

The effectiveness of vaccine in the outbreak of diphtheria: mathematical model and simulation

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Abstract. In December 2017, Indonesia suffered a diphtheria outbreak that struck in 28 provinces. This incident made the public and researchers concerned about the cause of the return of epidemic after the last case in the 1980s. Over the years, DPT (Diphtheria Pertussis Tetanus) vaccine is believed to be the only ways of preventing diphtheria outbreaks. In this paper, the authors will attempt to construct a mathematical model for the case of diphtheria outbreak by involving vaccine parameter in the susceptible compartment. The population assumed to be closed population and consisted of SEIR (Susceptible, Exposed, Infected, and Recovered) population. Furthermore, this model will be analyzed the stability and sensitivity using Eigen values and basic reproduction number (R_0). The simulation is done to provide an overview of the effectiveness of the vaccine dynamically. Analysis and simulation results show that vaccine plays an effective role in reducing the spread of diphtheria, but this vaccine is only a preventive, not as a cure.

1. Introduction

Diphtheria is an infection caused by *Corynebacterium diphtheria* [1]–[5]. The actual disease is caused when the bacteria release the toxin or poison into the body's person. Diphtheria can be invasive to anyone, but it is commonly attacked to the children on 5-7 years old who did not get the basic vaccine of diphtheria [6]–[10]. In 2013, the diphtheria case is reported reach 4,700 cases while in 1980 there was almost 100,000 cases worldwide [11]–[15].

Today, diphtheria itself is actually such a rare outbreak in the worldwide. But in November and December 2017, Indonesia has an outbreak with more than 600 cases around 28 provinces [16]. The government and all the public health are intensively campaigned and recommended to the society to get the vaccine.

From the beginning of the appearance, the diphtheria vaccine is believed to be the only prevention to control the spread of diphtheria [7], [8], [16]. It is given to the susceptible people, while the people have a different treatment with the serum for the cure [3], [11].

In this article, the authors try to construct the model for the diphtheria including the vaccine as control parameter and see how effective the vaccine is in the outbreak of diphtheria.



2. Methods

In this paper, we will construct epidemic model based on SEIR model, which population consist of four subpopulation such as susceptible, exposed, infected, and recovered population. This model using autonomous ordinary differential equation where each compartments depends on variable of time t implicitly [5], [10], [17], [18]. The assumptions are also given to create the simple model but still relevant to the real life problem.

2.1. Assumptions

Before we construct the formula for the diphtheria case, we begin to make some assumptions to understand several things that really influenced on the construction of mathematical model. Assumed that population is to be closed and the total population is constant. The vaccine is effective to prevent the diphtheria. What we focused on how effective the vaccine is. The vaccine is temporary vaccine, where everybody who has got the last vaccine more than three years should take another new one. The recruitment rate on susceptible subpopulation is constant. The natural death for each compartment has the same value and constant. There is no death caused by the infection. To give the overview of the assumption, here is the following interaction diagram that represents the model

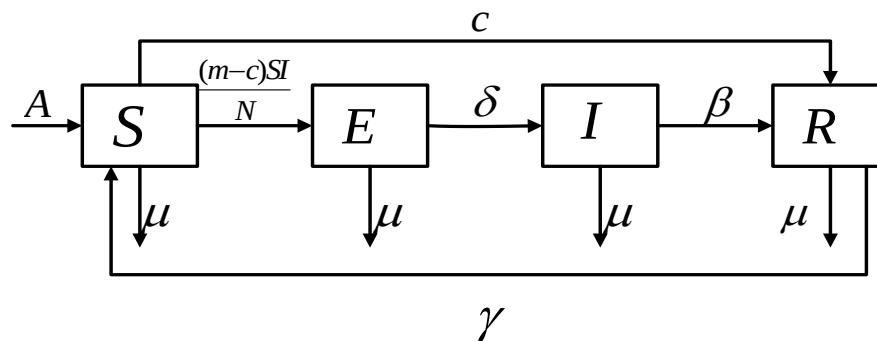


Figure 1. Diagram interaction of each compartment.

2.2. Mathematical model

Based on the diagram interaction above, here is the mathematical model that we construct for general case of diphtheria,

$$\dot{S} = A - \frac{(m-c)SI}{N} - (c + \mu)S + \gamma R \quad (1)$$

$$\dot{E} = \frac{(m-c)SI}{N} - (\delta + \mu)E \quad (2)$$

$$\dot{I} = \delta E - (\beta + \mu)I \quad (3)$$

$$\dot{R} = \beta I + cS - (\gamma + \mu)R \quad (4)$$

This following table is describe all variables and parameters that has been used for the model

Table 1. List of variables and parameters.

Notation	Description	Constraint
S	Susceptible subpopulation	$S > 0$
E	Exposed subpopulation	$E > 0$
I	Infected subpopulation	$I > 0$
R	Recovered subpopulation	$R > 0$
N	Total population	$N > 0$
A	Recruitment rate	$A > 0$
c	Probability of individual vaccine	$0 < c < 1$
m	Probability of disease spread	$0 < m < 1$
δ	Transition from exposed to infected subpopulation	$0 < \delta < 1$
μ	Natural death	$0 < \mu < 1$
β	Transition from infected to recovered subpopulation	$0 < \beta < 1$
γ	Transition from recovered to susceptible subpopulation	$0 < \gamma < 1$

The model has two solutions called equilibrium points which are disease free equilibrium denoted by $E_1 = (S, E, I, R)$ and endemic equilibrium denoted by $E_2 = (S^*, E^*, I^*, R^*)$. Disease free equilibrium happened where infected and exposed subpopulation remains zero. It means there is no infection around the population. Meanwhile, the endemic equilibrium is such a condition that there is infection around the population. That the reason why exposed and infected subpopulation always exist in the endemic equilibrium.

Furthermore, if there is an endemic around the population, the important thing to identify is basic reproduction number. Basic reproduction number or usually known as R_0 is the number that representing the average secondary infection caused by one individual infection [5], [10], [17], [18]. This number is the greatest eigen value from next generation matrix. For this model, basic reproduction number is describe as

$$R_0 = \frac{(m-c)(\mu+\gamma)\delta}{p(\mu^2 + (\delta+\beta)\mu + \delta\beta)} \quad (5)$$

where $R_0 < 1$ is the condition for disease free, while $R_0 > 1$ is the condition for endemic [17]–[21].

After we find basic reproduction number, next we have to solve the system to get the formula for both equilibrium points as follow

$$E_1 = \left(\frac{A(\mu+\gamma)}{\mu p}, 0, 0, \frac{cA}{\mu p} \right) \quad (6)$$

$$E_2 = (S^*, E^*, I^*, R^*) \quad (7)$$

where

$$S^* = \frac{Aqr}{\delta\mu(m-c)}$$

$$E^* = \frac{Ar^2qp(R_0 - 1)}{\mu[qr(\delta + \beta + \mu)pR_0 + \beta\delta^2(m - c)]}$$

$$I^* = \frac{Ar^2qp(R_0 - 1)}{\mu[qrpR_0 + (m - c)(\mu^2 + \mu\gamma + \mu\beta + \delta\beta + \gamma\beta)]}$$

$$R^* = \frac{Aq(c - \delta)\beta^2 + A\beta(\delta^2(m - \mu) + \mu^2(2c - \delta) + 3\delta\mu c) + Ac\mu q^2}{\mu[qrpR_0 + (m - c)(\mu^2 + \mu\gamma + \mu\beta + \delta\beta + \gamma\beta)]}$$

with

$$p = (c + \mu + \gamma)$$

$$q = (\delta + \mu)$$

$$r = (\beta + \mu)$$

and exist condition are $m > c$ and $R_0 > 1$.

The stability of these two equilibrium points will be analyzed through eigen value from Jacobian matrix [4], [13], [14], [18]. The general Jacobian matrix will be define as follow

$$J = \begin{bmatrix} -c - \frac{(m-c)\mu I}{A} - \mu & 0 & -\frac{(m-c)\mu S}{A} & \gamma \\ \frac{(m-c)\mu I}{A} & -\delta - \mu & \frac{(m-c)\mu S}{A} & 0 \\ 0 & \delta & -\beta - \mu & 0 \\ c & 0 & \beta & -\mu - \gamma \end{bmatrix}$$

By substituting each equilibrium point, then we going to get the eigen value that represent the stability of the equilibrium point. The eigen value must be negative so the equilibrium point remain stable.

3. Result

The result of the analysis above will be examine in the simulation. In this paper, the authors try to simulate the dynamical simulation of the system along the time t. The data has taken randomly based on the exist condition and the constraint that has been given in the methods. The initial conditions are the same for the whole simulations where

$$inc = \{(40, 10, 5, 6), (20, 5, 10, 2), (10, 15, 20, 8), (100, 10, 5, 20)\}$$

Table 2. Data of parameters for dynamical simulation.

Notation	Simulation		
	I	II	III
A	5	1	3
c	0.2	0.01	0.002

Table 2. Cont.

m	0.9	0.05	0.1
δ	0.9	0.02	0.2
μ	0.02	0.08	0.008
β	0.5	0.03	0.003
γ	0.5	0.001	0.00003

The first and second simulations obtained disease free condition, that means $R_0 < 1$. The first data give the result of $R_0 = 0.9510869565$, while the second data give the result of $R_0 = 0.06473526475$. Figure 2 and figure 3 below describe the dynamical simulation for the first and second data.

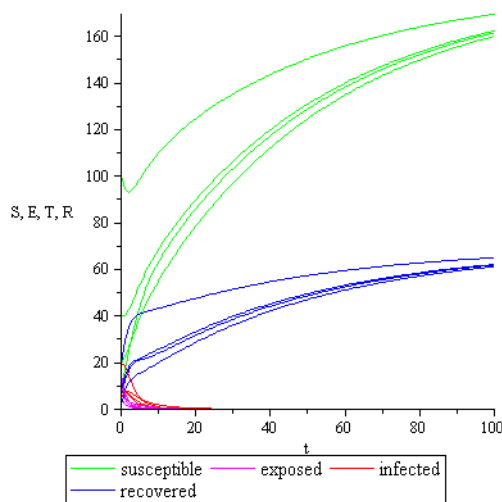


Figure 2. Dynamical simulation for $R_0 = 0.9510869565$

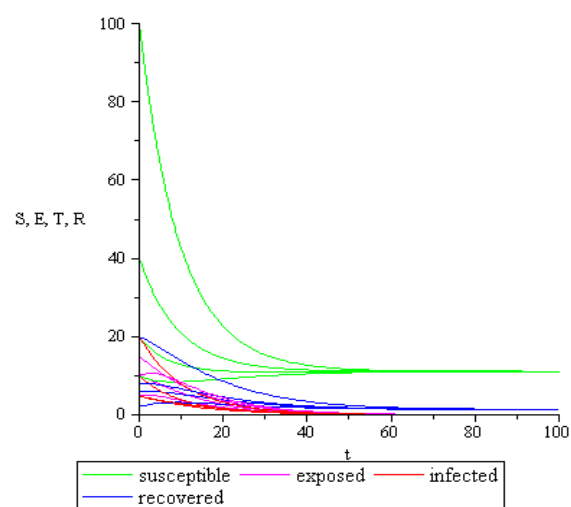


Figure 3. Dynamical simulation for $R_0 = 0.06473526475$

The third data give the result of $R_0 = 6.858271342$ that means it is in stable condition for endemic because $R_0 > 1$. The following graphic is the dynamical simulation for the last data (figure 4)

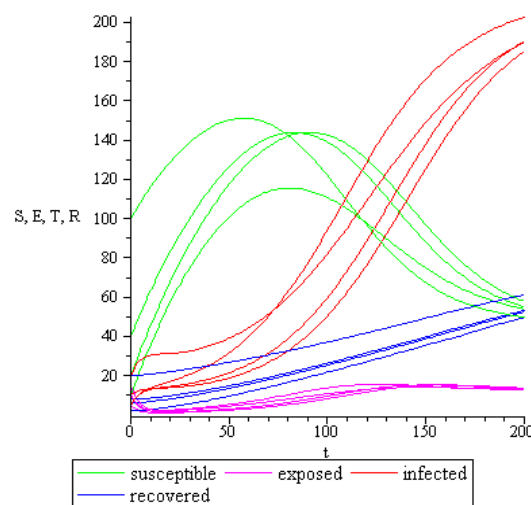


Figure 4. Dynamical Simulation for $R_0 = 6.858271342$

4. Discussion

In figure 2, the graphic is describing the disease free condition. The susceptible subpopulation increased followed by recovered subpopulation while exposed and infected subpopulation remains zero for a long time t . It happened because in disease free condition, the population is virgin population, there is no disease or infected around the population.

In figure 3 the graphic is still describes the disease free population, but the value is more less than the first one. It make the condition that susceptible and recovered subpopulations decrease in the beginning of time, but it is finally going constant along the time t . The exposed and infected subpopulation are also decrease but they remain zero for a long time t .

In figure 4 the graphic describe endemic condition, where exposed and infected subpopulation increased while the susceptible and recovered subpopulation are going decrease. The value is more than six that means one infected individual can infect six other individual at the same time. This value will be getting bigger if there is no prevention such as vaccine.

Based on the analysis and simulation, in the outbreak case of diphtheria, the spread of the disease must be greater that the action of prevention which is vaccine. It is correspond to the exist condition where $m > c$. It is also represents that the vaccine is effective to control the epidemic of diphtheria no matter what initial condition are. This vaccine is temporary but it is still effective because according to the simulation, the recovered subpopulation is automatically moved to the susceptible subpopulation and it will be increase the susceptible subpopulation no matter how big or small the transition parameter from recovered to susceptible subpopulation.

5. Conclusion

According to the explanation by analysis and simulation, the vaccine in the outbreak of diphtheria is effective to prevent the spread of diphtheria in the society. However, the exist condition could not be neglect in order to give the appropriate result. In the future, we would like to find the lower bound and upper bound for the parameter of the vaccine so we will know how effective the vaccine is. Also, this is such a model that represents the general case of the outbreak of diphtheria with vaccine as a prevention, not as a cure.

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References

- [1] C Definition and R Requirements 2016 *Case Definition*
- [2] M Mustafa, I Yusof, M Jeffree, E Illzam, S Husain and A Sharifa 2016 Diphtheria: Clinical Manifestations, Diagnosis, and Role of Immunization In Prevention *IOSR J. Dent. Med. Sci.* **15**(8) pp 71–76
- [3] U States, S Union and N I States 1924 Diphtheria: Questions and Answers *Immun. Action Coalit.* **4203**(651) pp 3–5
- [4] M A Yousuf 2015 *Publication First onlie e-Public*
- [5] R Q Zhang, H B Li, F Y Li, L X Han and Y M Xiong 2017 Epidemiological characteristics of measles from 2000 to 2014: Results of a measles catch-up vaccination campaign in Xianyang, China *J. Infect. Public Health* **10**(5) pp 624–629
- [6] Kolybo D V, Labyntsev A A, Korotkevich N V, Komisarenko S V, Romaniuk S I and Oliinyk O M 2013 Immunobiology of diphtheria. Recent approaches for the prevention, diagnosis, and treatment of disease *Biotechnologia Acta* **6**(4)
- [7] L Both, J White, S Mandal and A Efstratiou 2014 Access to diphtheria antitoxin for therapy and diagnostics *Eurosurveillance* **19**(24) pp 1–6

- [8] F T Cutts and M Hanson 2016 Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries *Trop. Med. Int. Heal.* **21**(9) pp 1086–1098
- [9] U Czajka, A Wiatrzyk, E Mosiej, K Formińska and A A Zasada Changes in MLST profiles and biotypes of *Corynebacterium diphtheriae* isolates from the diphtheria outbreak period to the period of invasive infections caused by nontoxigenic strains in Poland (1950–2016) *BMC Infect. Dis.* **18**(1) pp 1–8
- [10] M Kizito and J Tumwiine 2018 A Mathematical Model of Treatment and Vaccination Interventions of Pneumococcal Pneumonia Infection Dynamics *J. Appl. Math.* **2018**
- [11] J Driessen, Z D Olson, D T Jamison and S Verguet 2015 Comparing the health and social protection effects of measles vaccination strategies in Ethiopia: An extended cost-effectiveness analysis *Soc. Sci. Med.* **139** pp 115–122
- [12] P H Surveillance and C Diseases 2015 NICD Recommendations for the Management and Public Health Response to Diphtheria pp 0–15
- [13] M Torrea, J L Torrea and D Ortega 2017 A modeling of a Diphtheria epidemic in the refugees camps *bioRxiv* pp. 1–16
- [14] K Winter, S Nickell, M Powell and K Harriman 2017 Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis *Clin. Infect. Dis.* **64**(1)pp. 3–8
- [15] World Health Organisation (WHO) 2017 *Operational protocol for clinical management of Diphtheria Bangladesh* Cox's Bazar
- [16] I F Arifin and C I Prasasti 2017 Factors That Related With Diphtheria Cases of Children in Bangkalan Health Centers in 2016 *J. Berk. Epidemiol.* **5**(1) pp 26
- [17] A Nokkaew, C Modchang, S Amornsamankul, Y Lenbury, B Pimpunchat and W Triampo 2017 Mathematical modeling of infectious disease transmission in macroalgae *Adv. Differ. Equations* **2017**(1)
- [18] S Verguet, M Johri, S K Morris, C L Gauvreau, P Jha and M Jit 2015 Controlling measles using supplemental immunization activities: A mathematical model to inform optimal policy *Vaccine* **33**(10) pp 1291–1296
- [19] J Ojal et al 2017 Sustained reduction in vaccine-type invasive pneumococcal disease despite waning effects of a catch-up campaign in Kilifi, Kenya: A mathematical model based on pre-vaccination data *Vaccine* **35**(35) pp 4561–4568
- [20] M Pons-Salort et al. 2016 Preventing Vaccine-Derived Poliovirus Emergence during the Polio Endgame *PLoS Pathog.* **12**(7) pp 1–18
- [21] J M Prada, C J E Metcalf, S Takahashi, J Lessler, A J Tatem and M Ferrari 2017 Demographics, epidemiology and the impact of vaccination campaigns in a measles-free world – Can elimination be maintained? *Vaccine* **35**(11) pp 1488–1493