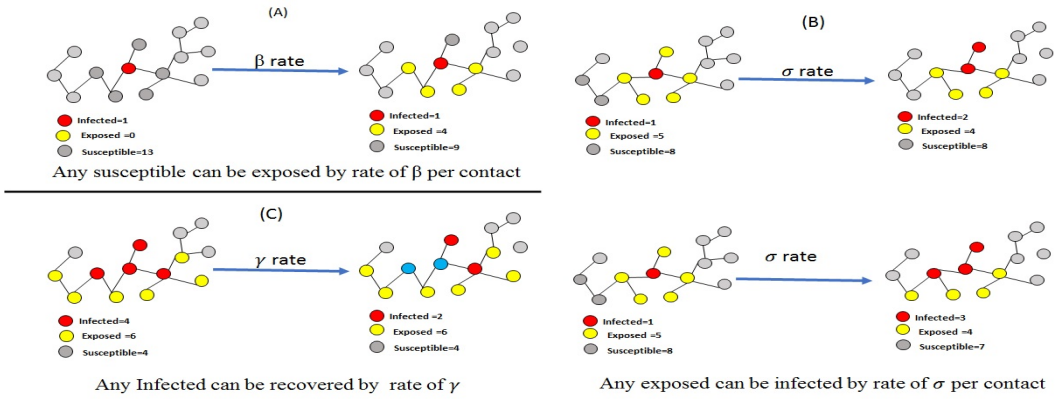

Figure 2: Exposed, infection and recovery transmission in SEIR model. (A) Any susceptible can be exposed by rate of per contact point. (B) Infection occurs at rate per contact and (C) recovery occurs at rate for infected population.

Disease Parameter			
Symbol	**Parameters**	**Value**	**References**
β	Infection rate	0.9	[29]
γ	Recovery rate	365/14	[29]
σ	Incubation rate	365/8	[29]
μ	Mortality rate	$85 * 10^{-7}$	[2]
ν	Vaccination rate	86.8*	[2]

Table 1: Demographic inputs and disease parameters that are fixed in the model. *This number is for 2017, rate may change each year.

NB-SEIR Model Implementation

Mossong *et al.*[30] suggested that different individuals have a different number of physical contacts for one day, and this number can be varied based on multiple factors including age, sex, and location. They found that everyone has an average of 13 contacts each day[30]. A scale-free network with a 13-minimum number of neighbors for each node was made using *barabasi.graph* function, which uses a preferential attachment mechanism to generate random scale-free networks[8]. To estimate initial SEIR values, we simulate infection by randomly choosing a node within the networks as the original infected person, and find its neighbors to determine the number of exposed persons. Since the graph model is unbalanced in edge distribution, we perform 1000 iterations of this process of random infection and exposure. The average number of neighbors (average of exposed individuals for all 1000 runs) is then used as the exposed number for the model. We then calculate the values of SEIR where N is equal to the population of Nebraska in the current year, R = 0, I = the number of infected individuals as given by CDC/HealthMap/Tycho aggregates, E is equal to the average exposed based on the network connectivity, and S is equal to N -(I + E + R). These initial values are subsequently used to run our standard SEIR model and compare the accuracy of the SEIR and NB-SEIR approaches. The work flow is illustrated Figure 3in the left and the Pseudocode can be found in Figure 3 in the right.

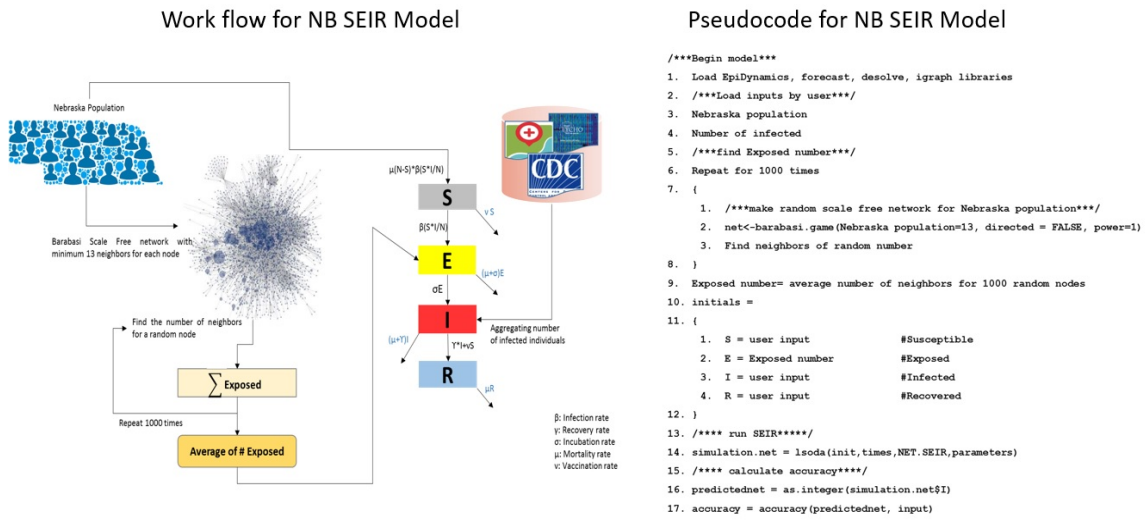

Figure 3: Left: work flow of SEIR and NB SEIR model. Right: Brief pseudo code for Network Base SEIR

Results

in this paper, we use our own methodology to improve the accuracy of predicted number of infected in SEIR model. Accuracy was found by comparing differences between predicted number of infected (from the standard SEIR and NB-SEIR model) and actual data aggregated from the CDC, HealthMap, and TYCHO. Evaluation measures used included the Root Mean Squared Error (RMSE) and Mean Error (ME) to scale the differences between the actual value and values predicted by the model. RMSE is the square root of the average of squared errors and is used to aggregate the magnitudes of the errors in predictions, also known as accuracy. ME measures the average of errors or deviations and

used to measure the quality of the estimator. Values closer to zero are better for both RMSE and ME. In Figure 4 (left), the predicted number of infected whooping cough with SEIR in 2015 is compared to the real number of infected individuals we gathered based on aggregated the CDC, HealthMap, and TYCHO data. Because the difference between the real number and the predicted number of infected individuals are very high, the plot cannot show it properly, the real number of infected seems flat. Table 2 shows the predicted number of infection, RMSE and ME for SEIR model years 2000-2017. It can be inferred from Table 2 that the standard SEIR model is inaccurate and the number of

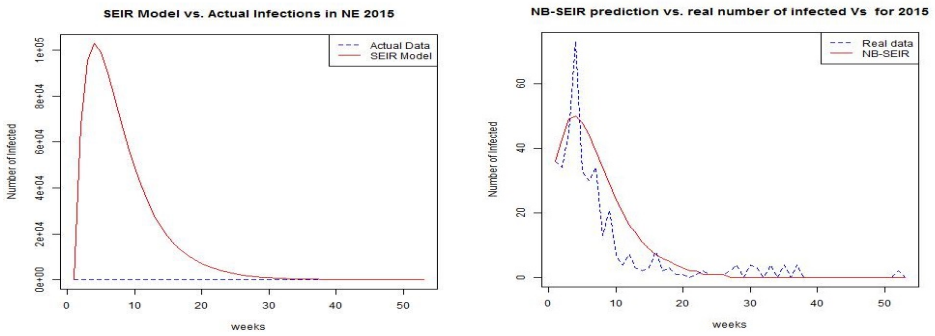

Figure 4: Left:Comparison of SEIR prediction and real number of infected individuals in Nebraska 2015 (because of big difference between predicted numbers by SEIR and the real numbers, the actual numbers are seems flat).Right:Comparison of NB-SEIR prediction and the real number of infected individuals in Nebraska 2015.

infected predicted is much higher than the real number of infected individuals. The SEIR model always starts with a portion of the whole population as Exposed number and the number of Infected defined as the transmission of Exposed individuals who have connections with an infected one at σ rate. The average number of neighbors calculated with the

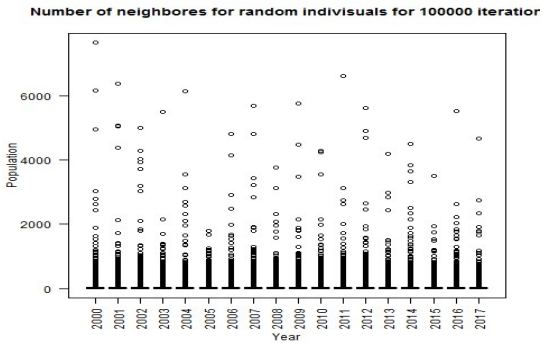

Figure 5: Number of neighbors (i.e. predicted number of expected individuals) for 100000 random nodes per year

PA network is used in our NB-SEIR model as the number of exposed individuals. Figure 4 (right) shows the NB-SEIR model for 2015, the comparison of predicted number of infected individuals in NB-SEIR model and the real number of reported cases in 2015 (with 36 number of infected for first week in both models). Comparison of this two models in Table 2 demonstrates higher accuracy in the NB-SEIR model when predicting the number of infected individuals in whooping cough. Figure 4 (right) shows that the epidemiology network model predicts a peak of infection.

In order to be sure that the random number does not affect the accuracy of the model, we repeated this process 100 times and the box plot shows that the variance of RMSE of each year is not very big, so we can be sure that even with 1000 different random nodes for 100 different random networks, the RMSE of NB-SEIR model still has a small variance. Figure 6 results demonstrates that the RMSE of NB-SEIR model was not significantly affected by this randomization.

		Standard SEIR			NB-SEIR		
Year	Actual Number of Infected	SEIR Prediction	ME	RMSE	NB-SEIR Prediction	ME	RMSE
2000	16	849510	-16028.20	31437.19	107	-1.92	4.25
2001	5	851790	-16071.40	31521.66	111	-2.00	4.36
2002	9	855328	-16138.10	31652.58	115	-2.00	4.58
2003	12	859593	-16218.50	31810.37	111	-1.87	4.35
2004	85	863808	-16296.70	31966.34	119	-0.64	6.21
2005	177	868547	-16384.30	32139.08	177	0.00	5.17
2006	37	872855	-16468.30	32300.87	115	-1.47	4.38
2007	45	877551	-16556.70	32474.96	111	-1.25	4.70
2008	170	883528	-16667.10	32695.70	160	0.19	8.29
2009	91	890808	-16806.00	32963.82	120	-0.55	3.44
2010	163	907386	-17117.40	33578.49	126	0.70	6.03
2011	42	913469	-17234.50	33803.25	149	-2.02	5.08
2012	90	920105	-17358.80	34049.29	111	-0.40	4.94
2013	117	926467	-17478.30	34284.58	119	-0.04	5.27
2014	243	932753	-17594.50	34516.21	164	1.49	10.46
2015	393	939148	-17712.40	34739.33	309	1.58	6.42
2016	100	945615	-17839.90	34991.77	143	-0.81	4.04
2017	45	954391	-18006.50	35318.00	126	-1.53	4.76

Table 2: The predicted number of infection, RMSE and ME for SEIR and NB-SEIR model years 2000-2017

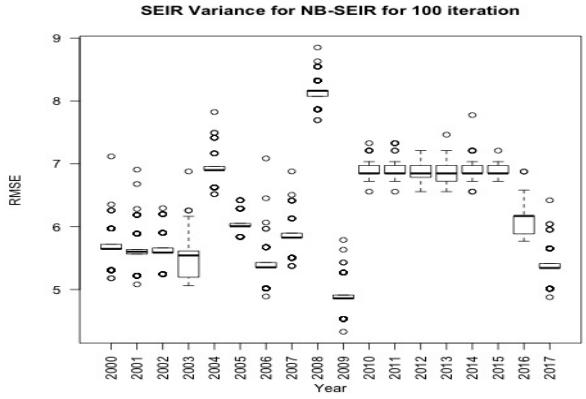

Figure 6: RMSE for 100 different NB-SEIR model for each year.

Discussion

A number of authors have speculated that the epidemic of whooping cough is based on randomness and may arise due to nonlinear spread in transmission and seasonal change in contact rates[21,31–34]. Additionally, several studies speculate that the epidemiological and social contact patterns of diseases fit the structure of a scale-free network[35–37]. Zhou *et al.* argued a fundamental connection between network traffic and network contagion on scale-free networks[10]. Based on these, we simulated a scale-free network to estimate the number of exposed individuals to make a better estimation of disease contagion. A number of authors have speculated that the epidemic of whooping cough is based on randomness and may arise due to nonlinear spread in transmission and seasonal change in contact rates[21,31–34], several studies speculate that the epidemiological and social contact patterns of diseases fit the structure of a scale-free network[35–37]. Therefore, to model the transmission of disease, we propose a Network-Based SEIR (NB-SEIR) model to simulate random transmission through social contact on scale-free networks generated using preferential attachment (PA). The aim of this paper is to demonstrate that the proposed NB-SEIR model increases the accuracy of prediction of infected

individuals. Specifically, this information can be used to quickly inform public health preparedness and prevention in states with low adherence to recommended vaccine schedules. In this work, we utilize whooping cough case reports in Nebraska from 2000 to 2017 to measure accuracy.

Having used the scale-free network to predict the number of exposed individuals and improve the SEIR accuracy in predicting the number of infected people, we used the SEIR and NB-SEIR models to predict the number of reported whooping cough cases in Nebraska from 2000 to 2017. We assume that instead of using a portion number of the population as exposed individuals, using the network properties can help to define a better estimation of exposed number. Mossong *et al.*[30] argued each individual has 13 connections with others during the day. In this work, we make an undirected network of the Nebraska population for each year with at least 13 connections for each node. For this purpose, a Barabasi network model with m= 13 as the number of neighbors was made using R. A random node in this network will be picked and the number of neighbors for this random node will be calculated. This process repeated 1000 times and for 100 different networks for each year. Then the average number of neighbors is calculated as an exposed number of individuals. In Figure 5, we show the number of neighbors for 1000 random nodes for each year and in 100 different random networks.

Applicability to other Diseases

The SEIR model that was used for our predictions can be easily applied to other contagious diseases with similar transmission patterns such as Influenza and Measles. Influenza is one of the most common contagious illness caused by influenza viruses. Influenza spreads simply through coughs and sneezes and can cause severe diseases and even death among high-risk populations, including the elderly, young children, and those with weakened immune systems or chronic illnesses. The Number of infected individuals in Nebraska for influenza in 2015 was gathered from the CDC[1] to evaluate this model. Table 3 show the result of the SEIR and the NB-SEIR models influenza in 2015 and reports the RMSE and ME for both models; once again, NB-SEIR outperforms SEIR.

	Standard SEIR			NB-SEIR		
Actual Number of Infected	SEIR Prediction	ME	RMSE	NB-SEIR Prediction	ME	RMSE
811	561070	-10774.21	10783.33	143	12.84615	17.883

Table 3: The predicted number of infection, RMSE, ME for SEIR and NB-SEIR model in 2015 for influenza

Conclusion

Reliable prediction of contagious diseases could impact the allocation of public health resources in prevention and in emergencies. In this study, we present an approach for predicting the number of infected individuals for whopping cough in Nebraska. The method presented in this study is based on the idea of social network contacts to improve the accuracy of prediction for the number of infected individuals. The database in used are aggregated from different reliable resources(CDC, HealthMap and TYHCO). The proposed NB-SEIR model can estimate the number of Infected more accurately than the standard SEIR model by better estimating the number of Exposed. This model shows a good improvement on the standard SEIR model, and can also find the peak of infection of disease successfully in the demonstrated case studies. As the next step, we are going to see how networks (social networks) changes over time and then evaluate our model based on the changes of networks and therefore exposed individual. This initial idea could be extended to more detailed models and observational studies.

Limitations

This is a preliminary method to improve the accuracy of the standard SEIR model. We can add several other important factors to the model. We did not consider birth rate, differential vaccination coverage and rate, weather changes and its' effect on the epidemiology. There are some other studies, which improve the SEIR standard equation. We did not consider those equations in our study because the focus of those papers was mainly to improve the number of surveillance individuals while we are working on the exposed population.

Supplementary files

All data and Codes we use for this paper is now available on line at:

https://github.com/kmcooper/SEIR

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