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MATHEMATICAL MODELING AND SIMULATION FOR CONTROLLING TYPHOID FEVER DISEASE

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Abstract: **we developed a mathematical model using a set of ordinary differential equations. This model was designed to investigate the transmission dynamics of typhoid fever, encompassing interventions such as enlightenment campaigns, treatment, and vaccination, all of which serve as crucial control measures. The findings of this study, shows the most effective way to control typhoid disease within a population is to use an effective educational enlightenment campaign on the radio, television, newspapers, in churches, mosques, and even in schools on the importance of individuals using safe water and better food hygiene practices. A typhoid patient should be encouraged to seek treatment at all times in order to protect their life and lower the disease's fatality rate. Finally, immunization of the vulnerable population should be encouraged, as prevention is preferable to cure. Sensitivity analysis was then carried out to determine which parameters that should be targeted by control intervention strategies of which the result shows that an increase in the enlightenment rate, treatment rate and rate of vaccination leads to a reduction in the prevalence of the disease. Finally, numerical simulation of the model was carried out and result shows that an increase in protection leads to low disease prevalence in a population.**

Keywords: **Mathematical Model, Ordinary Differential Equations, Transmission Dynamics, Typhoid Fever, Enlightenment Campaigns, Treatment, Vaccination, Control Measures, Educational Campaign, Water Hygiene, Food Hygiene, Disease Prevention, Sensitivity Analysis, Intervention Strategies, Disease Prevalence, Numerical Simulation, Protection.**

1. INTRODUCTION

Typhoid fever, caused by Salmonella Typhi bacteria, remains a significant global health concern, particularly in resource-limited regions. Efforts to understand the dynamics of typhoid transmission, control, and treatment have led to the development of mathematical models that provide valuable insights into the disease's complex behaviour. This paper aims to review relevant literature on mathematical models for typhoid fever transmission dynamics, shedding light on assumptions, variables, parameter definitions, and analyses. Through these models, researchers and public health officials can gain a deeper understanding of typhoid dynamics and devise effective strategies for disease control.

So much work have been done on the disease amongst which are shown below:

Typhoid fever derives its name from its resemblance to the symptoms of typhus. It is a prevalent infectious disease caused by the highly infectious and invasive Salmonella enteric serovar Typhi (S.Typhi), which primarily affects humans (Nthiiri et al., 2016). The transmission of this disease occurs through consumption of contaminated food, water, or beverages containing these bacteria. These bacteria travel through the human intestines and subsequently enter the bloodstream (Muhammad et al., 2015). Typhoid fever poses a substantial global health challenge, with its true impact difficult to gauge due to its clinical presentation resembling that of various other febrile infections. The disease exerts significant social and economic ramifications due to hospitalization of patients during acute phases and complications leading to income loss attributed to prolonged clinical illness (WHO, 2003).

Symptoms of typhoid fever encompass abdominal pain, fever, and a general sense of unwellness. As the disease progresses, high fever and severe diarrhea may manifest. The incubation period spans about 10-14 days, with occasional deviations of up to 3 days either way, totaling 21 days (Muhammad et al., 2015). The severity of the disease varies; for instance, when caused by S. Para typhi A, B, and at times C, it is less severe. It is particularly prevalent in regions such as Central America, the Indian subcontinent, South East Asia, and parts of Africa, including Nigeria. In the year 2000, an estimated 21.6 million cases of the disease resulted in 216,500 deaths worldwide (Muhammad et al., 2015).

Globally, typhoid fever affects millions annually, accounting for around 20 million reported cases and approximately 200,000 deaths. In Africa, the estimated incidence is 50 cases per 100,000 individuals. Vaccinating high-risk populations remains a key strategy for disease control, although the existing vaccines, both oral and injectable, are not entirely foolproof against the disease (Nthiiri et al., 2016). In resource-constrained regions, achieving public health goals for preventing and controlling the disease through safe water access, sanitation improvement, and medical care may pose challenges (Nthiiri et al., 2016). The significance of health education in raising public awareness and fostering behavioral changes cannot be overstated (WHO, 2003).

While typhoid fever is largely under control in Europe and North America, it remains endemic in many parts of the world, particularly in Asia, where it serves as a significant cause of febrile illness in densely populated, low-income settings. Notably, a characteristic of typhoid is the carrier state, where individuals who are asymptomatic continue to shed Salmonella Typhi bacteria in their stool or urine, perpetuating transmission (Conall, 2015).

Despite the World Health Organization's recommendation in 2003 for considering typhoid vaccination as a disease control measure, debates about vaccine effectiveness and its relationship with sanitation and hygiene improvements continue, reflecting contemporary policy deliberations. Health ministries and partners need to assess the integration of anti-typhoid vaccination alongside other measures like sanitation enhancements, water supply improvements, and hygiene practices to comprehensively combat the disease (Hardy, 2001).

Furthermore, an in-depth exploration into the efficacy of control strategies targeting the burden imposed by carriers on typhoid fever was undertaken in Kisii town. Moffat et al. (2014) formulated and analyzed a mathematical model to investigate the interplay between carriers, diagnosis, and health education in controlling typhoid fever in Kenya. The model considered diverse factors, including endogenous reactivation and exogenous re-infection in exposed individuals leading to typhoid fever. Treatment was recommended for all infected individuals except for those in a latent state. The model also integrated a contact structure, featuring non-homogeneous characteristics, modeled as a random graph, to represent potential modes of infection transmission. Notably, the research accommodated variations in the latent and infectious periods, allowing for distributions beyond the exponential. Numerical findings indicated that a reduction of 9.5% in typhoid carriers could pave the way for Kisii town in Kenya to attain a typhoid-free status by 2030 (Moffat et al., 2014).

Addressing the control of invasive Salmonella Disease in Africa, Malick et al. (2015) introduced the concept of human challenge models. Through human experimental oral challenge studies involving Salmonella, these models emerged as valuable tools for comprehending host-pathogen interactions and for testing novel diagnostic and vaccine candidates. The authors underscored the potential of human challenge studies to offer insights spanning from the initial point of infection to diagnosis, treatment, and convalescence, thereby facilitating progress in the control of invasive salmonella disease in Africa. They particularly highlighted the utility and safety of Salmonella Typhi human challenge models in vaccine evaluation, as demonstrated by the assessment of oral TY21a vaccination (Malick et al., 2015).

In the year 2015, Jones et al. contributed to the realm of disease dynamics by presenting a mathematical model elucidating the interplay between malaria and typhoid fever co-infections. The model introduced a heightened level of realism by subdividing the human population into four compartments: susceptible humans (S), infected humans (I), carrier humans (C), and recovered humans (R). Furthermore, an additional compartment denoting bacteria in the environment (B) was incorporated to account for typhoid's transmission through contaminated water and food. Notably, direct person-to-person transmission was omitted from the model due to the predominant water and foodborne nature of typhoid spread. By conducting a comprehensive mathematical analysis, the study revealed distinctive attributes of typhoid and malaria infection dynamics, thereby illuminating their interconnected relationships (Jones et al., 2015).

The outcomes of their investigation highlighted that the global dynamics of typhoid infection could be deciphered by a single threshold, denoted as Ro. Depending on whether the typhoid basic reproduction number is less than or greater than 1, the conditions for either global eradication or uniform persistence of the typhoid infection were established (Jones et al., 2015).

2. MODEL FORMULATION

In our study, we posit that susceptible populations (S) become exposed to bacteria at a level represented by (β) = ψBS, where ψ signifies the rate of interaction between susceptible individuals (S) and the bacteria (B). Additionally, the susceptible population is augmented due to the inclusion of recovered individuals who have lost their immunity and consequently become susceptible again at a rate denoted as (ρ). This category experiences reduction due to natural mortality, denoted as (μ), or due to vaccination against the disease at a rate of (Θ). Furthermore, a decline is attributed to the transition of susceptible individuals (S) to the exposed class (E), stemming from non-adherence to enlightening control measures to avoid exposure, which is marked as (x). Lastly, the acceptance of enlightenment control measures leading to vaccination at a rate of (z) also contributes to this decrease, thereby fostering an increase in vaccination rates.

The Exposed class (E) sees an increase via the progression of individuals from the susceptible class and the advancement of some vaccinated individuals who, through negligence, come into contact with bacteria (B) at a contact rate (δ), influenced by the declining rate of the vaccine indicated by (w). However, this population diminishes due to the transition of the exposed class to the infectious class at a rate (λ) and natural mortality at a rate of (μ).

Furthermore, the Infective compartment (I) experiences an upsurge owing to the progression of exposed individuals (E) to the infective class at a rate (λ). Conversely, this class is mitigated by treatment interventions at a rate (γ), contingent on the acceptance of enlightening control measures to undergo treatment at a rate (y). Ultimately, this class is diminished by natural death at a rate (μ) and disease-induced fatalities within the infective class at a rate of (d_1).

The Infective but on treatment class (IT) can be augmented through the progression of infected individuals undergoing treatment at a rate of (γ), conditioned by the acceptance of enlightening control measures to seek treatment at a rate of (y). This class declines due to the progression of successfully treated individuals to the Recovered class at a rate (ϕ). Mortality resulting from the disease at a rate (d_2) and natural death of individuals at a rate of (μ) also contribute to the reduction of this class, where (d_2) is less than (d_1). This discrepancy arises from the fact that the infective but on treatment class is undergoing treatment, leading to a reduction in the rate of disease-induced death within this compartment.

Furthermore, the Vaccinated class (V) expands due to the proportion of susceptible individuals (S) who receive vaccination at a rate (Θ), which is influenced by the rate at which susceptible individuals accept enlightening control measures to be vaccinated against the disease at a rate (z).

This class is diminished by the progression of vaccinated individuals to the Exposed class, where some proportion of vaccinated individuals, through negligence, encounter bacteria (B) at a contact rate of (δ), contingent upon the declining rate of the vaccine (w). Additionally, natural mortality at a rate of (μ) contributes to the reduction of this class.

The Recovered Class (R) grows due to the progression of the Treated Infectious class at a rate (ϕ). However, the Recovered class diminishes due to the rate at which Recovered individuals lose their immunity and become susceptible again at a rate (ρ). Furthermore, natural mortality at a rate (μ) also contributes to the decrease in this population.

Finally, the Bacteria Class (B) increases owing to the extent to which infected individuals release bacteria into food and water at a rate of k. Conversely, this class is reduced due to natural mortality at a rate of (μ_1). It is important to note that we assume that the multiplication rate of bacteria in water/food is considerably lower than the rate at which bacteria are shed by the infected class. In essence, we posit that bacteria do not multiply significantly in food or water.

2.1 Model Assumptions

1. Homogeneous Mixing: The population is assumed to mix homogeneously, meaning that individuals have equal chances of coming into contact with any other individual. This is often a simplification to make modelling more tractable.

2. Compartmentalization: The population is divided into distinct compartments, such as susceptible (S), exposed (E), infectious (I), treated infectious (I_T), vaccinated (V), recovered (R), and contacts (B). Individuals move between these compartments based on defined transition rates.

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3. Closed Population: The model assumes a closed population, meaning there is no immigration or emigration during the course of the analysis.

4. Constant Parameters: Many models assume that the parameters (transmission rates, recovery rates, etc.) remain constant over the time period of interest.

5. No Coinfections: The model does not consider the possibility of individuals being infected with multiple strains of the disease simultaneously.

6. Uniform Mixing and Contact Rates: The rate of contact between individuals and the probability of transmission are assumed to be the same for all individuals in the population.

7. Exponential Waiting Times: The model often assumes exponential distributions for the waiting times in each compartment, meaning the time spent in a particular state follows an exponential distribution.

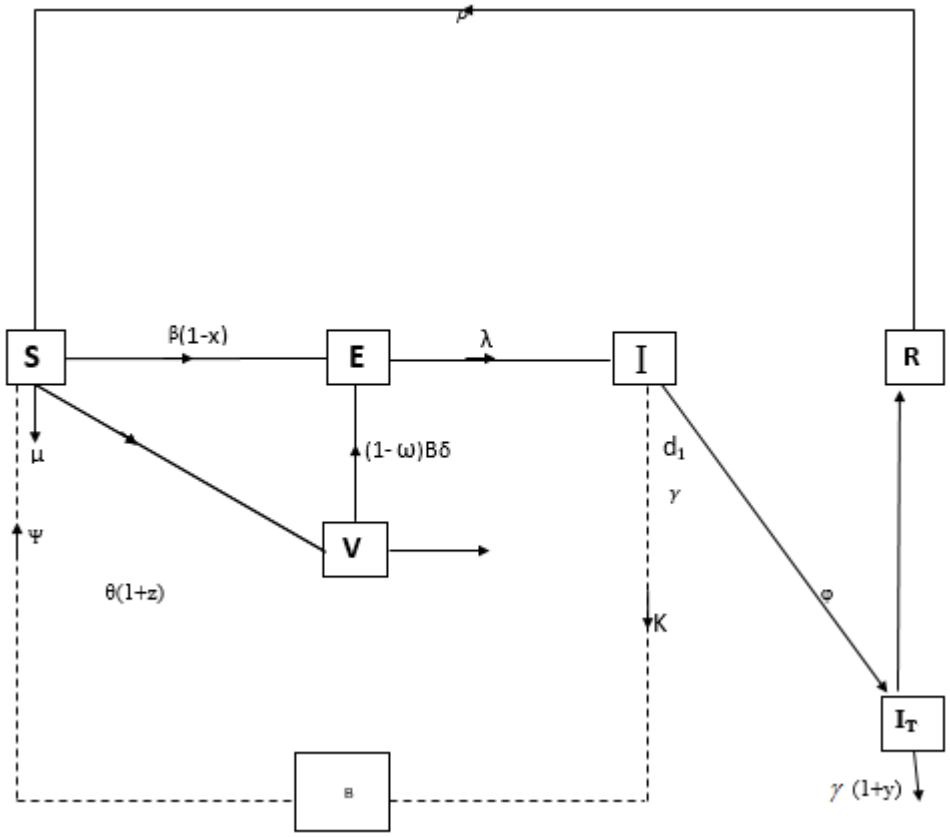

Figure 2.1: Schematic Diagram of Typhoid Fever

2.2 Variables and Parameters

Table 2.1: Description of state variables

State variable	Description
S(t)	Susceptible class with respect to time
E(t)	Exposed class with respect to time
I(t)	Infected Class with respect to time
$I_T(t)$	Infected but on treatment with respect to time
V(t)	Vaccinated class with respect to time
B(t)	Bacteria class with respect to time
S(t)	Susceptible class with respect to time

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Table 2.2: Description parameters

Parameter	Description
Λ	Recruitment level of the Susceptible Class
	Rate at which the Susceptible become exposed (Contact rate)
λ	Rate at which the exposed becomes infected and infectious.
Φ	Recovery rate for the Infected but on Treatment
Θ	Vaccination rate of the Susceptible class (control parameter)
(d_2) and (d_1)	Disease induced death rates for the Infected but on Treatment class and Infectious class respectively.
μ	Natural death rate
μ_1	Natural death rate of the Bacteria class
γ	Rate at which the infectious class accept treatment regime (control parameter)
ρ	Rate at which the Recovered becomes Susceptible again.
x	Rate of acceptance of Enlightenment to avoid being exposed (control parameter)
y	Rate of acceptance of Enlightenment to go for treatment (control parameter)
z	Rate of acceptance of Enlightenment to go for vaccination (control parameter)
ω	Efficacy rate of the vaccine
Δ	Rate at which some vaccinated individuals become exposed again by having a contact with the bacteria and this is subject to the waning rate of the vaccine
Ψ	Interaction rate between the Susceptible and the Bacteria.
k	The rate at which the infected shed bacteria into food and water

2.3 Model Equations

Equations (2.1) to (2.7) are the model equations from the above schematic diagram, figure 2.1

$$\frac{dS}{dt} = \Lambda - \psi(1-x)BS + \rho R - \theta(1+z)S - \mu S \quad (2.1)$$

$$\frac{dE}{dt} = \psi(1-x)BS + \delta(1-\omega)BV - (\lambda+\mu)E \quad (2.2)$$

$$\frac{dI}{dt} = \lambda E - \gamma(1+y)I - (d_1+\mu)I \quad (2.3)$$

$$\frac{dI_T}{dt} = \gamma(1+y)I - (\varphi + d_2 + \mu)I_T \quad (2.4)$$

$$\frac{dV}{dt} = \theta(1+z)S - \delta(1-\omega)BV - \mu V \quad (2.5)$$

$$\frac{dR}{dt} = \varphi I_T - (\alpha+\mu)R \quad (2.6)$$

$$\frac{dB}{dt} = KI - \mu_1 B \quad (2.7)$$

Remarks: $0 \leq x \leq 1$, x=0 implies that the Susceptible individuals are not educated or the educational campaign has no influence on the level at which the Susceptible individuals take in contaminated water/food.

Also $0 \leq y \leq 1$, y=0 implies that the Infected individuals are not enlightened on the need to always go for treatment or the educational campaign program has no influence on the level at which the Infected individuals go for treatment.

When $0 \leq z \leq 1$, z=0 implies that the Susceptible individuals are not vaccinated or the vaccine has no effect on the Susceptible individuals.

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Lastly $0 \leq w \leq 1$, w=0 implies that the vaccine wanes and the individuals loses protection by the vaccine, and as such the vaccinated class can become exposed again.

The total population is given by:

$N(t) = N_h(t) + N_b(t)$

N_h=Population of the humans

N_b=Population of the Bacteria

$$N(t) = S(t) + E(t) + I(t) + I_T(t) + V(t) + R(t) \quad (2.8)$$

The total population = the total population for Human + population of Bacteria.

2.4 Disease Free Equilibrium

At equilibrium states, the rate of change of the S, E, I, I_T, V, R and B are equal to zero.

At disease free equilibrium (DFE), there is no disease and so $E = I = I_T = B = V = 0$

$$\frac{ds}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dI_T}{dt} = \frac{dv}{dt} = \frac{dR}{dt} = \frac{dB}{dt} = 0$$

Where $S = S_0$, $E = E_0$ $I = I_0$, $I_T = I_{T0}$, $V = V_0$, $R = R_0$, $B = B_0$

From equation (1.1)

$0 = \Lambda - \psi(1 - x)BS, + \alpha R - \theta(1 + z)S - \mu S$

$$[\psi(1 - x)B + \theta(1 + z) + \mu]S = \Lambda + \rho R$$

Where R and B are the population of Removed class and Bacteria class at DFE

$$\Rightarrow S\frac{\Lambda}{\theta(1 + z) + \mu}$$

From equation (2.6)

HENCE = $-(\alpha + \mu)RR = 0$,

But $S = \frac{\Lambda}{\theta(1+z)+\mu} V = \frac{\theta(1+Z)\Lambda}{[\mu][\theta(1+Z)+\mu]}$ (2.9)

From equation (2.7), we know that B = 0

Equation (2.8) becomes

$$S = \frac{\Lambda}{\theta(1+Z)+\mu} \quad (2.10)$$

Equation (2.9) also becomes

$$V = \frac{\theta(1+Z)\Lambda}{\mu[\theta(1+Z)+\mu]} \quad (2.11)$$

Hence [E, I, I_T, V, R, B] = $\left[\frac{\Lambda}{\theta(1+Z)+\mu}, 0, 0, 0, 0, 0, 0\right]$ (2.12)

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2.5 Simulation of the Model

The simulation of the model equations was carried out using some mathematical tools as seen below to show different compartments in the models without control as seen in Figure 2.2 and models with control as seen in figure 2.2 below.

Table 2.3 show the sensitivity indexes for the control model to the parameters involved in the model (2.1) - (2.7), this analysis shows us how to reduce human mortality due to typhoid fever, it helps us to find out which parameters should be targeted by intervention strategies, and it also allows us to know how important each parameter is to disease transmission.

To determine which of the model's parameters (2.1) - (2.7) has a large influence on and to identify critical parameters that contribute to the reduction of typhoid fever transmission in the community. The normalized forward sensitivity index of a variable to a parameter is the ratio of the parameter's relative change.

Table 2.3: Numerical value of the sensitivity index

S/N	PARAMETERS	SENSITIVITY INDEX
1	Λ	1
2	$\boldsymbol{\theta}$	-1.907
3	$\boldsymbol{\Psi}$	9.956
4	δ	1.215
5	$\boldsymbol{\gamma}$	-3.6182
6	μ_1	-4.2884
7	$\boldsymbol{\mu}$	-0.02538
8	ω	0.251
9	Z	-0.000039
10	y	-0.0006676
11	x	-0.2015
12	k	1.007
13	$\boldsymbol{\lambda}$	6.09

We conclude from the sensitivity analysis conducted as given in the table above, the positive values increase the endemicity of the disease and the negative values decrease the endemicity of the disease.

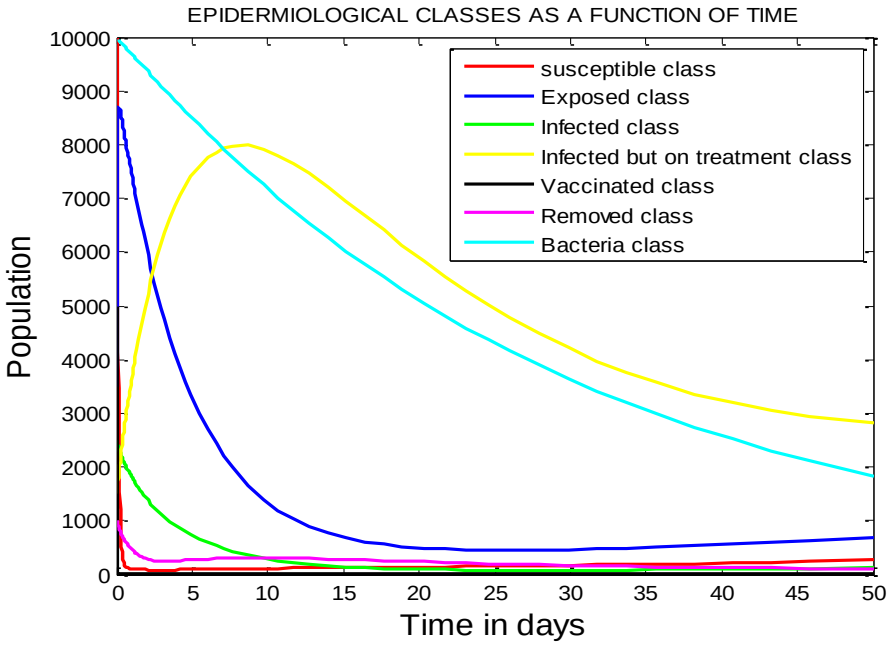

Figure 2.2: Different Classes for Models without Control.

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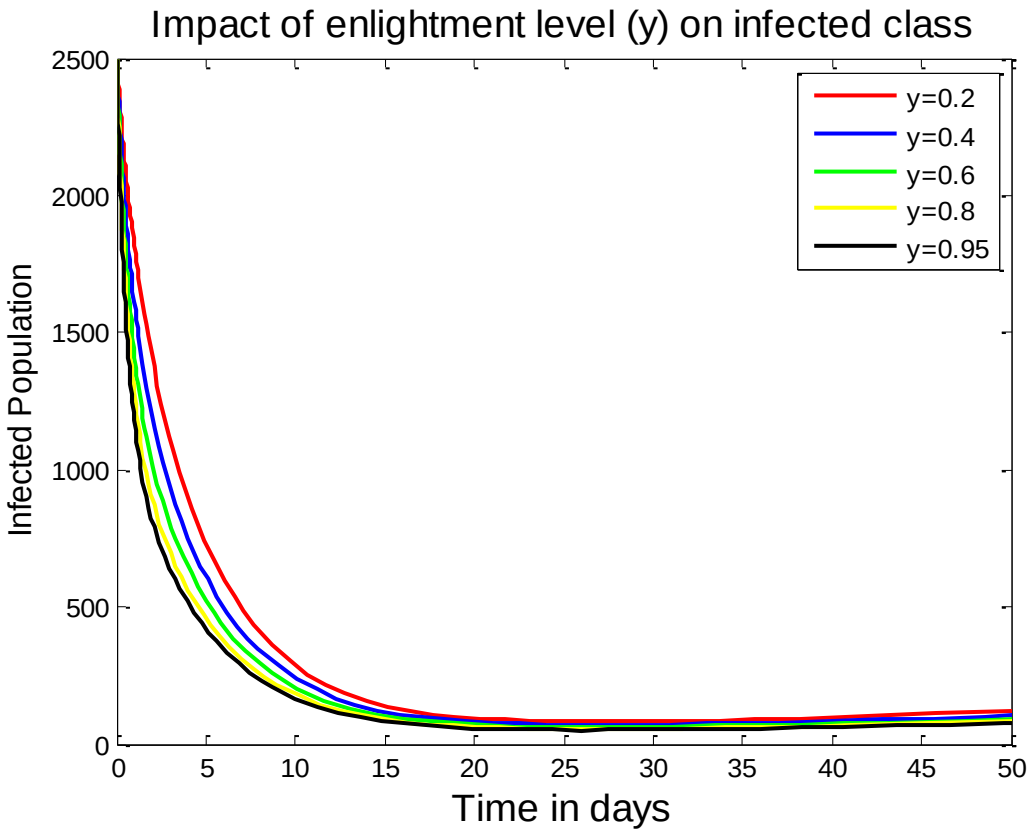

Fig 2.3 Impact of the Enlightenment level (y) on the Infected Class

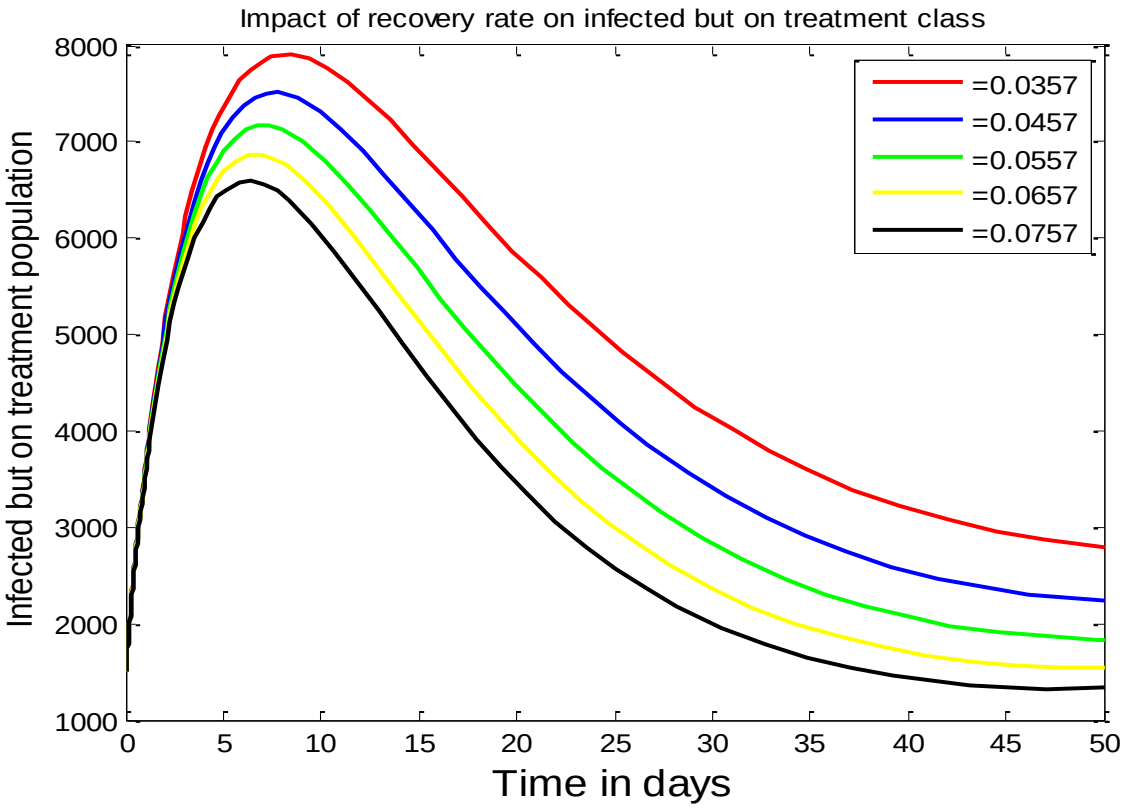

Figure 2.4: Impact of Recovery Rate (ϕ) on the Infected but on Treatment population

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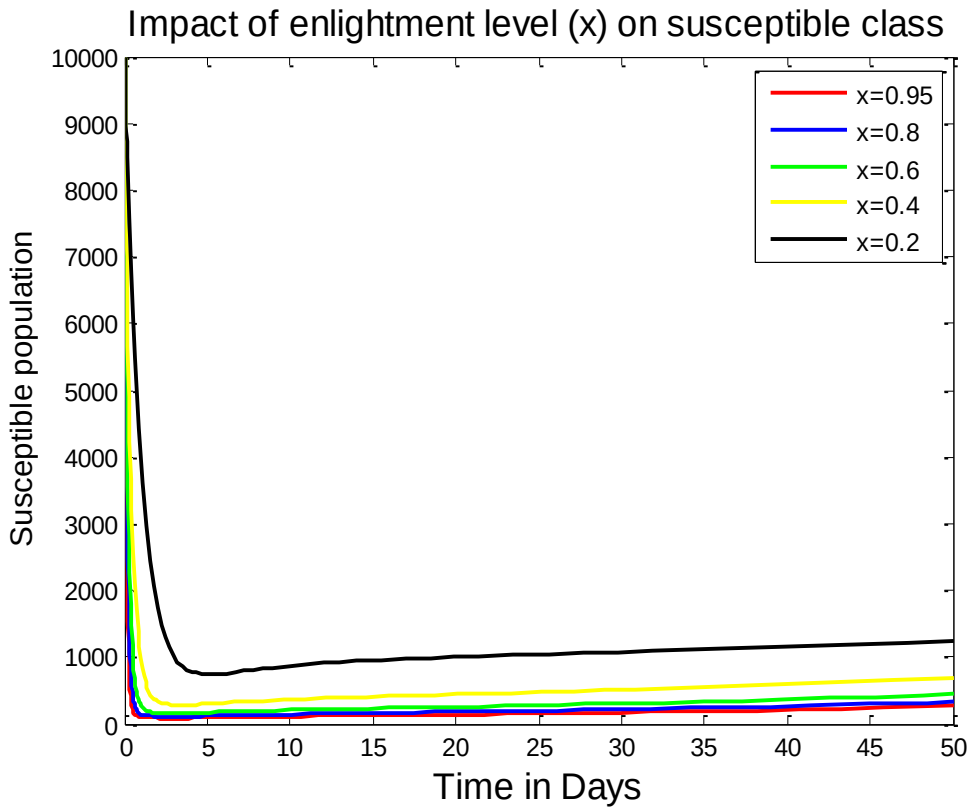

Figure 2.5: Impact of Enlightenment rate (X) on the Susceptible population

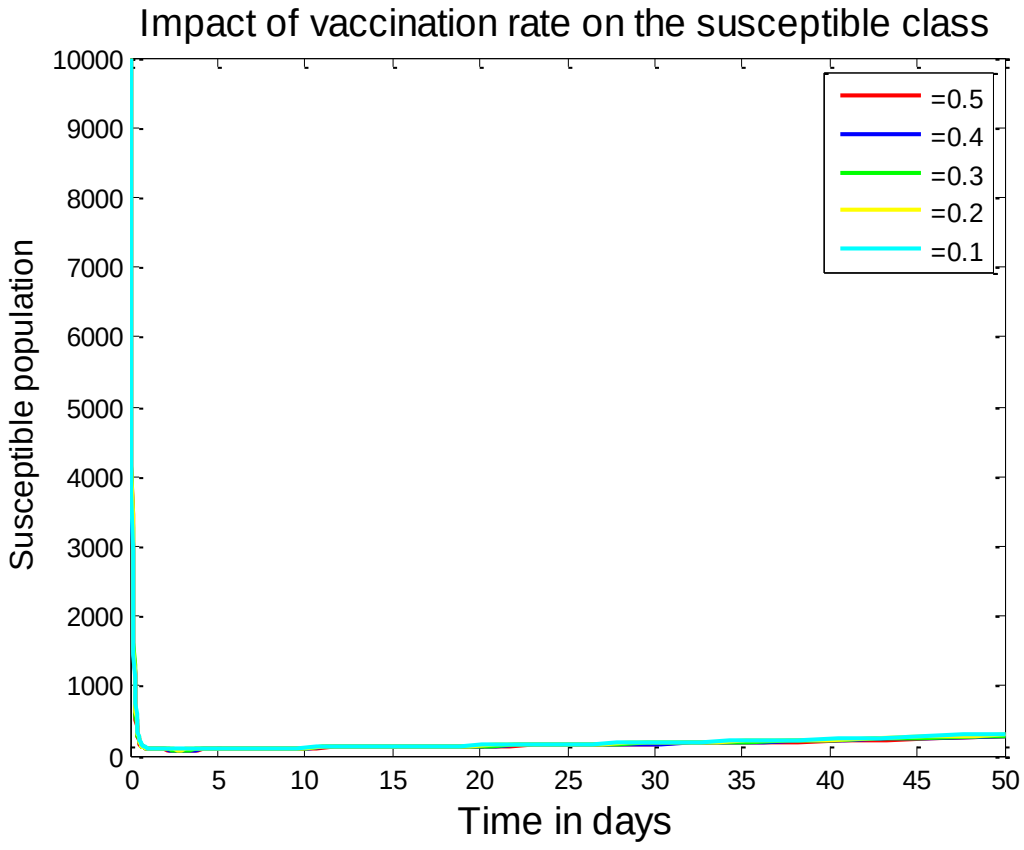

Figure 2.6: Impact of vaccination rate (Ɵ) on the susceptible class

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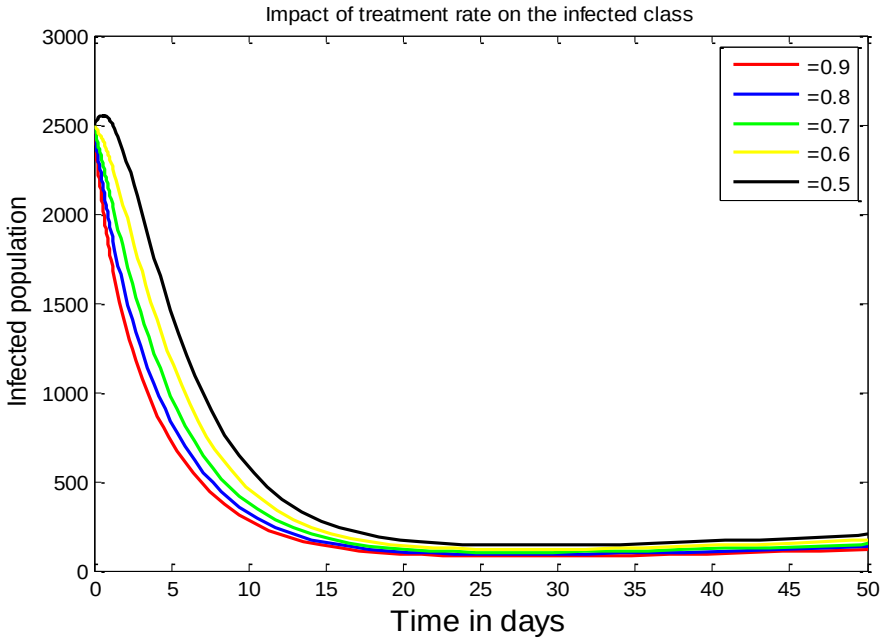

Figure 2.7: Infected Population

3. RESULTS AND DISCUSSION

Figure 2.2 illustrates the susceptible population's decline and eventual stabilization, driven by an enlightenment campaign promoting vaccination and avoidance of contaminated water and food. The Exposed class exhibits notable fluctuations before reaching an equilibrium state, influenced by the acceptance and rejection of the campaign. The Infected Class experiences a significant decrease due to patients embracing treatment after the awareness campaign. The Infectious but on treatment class initially surges due to patients not adhering to therapy, but it later diminishes as effective treatment is embraced. Maintaining discipline ensures survival. The Vaccinated class dwindles to zero since the susceptible population is entirely reduced, leaving no candidates for vaccination. The Removed or Recovered class declines due to immunity loss, rendering individuals susceptible again. The Bacteria class decreases due to reduced shedding rates from fewer infections and our assumption that bacteria doesn't multiply via cell division.

In Figure 2.3, intensifying enlightenment rates for Infected individuals to seek treatment diminishes their population. Untreated infections lead to inevitable Typhoid-related death, prompting more Infected individuals to seek treatment and lowering their numbers.

Figure 2.4 reveals that higher Recovery rates reduce the population of Infected but on treatment class. Recovered individuals transition out of the treatment class as they recuperate from Typhoid.

Figure 2.5 showcases that elevated enlightenment campaigns advocating safe water access and food handling practices curtail the susceptible population, preventing exposure to the bacteria.

In Figure 2.6 shows an increased vaccination rate reduces vulnerability within the susceptible population to Typhoid.

Figure 2.7 indicates that higher treatment rates correlate with a decreased infected population. Low awareness campaigns lead to an initial rise in infections, but sustained awareness prevents Typhoid-related deaths over time.

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