The Silent Epidemic:
Global Threat of Antibiotic Resistant Bacteria: Carbapenem-Resistant Enterobacteriaceae (CRE)

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Abstract

In silico mathematical modeling and optimization has been a reliable means to predict the morbidity of diseases. Diseases associated with Carbapenem-Resistant Entero-bacteriacae (CRE) are difficult to treat and have been with high mortality rates due to the highly adaptive nature of this bacterial family. Currently, CRE is resistant to almost all antibiotics available (Chen, Todd, Kiehlbauch, Walters, & Kallen, 2016) with mortality rates of about 45% ("Vital Signs", 2013). To better evaluate the severity of CRE outbreaks in Canada and the United States (US), a Python program that analyzes and predicts the potential of outbreaks escalating into epidemics was developed. The program uses two mathematical models that compare and graph the relative amounts of individuals/patients that are susceptible, infected or dead. The first model is deterministic which involves static rates taken from various data sources, whereas the second model is stochastic, which reflects dynamic rates according to parameters like time and changes in infectivity rate. Both models predicted epidemics in Canada and the US under current conditions, as expected.

Introduction

Carbapenem-Resistant Enterobacteriaceae (CRE) are gram-negative bacteria with highly evolved antibiotic resistance mechanisms. CRE mostly owe their rapid evolution of resistance to mobile genetic elements on their plasmids that can be transferred efficiently amongst bacteria (Kumarasamy et al., 2010). The resistance arises from certain genes that code for enzymes classified as β-lactamases, which cleave β-lactams—varied antibiotic molecules that inhibit bacterial cell wall synthesis (Nordmann, Dortet, & Poirel, 2012). Moreover, the mobility of plasmid genes and frequent global travel facilitate the spread of β-lactam resistance in global bacterial populations (Kumarasamy et al., 2010). Carbapenems are often the selected treatment for severe infections by extended-spectrum β-lactamase (ESBL) producing bacteria (Muhammed, Flokas, Detsis, Alevizakos, & Mylonakis, 2017; Harris, Tambyah, & Paterson, 2015), which are resistant to newer β-lactams such as third-generation cephalosporins and monobactams (Abreu, Marques, Monteiro-Neto, & Gonçalves, 2013). However, heightened use of carbapenems eventually selects for carbapenem resistance (McLaughlin et al., 2013).

Carbapenemases are β-lactamases that inactivate carbapenems. To date, there are several carbapenemases that have been identified, the most clinically significant being KPC, NDM, VIM, and IMP types (Tzouvelekis, Markogiannakis, Psichogiou, Tassios, & Daikos, 2012). Hypothetically, if any KPC carbapenemase were expressed in conjunction with any NDM, VIM, or IMP carbapenemase, the bacterium would have additional resistance to β-lactams such as all generations of cephalosporins, and aztreonams (Nordmann et al., 2012). Furthermore, NDM-1 is prevalent in parts of India and China (Liu et al., 2015; Kumarasamy et al., 2010), and KPC-2 and KPC-3 have become endemic in China, the US, and Italy (Munoz-Price et al., 2013).

The evident risk of CRE warrants its place in the first list of antibiotic-resistant priority pathogens, published by the World Health Organization (Lawe-Davies & Bennet, 2017). It catalogues the 12 families of bacteria that pose the greatest threat to human health, including Acinetobacter baumannii, Staphylococcus aureus, and Pseudomonas aeruginosa (Lawe-Davies &

Bennet, 2017). The family of interest, Enterobacteria-ceae, is categorized under 'Priority 1' (Lawe-Davies & Bennet, 2017). Bacterial families under 'Priority 1' are said to be critical threats, meaning that they often cause deadly infections, like pneumonia, and are resistant to numerous types of antibiotics, including carbapenems and third-generation cephalosporins (Lawe-Davies & Bennet, 2017). It is worthy to note that carbapenems and third-generation cephalosporins are the most effective antibiotics thus far to treat multidrug resistant bacteria (Lawe-Davies & Bennet, 2017). In addition, risk factors like the misuse of antibiotics (Bell et al., p. 11), inadequate hygiene in hospitals ("Antimicrobial Copper", 2015), direct contact with infected individuals ("Health-care-associated Infections", 2015), touching contaminated medical equipment (Russotto, Cortegiani, Raineri, & Giarratano, 2015; Roux, Aubier, Cochard, Quentin, & Mee-Marquet, 2013), and decreased antibiotic production ("Antimicrobial Copper", 2015) would increase the likelihood of a CRE epidemic.

In 2016, a CRE isolate from a fatal clinical case was tested against all 26 available antibiotics inthe US, and was found to be resistant to all of them (Chen, Todd, Kiehlbauch, Walters, & Kallen, 2016). CRE infections have also become endemic in many countries, including the US, Greece, Brazil, Israel, and China (Munoz-Price et al., 2013). A study by Thaden et. al concluded that, in community hospitals in the Southeastern US, diagnoses of CRE increased by five times from 2008 to 2012 (2014). In a study conducted in a Greek tertiary care university hospital, the number of carbapenem-resistant K. pneumoniae infections increased from 17 cases to 96 cases between 2005 and 2014 (Spyropoulou et al., 2016). A Europe-wide assessment of 38 countries found that 13 (34.2%) countries reported increasing rates of CRE infections, 16 (42.1%) reported no change in their epidemiological situations, and 9 (23.7%) reported improvement between 2013 and 2015 (Albiger, Glasner, Struelens, Grundmann, & Monnet, 2015).

It is important to create a mathematical model that can predict a CRE epidemic under current conditions, since data suggest that an epidemic may be imminent. Current conditions include the misuse of antibiotics in Canada ("CARSSR", 2016) and in the United States (Cable, 2017) . The model will use data from the United States (US) and Canada, due to their close interaction as countries. Additionally, giving experts and medical professionals access to a predictive program would aid in slowing the already increasing global incidence of CRE.

Python will be used to build this model, because in comparison to other programming languages, Python will provide a more mathematically rounded approach to the calculation of differential equations. Subsequently, these equations serve to model the spread of CRE infection and predict the consequences. However, given the epidemiology and high mortality of CRE infections, one can expect the model to predict a CRE epidemic in both Canada and the US.

Methods

The purpose of making the deterministic model, which consists of static rates, was to offer a comparison to and act as a basis for the stochastic model, which consists of changing rates. This enables us to assess the validity of the procedure, and to strengthen any conclusions. A deterministic SIR (Susceptible, Infected, and Recovered) model was created using the Python package, SciPy, which contains functions that solve and integrate the differential equations. The equations were run through the program for a calculation period of 160 months. The model consisted of eight parameters: mortality rate (g), recovery rate (rec), infection rate (b), susceptible population (S), total population (N), recovered population (R), infected population (I), and dead population (D). Mortality rate per annum was defined to be 40-50% ("Vital Signs", 2013), and we used 50% to model a worst-case scenario. The model is based on one month-intervals and thus, in the code, the monthly mortality rate was set as 0.042%. The value was derived from the yearly mortality rate. The recovery rate derived via empirical data from a study by Patel, Huprikar, Factor, Jenkins, and Calfee (2008).

Recent medical censuses performed in Canada and the U.S. ("Biggest Threats", 2016; "Canadian Antimicrobial", 2016) show that CRE infection rates are 0.2 and 0.26, respectively. For the general purposes of a model, the total population (N) in the simulation was set to be 1000, and the unit for population is in thousands. Susceptible (S), Infected (I), and Dead (D), were calculated via 3 separate differential equations, and are functions of a set of initial conditions (where $I_0 = 1$, as there must be one individual infected to start an epidemic; $R_0 = 0$, since it is impossible for recovery if infection has just started; $S_0 = N - I_0 - R_0 = 999$ individuals) and the infection, recovery, and death rates.

$$\frac{dS}{dt} = bSI \mid \frac{dI}{dt} = bSI - recI - gI \mid \frac{dR}{dt} = bSI - recI - gI \ (1)$$

To construct a stochastic model, the probabilities of each parameter increase by a set value with equations based on the prior deterministic model. SciPy was used to solve the differential equations. After running both programs, graphs produced from the stochastic model were compared with those from the deterministic model. If the shapes of the graphs are similar qualitatively, the coding procedure is valid. Additionally, similar graphs would serve to further support or falsify the hypothesis.

Epidemics are characterized by a dramatic rise in infection rates, then a sharp decrease or gradual decrease ("Descriptive Epidemiology"). In this simulation, the epidemic is allowed to dissipate on its own, resulting in a gradual decrease of infection cases ("Descriptive Epidemiology"). Moreover, the model a sumes that once individuals recover, they are no longer susceptible. Therefore, the infected curve should resemble a typical point-source epidemic curve, as there cannot be another subsequent outbreak. Also, with no more susceptible individuals at the end of the simulation, all three curves will approach a final slope of 0, or equilibrium, since the number infected and dead depend on the number susceptible. The approach to equilibrium and the shape of the infected curve apply to both stochastic and deterministic models. Should the curves behave in the ways stated, then one can conclude that both models predict a CRE epidemic under current conditions.

Results

When the program was run, it produced four graphs. Figures 1 and 2 represent the models for the Canadian data. Figures 3 and 4 repr sent the American data. All curves in Figures 1-4 approach equilibrium. It is seen that in both deterministic models, Figure 1 and Figure 3, the infected curve of Canada reaches a hig er Y-value than that of the US. This also occurs in the stochastic models Figures 2 and 4.

Discussion

In order for the graphs to model a CRE epidemic, all curves must approach equilibrium, and the infected curve must resemble a typical point-source epidemic curve. All graphs produced from the simulation model the dynamics of an epidemic, because the susceptible curves (A),
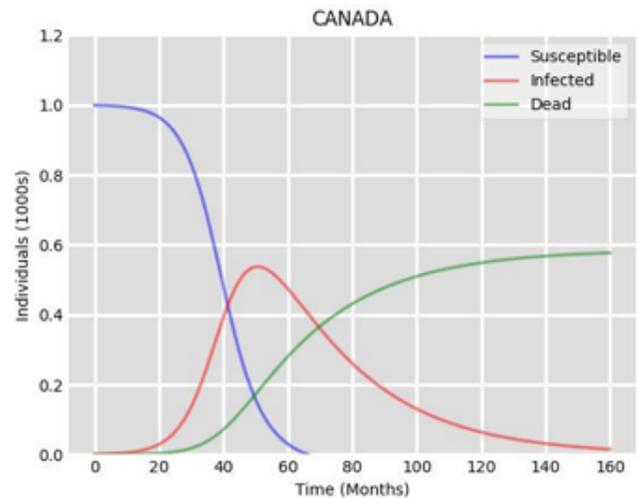

Fig. 1. This is a deterministic graph using Canadian data.

infected curves (B), and dead curves (C) all approach equilibrium. Curve B also resembles a point-source epidemic curve in all graphs. Thus, the deterministic and stochastic models predict epidemics in both countries. However, deterministic models of Canada and the US (Figures 1 and 3) suggest that the Canadian population comprises of more infected individuals than the United States. The same relationship can also be seen when comparing the stochastic models of the two countries (Figures 2 and 4). Taking the maxima of curve B from the deterministic models for Canada and the US, the models predict 18.3% more infections in Canada than in the US. Comparing the maxima of curve B from the stochastic models results in a 29.5% greater number of infections. These results suggest that Canada has a greater risk of a CRE epidemic than does the US.
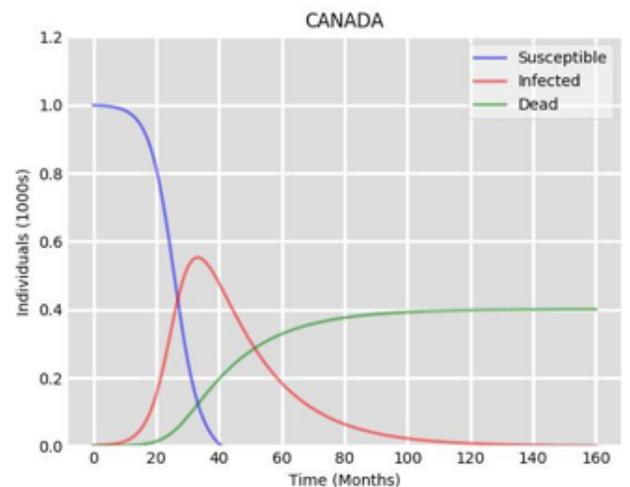

Figure 2. This is a stochastic graph using Canadian data.

This conclusion is supported by the minimal usage of of antimicrobial copper surfaces in the intensive care units (ICUs) of Canadian hospitals ("Antimicrobial Copper", 2015). ("Antimicrobial Copper", 2015). In contrast, the US has implemented antimicrobial copper surfaces ("Hospital-acquired Infection Risk", 2016), which means that American ICU patients have a lower risk of being infected. American ICUs are more prepared because CRE outbreaks appeared much earlier in the US than in Canada. Moreover, it is apparent from the disuse of copper surfaces that the Canadian medical sector has not begun to address CREs as a pertinent issue. To make matters worse, Canadians consume 6387.5 antibiotics per 1000 persons yearly (CARSSR, 2016), while Americans consume 835 antibiotics per 1000 persons yearly (6). That is, Canadians consume 7.6 times more antibiotics yearly than Americans. Together, these factors and the data explain the higher risk of a CRE epidemic in Canada.
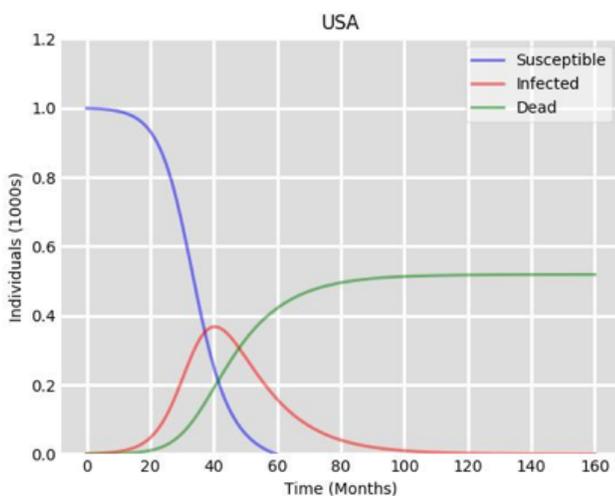

Figure 3. Deterministic graph of American data.

However, the models are not without its limitations. Specifically, the Canadian models are limited because Canada does not publish much data regarding CRE epidemiology, unlike the US. Therefore, the Canadian model would be re presentative of a few centres, but not necessarily the whole country. Nonetheless, the model serves to bring the CRE issue to light, which could inspire more research into the subject. The models also assume that after recovery, patients become immune to infection. This assumption was implemented for the sake of simplicity,

though it does not take away from the conclusion, as the models still predicted epidemics while still assuming immunity. That is, models that account for reinfection would result in a similar or more grave prediction. Finally, the models do not account for conditions such as increases in sterility and antibiotic production, so the behaviour of the curves is idealized. Because of the simplicity of the model, there is no reliable way of determining quantitatively how much more at risk Canada is for a CRE epidemic. The idealisation of curves also means that no sampling was involved in the data, hence preventing statistical analysis. Nevertheless, that is not to say that the general trends produced by the simulation do not apply to reality, because the parameters were based on empirical values.
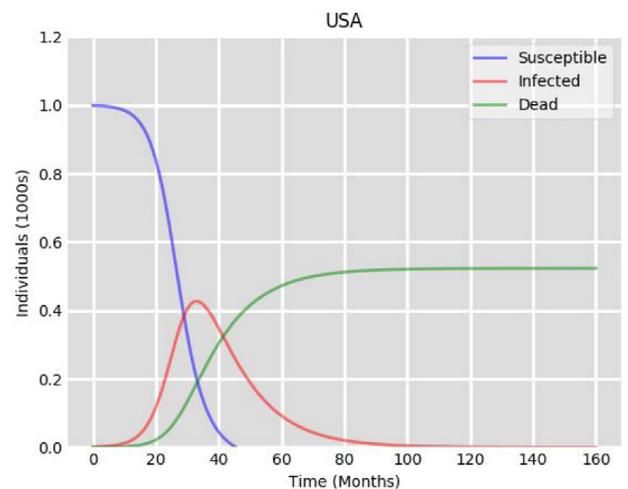

Figure 4. Stochastic model of American data. As shown, the U.S. graph approaches equilibrium much faster than the graph of Canadian data.

Conclusion

The hypothesis that CRE will become an epidemic in both the US and Canada is supported by the mathematical models. What has also been found through the model is that Canada is more at risk of a CRE epidemic. It should be acknowledged that there is still much research to be done on CRE epidemiology. Expanding data regarding CRE outbreaks in Canada is necessary to facilitate the development of better in silico predictive models. Finally, it is advised that hospitals become more vigilant when approaching hygiene and antibiotic use issues. More resources should also be put into early CRE detection techniques. Such steps are instrumental to hindering the evolution of antibiotic resistance, and minimising the risk of CRE epidemics.

PERCENTAGE OF INFECTED POPULATION AFTER ~35 MONTHS		
Country	Deterministic Model	Stochastic Model
Canada	43.4%	55.3%
US	36.7%	42.7%

Supp. Table 1. Maximum points on the Infected curve of both models for hospitals in both countries. Theses were all taken at about 35 calculated months under current conditions. The data show that Canada has more infected individuals at the epidemic's peak than the United States. Canada's higher percentage correlates with the higher misuse of antibiotics which directly contributes to the evolution of antibiotic resistance in CRE.

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