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Basic reproduction number and sensitivity analysis of Legionnaires' disease model

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Abstract

Legionnaires' disease is a very serious type of pneumonia (lung infection) caused by bacteria called Legionella. In this research, a mathematical model for the transmission dynamics of legionnaires' is developed. Four different reproduction numbers were obtained indicating the type of interaction between susceptible and infected and how the disease is propagated between adults and children and vice versa. The research shows that, using the human control reproduction number (R_E) as response function, the sensitive parameters in the formulated system (1) are the transmission probability (β), pubic enlighten awareness (θ), modification parameter (η), progression rate (α_c) and (α_a), recover rate (q_a) and natural mortality rate (μ_a).

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1.0 Introduction

Legionella pneumophila (*L. pneumophila*) is one of the important pneumolphila which is among the important pathogenic organism that can cause Legionellosis (Wee *et al.*, 2021). The water-associated transmission of *L. pneumophila* was first recognized in 1980 during an outbreak in a British hospital transplantation ward that was linked to the ward's showers (Mark *et al.*, 2019). Legionellosis has two distinct disease end points: Pontiac fever and Legionnaires' disease (LD). Legionnaires' disease is a serious type of pneumonia (lung infection) caused by Legionella bacteria. People can get sick when they breathe in small droplets of water or accidently swallow water containing Legionella into the lungs (Centers for Disease Control and Prevention, 2021). The reported incidence of Legionnaires' disease (LD) has increased over the past decade, and Legionella is now the leading cause of drinking-water-related infectious disease outbreaks in the United States (Beer *et al.*, 2012). Legionnaires' disease (LD) is unique in that it is a waterborne disease that can cause a severe, atypical type of pneumonia through inhalation of Legionella-containing aerosols. While outbreaks are highly publicized, they constitute only a small proportion of the total burden of Legionnaires' disease (LD) (Centers for Disease Control and Prevention, 2021; World Health Organization, 2022). More recently, the total incidence of reported Legionnaires' disease (LD) averaged between 1 and 3 cases per 100,000 population in the northeastern region of the United States (Kelsie *et al.*, 2019). Legionnaires' disease signs and symptoms are similar to other types of pneumonia, the most common symptoms were

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cough (68%) and fever (59.3%) more than half of patients (18, 56.2%) with legionnaires' disease could initially present with extrapulmonary manifestations. Sixteen (50%) patients had delay in initiation of appropriate antibiotic therapy (Wei *et al.*, 2019). There is reason to suspect that the disease is underdiagnosed and that reported rates are probably underestimates of true rates (Centers for Disease Control and Prevention United States, 2021). Due to the increased susceptibility of patients in healthcare environments, *L. pneumophila* is also a significant healthcare-associated infection hazard (Yaslianifard *et al.*, 2012). Many authors have worked on Legionnaires' disease transmission dynamics model.

Sensitivity analysis (SA) refers to a broad set of mathematical approaches designed to quantify how variation in model outputs may be attributed to model inputs (e.g. initial conditions and rate constants). These approaches allow researchers to assess how much trust to put in results obtained from a particular mathematical model (Kathryn *et al.*, 2019). The contribution of parameter to the reproduction number, reveals the effectiveness of each of the parameter value to persistence of the disease in the environment with time (Osman *et al.*, 2018). The level of contribution of each parameter of the model is usually evaluated by the relationship between each parameter and the reproductive number (Osman and Makinde, 2018). In an article published by Osman *et al.* (2018) on Modelling and Analysis of Trypanosomiasis Transmission Mechanism shows that an increase in both the animal and vector recruitment rates would increase the basic reproduction number. On a paper published by Yustina *et al.* (2020) on African trypanosomiasis dynamics: modelling the effects of treatment, education, and vector trapping shows that the most sensitive parameters are the tsetse fly biting rate on cattle, and tsetse fly natural mortality rate followed by tsetse fly recruitment rate. Increasing tsetse fly death rate and reducing tsetse fly biting rate through public health education can equally reduce the disease burden in the population.

2.0 Materials and Methods

We formulated a mathematical model where the human population is classified into adults and children. The variables $N_a(t)$ and $N_c(t)$ represent the total adults and children population respectively at time t. Table 1 specifically shows the classification of the total population into the following mutually exclusive compartments $(S_a(t), S_c(t))$ denote susceptible adults and children respectively; $(E_a(t), E_c(t))$, represent adults and children who are exposed to legionnaires; $(I_{am}(t), I_{cm}(t))$ are adults and children with mild disease ; $(I_{as}(t), I_{cs}(t))$ denote adults and children with severe infection; $(R_a(t), R_c(t))$ represent recovered adults and children population. Hence, we have that,

$$\begin{aligned} N_c &= S_c + E_c + I_{cm} + I_{cs} + R_c \\ N_a &= S_a + E_a + I_{am} + I_{as} + R_a \\ N &= N_c + N_a \end{aligned} \tag{1}$$

Susceptible adults and children contract legionnaires' when exposed to infected human population with force of infection given by

$$\lambda = \frac{\beta\left(I_{as} + I_{am} + \eta\left(I_{cs} + \eta_c I_{cm}\right)\right)(1-\theta)}{N} \tag{2}$$

Where λ is the disease force of infection?

The differential equations below describe the legionnaires' transmission dynamics

$$
\begin{aligned}
\frac{dS_c}{dt} &= \pi_c + \omega_c R_c - (\lambda + \gamma + \mu_c) S_c \\
\frac{dE_c}{dt} &= \lambda S_c - (\alpha_c + \mu_c) E_c \\
\frac{dI_{cm}}{dt} &= \alpha_c \varphi_c E_c + (1 - q_c) \sigma_{cs} I_{cs} - (\sigma_{cm} + \mu_c + \delta_{cm} + \chi_c) I_{cm} \\
\frac{dI_{cs}}{dt} &= \alpha_c (1 - \varphi_c) E_c + \chi_c I_{cm} - (\sigma_{cs} + \delta_{cs} + \mu_c) I_{cs} \\
\frac{dR_c}{dt} &= \sigma_{cm} I_{cm} + q_c \sigma_{cs} I_{cs} - (\omega_c + \gamma + \mu_c) R_c \\
\frac{dS_a}{dt} &= \pi_a + \omega_a R_a - (\lambda + \mu_a) S_a + \gamma S_c \\
\frac{dE_a}{dt} &= \lambda S_a - (\alpha_a + \mu_a) E_a \\
\frac{dI_{am}}{dt} &= \alpha_a \varphi_a E_a + (1 - q_a) \sigma_{as} I_{as} - (\sigma_{am} + \mu_a + \delta_{am} + \chi_a) I_{am} \\
\frac{dI_{as}}{dt} &= \alpha_a (1 - \varphi_a) E_a + \chi_a I_{am} - (\sigma_{as} + \delta_{as} + \mu_a) I_{as} \\
\frac{dR_a}{dt} &= \sigma_{am} I_{am} + q_a \sigma_{as} I_{as} - (\omega_a + \mu_a) R_a + \gamma R_c
\end{aligned} \tag{3}
$$

Table 1: Description of the variables and parameters of the Legionnaires' Model

Variables	Descriptions
S_a, S_c	Class of susceptible adults and children
E_a, E_c	Class exposed adults and children
I_{am}, I_{cm}	Class of adults and children with mild infection
I_{as}, I_{cs}	Class of adults and children with severe infection
R_a, R_c	Recovered adults and children population
Parameters	**Description**
π_a, π_c	Human recruitment rate for adults and children
μ_a, μ_c	Natural death rate for adults and children
β	Transmission probability per contact for adults and children
α_a, α_c	Rate of progression from exposed adults and children class to mild stages of infection
φ_a, φ_c	Fraction of exposed human (adults and children) who become infected at mild stages
$(1-\varphi_a)(1-\varphi_c)$	Remaining fraction of exposed human (adults and children) who acquire severe infection
χ_a, χ_c	Progression rate to severe stages of infection from mild stage for adult and children
δ_{am}, δ_{as}	Death rates due to infection for adults at mild and severe stages
δ_{cm}, δ_{cs}	Death rates due to infection for children at mild and severe stages
σ_{cm}, σ_{cs}	Recovery rates for children having mild and severe infection
σ_{am}, σ_{as}	Recovery rates for adult having mild and severe infection

γ	Growth and maturation rare
q_a, q_c	Proportion of recovered adults and children who clear all the bacteria from the body
$(1-q_a)(1-q_c)$	Proportion of those that still carry the bacteria
ω_a, ω_c	Reversion rate from recovered class to susceptible class for adults and children
θ	Public enlightenment awareness
η	Modification parameter
η_c	Modification parameter for children due to infection

2.1 The Basic Reproductive Number

In this section, we use the concepts of Next Generation Matrix to establish the linear stability of the disease-free equilibrium (ξ0). We computed the basic reproduction number. The basic reproductive number is the number of secondary infections produced by one infected person in a completely susceptible human population. The reproductive number combines the biology of infections with the social and behavioral factors causing contact rates (Ebenezer and Kazeem, 2016). The basic reproductive number is the threshold parameter that governs the spread of a disease. The next-generation matrix is defined as; $R_E = fv^{-1}$

Where ρfv^{-1} denotes the spectral radius of $R_E = fv^{-1}$

$$f = \begin{bmatrix} 0 & a\eta_c & a & 0 & b & b \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & c\eta_c & c & 0 & d & d \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{4}$$

Where,

$$a = \frac{\beta\eta(1-\theta)S_c^*}{N}, b = \frac{\beta(1-\theta)S_c^*}{N}, c = \frac{\beta\eta(1-\theta)S_a^*}{N}, d = \frac{\beta(1-\theta)S_a^*}{N} \tag{5}$$

and

$$v = \begin{bmatrix} k_2 & 0 & 0 & 0 & 0 & 0 \\ p_1 & k_3 & p_2 & 0 & 0 & 0 \\ p_3 & p_4 & k_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_7 & 0 & 0 \\ 0 & 0 & 0 & p_5 & k_8 & p_6 \\ 0 & 0 & 0 & p_7 & p_8 & k_9 \end{bmatrix} \tag{6}$$

where;

$$k_9 = (\gamma + \mu_c), k_9 = (\alpha_c + \mu_c), k_3 = (\sigma_{cm} + \mu_c + \delta_{cm} + \chi_c), k_4 = (\sigma_{cs} + \delta_{cs} + \mu_c), k_4 = (\omega_c + \gamma + \mu_c)$$
$$k_6 = (\mu_c), k_7 = (\alpha_a + \mu_a), k_8 = (\sigma_{am} + \mu_a + \delta_{am} + \chi_a), k_9 = (\sigma_{as} + \delta_{as} + \mu_a), k_{10} = (\omega_a + \mu_c), p_1 = -\alpha_c\varphi_c, \tag{7}$$
$$p_2 = -(1-q_c)\sigma_{cs}, p_3 = -\alpha_c(1-\varphi_c), p_4 = -\chi_c, p_5 = -\alpha_a\varphi_a, p_6 = -(1-q_a)\sigma_{as}, p_7 = -\alpha_a(1-\varphi_a), p_4 = -\chi_a$$

Then the control reproduction number is given as

$$R_E = \frac{R_{0,4}^a + R_{0,1}^c + \sqrt{\left(R_{0,1}^c - R_{0,4}^a\right)^2 + 4R_{0,4}^c R_{0,1}^a}}{2} \tag{8}$$

where;

$$R_{0,1}^{c}=\frac{\beta\eta\eta_c\left(1-\theta\right)S_c^*\left[\left(1-q_c\right)\sigma_{cs}\left(\alpha_c\left(1-\theta_c\right)\right)-k_4\alpha_c\varphi_c\right]}{Nk_2\left[k_3k_4-\left(1-q_c\right)\left(\sigma_{cs}\chi_c\right)\right]}+\frac{\beta\eta\left(1-\theta\right)S_c^*\left[\left(\alpha_c\varphi_c\chi_c\right)-k_3\alpha_c\left(1-\varphi_c\right)\right]}{Nk_2\left[k_3k_4-\left(1-q_c\right)\left(\sigma_{cs}\chi_c\right)\right]} \quad (9)$$

$$R_{0,4}^{c}=\frac{\beta\left(1-\theta\right)S_c^*\left[k_9\left(-\alpha_a\varphi_a\right)-\left(\left(1-q_a\right)\sigma_{as}\right)\left(\alpha_a\left(1-\varphi_a\right)\right)\right]}{Nk_7\left[k_8k_9+\left(1-q_a\right)\left(\sigma_{as}\chi_a\right)\right]}+\frac{\beta\left(1-\theta\right)S_c^*\left[k_8\left(-\alpha_a\left(1-\varphi_a\right)\right)+\alpha_a\varphi_a\chi_a\right]}{Nk_7\left[k_8k_9+\left(1-q_a\right)\left(\sigma_{as}\chi_a\right)\right]} \quad (10)$$

$$R_{0,1}^{a}=\frac{\beta\eta\eta_c\left(1-\theta\right)S_a^*\left[\left(1-q_c\right)\sigma_{cs}\left(\alpha_c\left(1-\theta_c\right)\right)-k_4\alpha_c\varphi_c\right]}{Nk_2\left[k_3k_4-\left(1-q_c\right)\left(\sigma_{cs}\chi_c\right)\right]}+\frac{\beta\eta\left(1-\theta\right)S_a^*\left[\left(\alpha_c\varphi_c\chi_c\right)-k_3\alpha_c\left(1-\varphi_c\right)\right]}{Nk_2\left[k_3k_4-\left(1-q_c\right)\left(\sigma_{cs}\chi_c\right)\right]} \quad (11)$$

$$R_{0,4}^{a}=\frac{\beta\left(1-\theta\right)S_a^*\left[k_9\left(-\alpha_a\varphi_a\right)-\left(\left(1-q_a\right)\sigma_{as}\right)\left(\alpha_a\left(1-\varphi_a\right)\right)\right]}{Nk_7\left[k_8k_9+\left(1-q_a\right)\left(\sigma_{as}\chi_a\right)\right]}+\frac{\beta\left(1-\theta\right)S_a^*\left[k_8\left(-\alpha_a\left(1-\varphi_a\right)\right)+\alpha_a\varphi_a\chi_a\right]}{Nk_7\left[k_8k_9+\left(1-q_a\right)\left(\sigma_{as}\chi_a\right)\right]} \quad (12)$$

Where $R_{0,1}^{c}$ basic reproduction is number due to interaction of children among themselves and defines the secondary number of infections derived from children with severe case in a susceptible human population. $R_{0,4}^{c}$ and is the reproduction number as a result of interaction between infected children and uninfected adults while $R_{0,4}^{a}$ represents the reproduction number as a result of interaction between infected adults and their uninfected children in a susceptible human population. Also $R_{0,1}^{a}$ shows the reproduction number due to interaction between adults and defines the secondary number of infections derived from adults with severe case in a human population.

3.0 Results and Discussion

3.1 Sensitivity analysis of legionnaire's model

In this work, we adopted the normalized forward sensitivity index of a variable, d, which depends differentially on a parameter, *S*, defined as: $S=\frac{d}{R_E}\cdot\frac{\partial}{\partial d}R_E$; where d is one of the parameters in the basic reproduction number whose sensitivity is to be determined. Globally, the purpose of sensitivity analysis is to determine how robust a parameter value is to the model. This is usually done to help identify the parameters with high impact on the basic reproduction number (R_E). The basic reproduction number is usually analyzed to find out whether or not treatment of the infective, mortality and vaccination could help in the control or eradication of the disease in the population (Ebenezer and Kazeem, 2016). Generally speaking, initially disease transfer is directly related to the basic reproduction number (Chitnis *et al.*, 2008). We shall calculate the sensitivity indices of the basic reproduction number $R_{0,1}^{c}, R_{0,4}^{c}, R_{0,1}^{a}, R_{0,4}^{a}$. The parameter values used in this section are shown in Table 2.

Table 2: Description of state variables and parameter

Parameters	Value	References
$\mu_c;\mu_a$	0.002;0.05	Erinle (2005)
α_c,α_a	0.1, 0.001	Ndelwa *et al.* (2015)
φ_c,φ_a	0.05, 0.20	Otoo *et al*. (2019)
$\chi_c;\chi_a$	0.0109; 0.04096	Ndelwa *et al.* (2015)
$\delta_{cm};\delta_{as}$	0.33; 0.33	Kizito and Tumwiine (2017)
$\sigma_{cm};\sigma_{am}$	0.0221; 0.33	Ndelwa *et al.* (2015)
σ_{as}	0.34	Otieno *et al.* (2013)
$q_c;q_a$	0.5; 1	Otieno *et al.* (2013)
$\eta_c;\eta$	0.05; 0.56	Estimated
θ	3	Estimated
β	10	Assumed

3.2 Sensitivity Analysis of $R_{0,1}^{c}, R_{0,4}^{c}, R_{0,1}^{a}, R_{0,4}^{a}$

Since we have the explicit expressions for $R_{0,1}^{c}, R_{0,4}^{c}, R_{0,1}^{a}, R_{0,4}^{a}$; we can derive an analytical expression for their sensitivity to each parameter using the normalized forward sensitivity index as described by (Chitnis *et al.*, 2008). The sensitivity indices of $R_{0,1}^{c}, R_{0,4}^{c}, R_{0,1}^{a}$, and $R_{0,4}^{a}$ with respect to the parameters β and θ equals to 1.000000000 and 1.000000000 respectively. Table 3 shows the sensitivity indices of the parameters in the $R_{0,1}^{c}; R_{0,4}^{c}; R_{0,1}^{a}$ and $R_{0,4}^{a}$.

Table 3. Sensitivity indices of $R_{0,1}^{c}; R_{0,4}^{c}; R_{0,1}^{a}$ **and** $R_{0,4}^{a}$

Parameters	$R_{0,1}^{c}$	$R_{0,4}^{c}$	$R_{0,1}^{a}$	$R_{0,4}^{a}$
β	**1.000000000**	**1.000000000**	**1.000000000**	**1.000000000**
θ	**1.000000000**	**1.000000000**	**1.000000000**	**1.000000000**
η	**1.000000000**		**1.000000000**	
η_c	- 0.1144091273		- 0.1144091273	
α_c	**1.000000000**		**1.000000000**	
φ_c	- 0.05789321030		- 0.05789321030	
χ_c	0.4348953869		0.4348953869	
σ_{cm}	0		0	
σ_{cs}	0.3254848093		0.3254848093	
δ_{cm}	0		0	
q_c	- 0.3254848092		- 0.3254848092	
μ_c	0		0	
α_a		**1.000000000**		**1.000000000**
φ_a		- 0.08117758182		- 0.08117758182
χ_a		- 0.01179424570		-0.01179424570
σ_{as}		0		0
σ_{am}		- 0.05934952371		- 0.05934952371
δ_{as}		- 0.05018516586		- 0.05018516586
q_a		- 0.3552434694		- 0.3552434694
μ_a		- 1.003026453		- 1.003026453

The most sensitive parameter was $\theta, \beta, \eta, \alpha_C$ and α_a for all the basic reproduction number. The least sensitive parameter for $R_{0,4}^{c}$ and $R_{0,4}^{a}$ was χ_a and for $R_{0,1}^{c}$ and $R_{0,1}^{a}$ was φ_c. The negative sign of the sensitivity indices for $R_{0,1}^{c}; R_{0,4}^{c}; R_{0,1}^{a}$ and $R_{0,4}^{a}$, reveals that increase in the parameters lead to the decrease in the corresponding basics reproduction number. Therefore, from the Table 3 it shows that an addition or reduction in the values of $\beta, \eta, \theta, \sigma_{cs}, \chi_c, \alpha_c$ and α_a will have an impact in increase or decrease in the spread of the Legionnaires' disease in the human population. For instance,

$$s_1 = \frac{\partial R_{0,1}^{C}}{\beta} \cdot \frac{\beta}{R_{0,1}^{C}} = 1.000000000$$ shows that

increasing or reducing the transmission rate by 5 percent may increase or reduce the number of secondary infections by 5 percent. Also from Table 2, it shows a reduction in the basic reproduction numbers $R_{0,1}^{c}; R_{0,4}^{c}; R_{0,1}^{a}$ and $R_{0,4}^{a}$ with respect to the values of $\sigma_{am}, \eta_c, \mathrm{q}_c, \delta_{as}, \varphi_c, \varphi_a, \mathrm{q}_a, \chi_a$ and μ_a

4.0 Conclusion

In this research, background of the study has been extensively discussed and a mathematical model of Legionnaires' disease has been formulated for the transmission dynamics. The model consists of both adults and children population. The population was subdivided into five (5) different classes that consist of susceptible, exposed, mild stage, severe stage and recover. The basic reproduction number for the model was carried out and sensitivity analysis was performed. This research has been carried out to investigate the transmission dynamics of Legionnaires' disease in a human population and control strategies in the population, the model has various control strategies that could be implemented to reduce the presence of Legionnaires' disease in a society. The research shows that, using the basics reproduction number (R_E) as response functions, as in Table 2 that system one has $\sigma_{am}, \eta_c, \mathrm{q}_c, \delta_{as}, \varphi_c, \varphi_a, \mathrm{q}_a, \chi_a$ and μ_a as the top Partial rank correlation coefficient ranked parameters. This proved that concentrating on these sensitive parameters can help in eliminating Legionnaires' disease in the population. It has been found that transmission probability per contact for adults and children, pubic enlighten awareness, modification parameter, rate of progression from exposed adults and children class to mild stages of infection, proportion of recover adults and children who clear all the bacteria from the body and natural deaths rate for adults are the most sensitive down to the least sensitive parameters in the basic reproduction numbers. Therefore, transmission probability per contact for adults and children, pubic enlighten awareness, modification parameter and rate of progression from exposed adults and children class to mild stages of infection contribute to the increase of the basic reproduction numbers while proportion of recovered adults and children who clear all the bacteria from the body and natural deaths rate for adults are the decreasing function of the basic reproduction numbers. This shows that reducing the rate of transmission probability per contact for adults and children, pubic enlighten awareness, modification parameter and rate of progression from exposed adults and children class to mild stages of infection well help in reducing the basic reproduction number while increasing the rate of proportion of recovered adults and children who clear all the bacteria from the body and natural death rate for adults will decrease the basic reproduction numbers.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

All authors have read and consented to the submission of the manuscript.

Availability of data and material

Not Applicable.

Competing interests

All authors declare no competing interests.

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