Mathematical Modelling of Diphtheria Transmission Dynamics for Effective Strategies of Prevention and Control with Emphasis on Impact of Vaccination and Waning Immunity

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Abstract

Diphtheria is a grave bacterial infection that, if not treated, can result in serious respiratory diseases and even mortality. Despite the existence of effective vaccines, diphtheria continues to be a significant public health issue in many regions of the world. This paper presents a novel mathematical model consisting of five compartments: Susceptible (S), Infected (I), Vaccinated (V), Vaccine-Induced Immunity (W), and Recovered (R). The aim is to enhance our understanding of diphtheria transmission dynamics and the effects of vaccination and waning immunity. The purpose of the model is to examine the patterns of diphtheria transmission and forecast the results in different situations, aiding in the assessment of the efficacy of different control methods. The model's key properties, such as the disease-free equilibrium and basic reproduction number, are analyzed to evaluate the circumstances in which diphtheria can either spread or be controlled. The study used numerical models to investigate the impact of vaccination coverage, waning immunity, and vulnerability on the spread of diphtheria. These simulations provide valuable insights into the ways in which these elements impact the transmission and management of the disease. The findings indicate that the integration of vaccination, efficacious treatment, and contact tracing can effectively control and diminish diphtheria outbreaks.

Keywords: Vaccination impact, Waning immunity, Disease-free equilibrium, Control measures, Infection spread

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I. INTRODUCTION

Diphtheria is a severe infection caused by the bacterium Corynebacterium diphtheriae, which produces a toxin leading to serious illness. The bacteria are primarily transmitted through respiratory droplets from coughing or sneezing but can also spread through contact with infected sores or ulcers. Those at elevated risk include individuals living in the same household or those with frequent close contact with infected individuals (CDC, 2022). Symptoms typically appear 2-5 days post-infection and vary in severity, including sore throat, hoarseness, a thick gray membrane covering the throat and tonsils, fever, chills, and fatigue. If untreated, diphtheria can cause complications such as respiratory issues, heart damage, and nerve damage (Mayo, 2023). Since December 2022, the NCDC has reported multiple diphtheria outbreaks across various states. By June 30, 2023, 798 confirmed cases were reported from 33 Local Government Areas (LGAs) in eight states, with Kano accounting for the majority (782 cases). The cases predominantly affected children aged 2-14, resulting in 80 deaths among confirmed cases (NCDC, 2023). From June to August 2023, Nigeria saw a significant increase in diphtheria cases, with 5,898 suspected cases reported from 59 LGAs in 11 states. Week 34 alone saw 234 suspected cases from 20 LGAs in five states, with one laboratory-confirmed case (WHO, 2023).

Reports suggest that even vaccinated individuals with lower immunity may still contract a mild form of diphtheria, highlighting the need for models to predict optimal vaccination coverage. Kanchanarat et al. (2022) developed a mathematical model to study diphtheria transmission, incorporating factors such as asymptomatic infection, population growth, and vaccination rates. Their analysis indicated that achieving a certain vaccination coverage level could eradicate diphtheria. Using data from Thailand, sensitivity analysis identified immunization rates and asymptomatic carriers as key factors in controlling diphtheria. Simulations demonstrated that the incubation period for asymptomatic cases affects the required vaccination coverage for eradication, emphasizing the importance of high immunization rates. Truelove et al. (2020) conducted nine systematic reviews to address gaps in diphtheria epidemiology and transmission, discovering a median incubation period of 1.4 days and an average colonization duration of 18.5 days in untreated patients. Their findings showed that

while three doses of the diphtheria toxoid vaccine are 87% effective against symptomatic disease, vaccination alone is insufficient to control outbreaks, necessitating additional measures such as isolation, antibiotics, and diphtheria antitoxin to limit morbidity and transmission.

Diphtheria vaccination is a key part of Nigeria's childhood immunization schedule, included in the pentavalent vaccine series. Despite this, global vaccination coverage rates have declined. The third dose of the diphtheria-tetanus-pertussis vaccine (DTP3) coverage dropped from 86% in 2019 to 81% in 2021, with Nigeria's overall vaccination coverage remaining low at 56%. Coverage rates vary significantly across states, from below 20% to 80%. This poor coverage fails to meet the herd immunity threshold of 75-80%. Factors contributing to low vaccination rates in Nigeria include maternal education levels, misconceptions about vaccines, household decision-making dynamics, misinformation, vaccine mistrust, adverse events following immunization, vaccine unavailability, distance from health facilities, and healthcare worker shortages (Adegboye et al., 2023).

In response to a 2017 diphtheria outbreak in Indonesia, Arguni et al. (2021) studied predictors of mortality in pediatric patients with clinical diphtheria. Their retrospective cohort study of medical records from five Jakarta hospitals and one in Tangerang District (January 2017 to August 2018) found a case fatality rate of 3.5%, with all fatal cases showing myocarditis. Key mortality predictors included incomplete diphtheria immunization, stridor, bull neck, high white blood cell count, and low platelet count. The COVID-19 pandemic's impact on healthcare infrastructure has hampered vaccination efforts, leading to increased diphtheria cases. Fauzi et al. (2024) used an SIR model incorporating DPT and booster vaccinations to estimate the basic reproduction number (R = 1.17) in West Java, indicating outbreak risk. Spatial analysis revealed diphtheria case clusters forming hotspots, suggesting significant risk in urban and rural areas. Simulations showed that increasing booster vaccination coverage could reduce case numbers, providing essential data for developing effective prevention and intervention strategies.

Diphtheria, a vaccine-preventable disease, often requires booster doses as immunity from initial childhood vaccines wanes over time. Madubueze and Tijani (2023) developed a mathematical model to analyze booster vaccination and environmental contamination's effectiveness in controlling diphtheria. The model's basic reproduction number (R) was used to assess the stability of a disease-free state, incorporating four control measures: disinfection, screening/treatment, booster immunization, and improved hygiene. Analysis suggested that combining booster immunizations with other measures significantly reduces diphtheria rates. When resources are limited, combining environmental disinfection with booster vaccination or screening/treatment with booster vaccination is recommended. The most effective strategy combines environmental disinfection, screening and treating asymptomatic carriers, and booster vaccinations.

.Diphtheria re-emergence in India predominantly affects children over five years old. Murhekar et al. (2021) studied age-specific immunity against diphtheria among 5-17-year-olds using residual serum samples from a cross-sectional serosurvey. Testing 8,309 samples across various regions, they found 29.7% of children were immune, 10.5% were non-immune, and 59.8% were partially immune. Regional non-immunity rates varied, with 6.0% in the south and 16.8% in the northeast. The study highlighted the need to enhance primary and booster vaccination coverage to close the immunity gap. Although diphtheria cases have decreased dramatically since vaccinations began, occasional outbreaks still occur. The World Health Organization (WHO) recommends booster doses following the initial series, but the optimal interval between doses is unclear. Kitamura et al. (2022) conducted a review and quantitative analysis of 15 cross-sectional seroprevalence studies to determine the duration of protective immunity after various vaccination doses. They found that antibody geometric mean concentration (GMC) declines to 0.1 IU/ml in 2.5 years after three doses, in 10.3 years after four doses, and in 25.1 years after five doses, providing insights into optimal booster timing.

Children typically receive three diphtheria vaccine doses in their first year, but immunity can wane, necessitating booster doses for continued protection. Olayiwola and Alaje (2024) developed a mathematical model to assess diphtheria transmission, dividing individuals into susceptibility, vaccination, infection, and recovery groups. The model demonstrated stability and calculated the effective reproduction number, with sensitivity analysis highlighting key control factors such as transmission rate, birth rate, and fading immunity. The study emphasized the importance of booster doses, treating infected individuals, and screening/treating asymptomatic carriers for diphtheria control, providing valuable guidance for healthcare authorities.

Recently, Akponana et al. (2024) conducted an investigation into transmission dynamics to inform effective strategies for controlling and preventing outbreaks of diphtheria is considered. The authours conducted basic properties of the model. The analysis highlights the importance of vaccination coverage, waning immunity, and susceptibility to the disease in diphtheria transmission. The models also suggest that a combination of vaccination, treatment, and contact tracing can be effective in controlling diphtheria outbreaks.

Despite the availability of effective vaccines, diphtheria still poses a significant public health challenge in many parts of the world. Hence this research is poised to study Diphtheria Transmission

Dynamics for Effective Strategies of Prevention and Control with Emphasis on Impact of Vaccination and Waning Immunity.

II. MODEL FORMULATION

The suggested mathematical model for diphtheria transmission is intended to describe the dynamics of disease spread and immunization in a population. It broadens the basic epidemiological framework by incorporating many compartments that represent various states of individuals in relation to the disease. The model categorizes the population into five compartments: susceptible (S), infected (I), vaccinated (V), vaccine-induced immunity (W), and recovered (R). The recruiting rate (Λ) reflects new persons joining the susceptible class. The transition rate (β) measures how quickly the disease spreads from infected to susceptible individuals. Infected

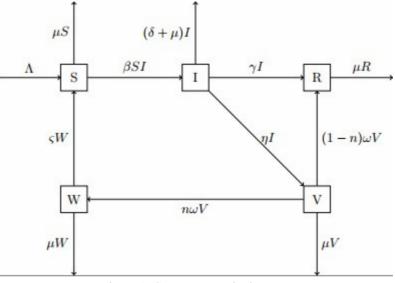


Figure 1: Compartmental Diagram

individuals transmit the disease at a rate proportional to (β SI). The natural death rate (μ) decreases the population in each compartment over time. Vaccinated individuals can shift to the immunity or recovery class. The compartmental diagram for the mathematical model describing the interactions between the various compartments is shown in the figure below:

<u>below</u> <u>The dynamics of each compartment are described by a set of differential equations which are given</u>

with The total population is given by at any time.

Table 1. Biological description of model parameter		
Parameters	Biological significance	Values
	Recruitment into susceptible class	0.2
	Transmission rate	0.2
	Rate of infected individuals getting vaccinated	0.2
	Natural death rate	0.001
	Disease induced death rate	0.008
	Recovery rate	0.1
	Rate of vaccinated individuals transitioning from V	0.2
	to either W or R classes	
	Waning rate of immunity	0.05
III Analysis of the model		

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Qualitatively study the dynamical properties of the model described by equations (1)-(5) is given as follows: *3.1.* **Positivity and boundedness**

For the model to be epidemiologically meaningful and mathematically well posed, it is necessary to establish that all solutions of system with positive initial data will remain positive for all times .

3.1 Positivity of Solution

From equations (2) to (5) we have

And by the first equation

That is

Thus

It could be observed from equations (6)-(10) that,

(1)

(2)

It follows that all solutions of the model are non-negative.

3.3 Boundedness

Therefore, adding all the equations of the system together, gives That is

If we assume that the rate of recruitment into susceptible class is more that the death due the disease, thus

Integrating the above,

The equation above implies that maximum total population is the population before the outbreak of the disease. It follows that the feasible solution sets of the model remain in the regions: . If the population exceeds the threshold, it decreases until it reaches the carrying capacity. Conversely, if the population is below the threshold, the model's solutions stay within a defined region for all times .

3.3. Equilibrium States

Determining the equilibrium points in mathematical models of infectious diseases is vital for guiding disease control methods and estimating the feasibility of eliminating the disease. In these models, two important types of equilibrium points are of primary importance: the Disease-Free Equilibrium (DFE) and the Disease-Endemic Equilibrium (DEE). Analyzing these equilibrium points gives information on the underlying dynamics of disease transmission, enabling researchers and public health professionals make informed decisions about managing and preventing the spread of infectious illnesses.

3.3.1. The Disease-Free Equilibrium (DFE)

The Disease-Free Equilibrium (DFE) in infectious disease models is the condition when the number of diseased persons in a population is zero, indicating that the disease is not circulating. It reflects a stable state where no new infections are occurring, giving a theoretical benchmark for evaluating disease management efforts. Analyzing the DFE helps epidemiologists understand the conditions needed to limit disease transmission and to assess the efficacy of public health initiatives, such as vaccination and treatment. In this situation, when there are no infected individuals (I= 0), the system becomes;

Therefore DFE,

3.3.2. The Disease-Endemic Equilibrium (DEE)

In mathematical models of infectious diseases, the Disease-Endemic Equilibrium (DEE) shows a steady disease prevalence in a population. This equilibrium points balances new infections and recoveries, keeping the number of affected people generally constant without vanishing. The Disease-Free Equilibrium (DFE) implies that the disease is absent from the population, while the DEE indicates that it is endemic but managed. Epidemiology relies on this notion to understand disease behavior, outbreaks, and the effects of immunization, therapy, and public health policies.

Solving the entire system of equations, we get DEE to be

3.4 Stability Analysis

Stability analysis is used to examine whether diphtheria spreads continuously, declines, or rises in a population. Epidemiological modeling relies on it to forecast infectious disease behaviour like diphtheria and assess intervention efficacy.

At the DFE, the Jacobian of the system of equation is computed and evaluated at DFE point

The eigenvalues gotten are

Given that, we have all eigenvalues to have negative real parts, this shows that the DFE is stable. This means that if the system is slightly perturbed through the introduction of a small number of infected individuals, the system will return to the DFE which indicates that the disease will not spread in the long term and the population will eventually return to a state with no infections.

3.4. The Basic Reproduction Number

The basic reproduction number is the average number of secondary infections caused by a single infectious individual in an entirely susceptible population during his/her infective period. The next generation matrix approach is used to obtain . Let and obtain that

where:

Evaluating the derivatives of and at the disease-free equilibrium point obtained above, yields as seen below:

By solving the dominant eigenvalue of the next generation matrix , we get the basic reproduction number to be

Therefore, the basic reproduction number of the given system of equations denoted by is:

3.5. Parameter Effects on the BRN

Sensitivity analysis is used to obtain the sensitivity index that is a measure of the relative change in a state variable when a parameter changes. We compute the sensitivity indices of to the model parameters with the approach used by Chitnis et al. (2008). These indices show the importance of each individual parameter in the disease transmission dynamics and prevalence. The sensitivity of a parameter, say, of is defined as

Therefore the table, (Table 2) below present the sensitivity indices of the parameters on Basic Reproduction Number

Parameter	Sensitivity Index
	1.00000
	1.00000
	-0.02589
η	-0.64725
	-0.32362
	-1.00324

 Table 2: Sensitivity analysis on Basic Reproduction Number

III DISCUSSION OF RESULTS

In epidemiological models such as SIVWR, the transition rate from the Vaccinated (V) compartment to either the Vaccine-Induced Immunity (W) or the Recovered (R) compartment as shown in Figure 1, 2 and 4 represents the rate at which vaccinated individuals either develop immunity or recover without acquiring immunity. When the transition rate from V to W is high, it indicates that a significant portion of vaccinated individuals rapidly develop immunity. This trend leads to a larger W compartment, signaling a strong immune population, which in turn reduces the risk of disease transmission within the community. The growth of W also reduces the number of individuals in the V compartment, as more people transition to immunity. On the other hand, a lower transition rate from V to W suggests that a smaller fraction of vaccinated individuals develop immunity, potentially leaving the population more susceptible to outbreaks. This results in a smaller W compartment and a larger V compartment, indicating that vaccinated individuals are taking longer to become immune, thus impacting the overall disease dynamics. The transition rate from V to R influences the size of the Recovered compartment. A higher transition rate from V to R indicates that more vaccinated individuals recover without gaining vaccine-induced immunity. This trend could reflect limitations in vaccine effectiveness or other recovery pathways that do not result in lasting immunity. As a result, the size of the R compartment increases.

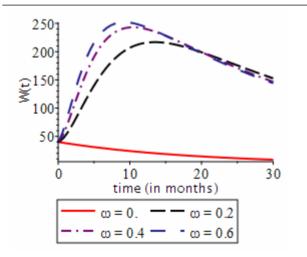


Figure 1: Effect of the transition rate from V to either W or R on the vaccine-induced immunity population.

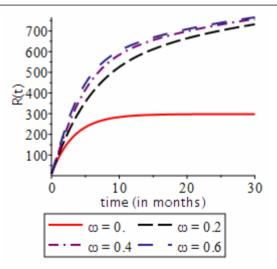
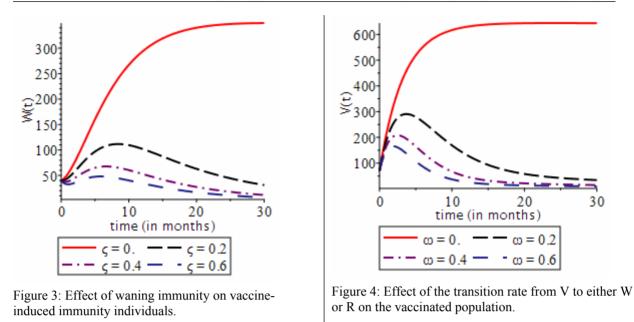


Figure 2: Effect of the transition rate from V to either W or R on the recovered population.



A lower transition rate from V to R, however, suggests that fewer vaccinated individuals recover without immunity, potentially indicating a more robust vaccine-induced immune response. This pattern results in a smaller R compartment, emphasizing that more individuals from the vaccinated group are transitioning to vaccine-induced immunity. Broadly, these transition rates are crucial in determining the effectiveness of vaccination campaigns and understanding the balance between achieving vaccine-induced immunity and other recovery outcomes. They offer insights into disease control, informing public health strategies to manage and mitigate outbreaks effectively. By analyzing these rates, policymakers can adjust vaccination protocols to promote a quicker transition from V to W, ideally leading to a more resilient population with a higher level of immunity.

The natural death rate as seen in Figure 9, 10 and 11 has a significant impact on the dynamics of disease transmission and the strategies used to manage public health. In the Infected (I) class, a high natural death rate can lead to a quicker reduction in the number of infected individuals, thereby shortening the duration of an outbreak and reducing the potential for disease transmission. However, this increase in natural mortality may also place a strain on healthcare systems, requiring more resources for end-of-life care and managing higher death rates. This scenario could also indicate a greater risk for vulnerable populations, emphasizing the need for stronger healthcare support and effective disease management. Conversely, if the natural death rate in the Infected class is low, it implies that infected individuals remain in the population for a longer period, possibly leading to a prolonged outbreak. This can increase the risk of transmission and impose a heavier burden on healthcare resources due to the extended care required for these individuals. The longer duration could also affect the overall recovery rate and increase the spread of the disease to susceptible individuals. In the Vaccinated (V) class, a high natural death rate leads to a decrease in the vaccinated population, which can weaken the community's immunity over time. This reduction in vaccinated individuals might hinder the ability to achieve or maintain herd immunity, thereby increasing the risk of new outbreaks. It could also suggest a need for more frequent booster shots or additional vaccination campaigns to maintain a protective level of immunity within the population while on the other hand, a lower natural death rate in the Vaccinated class helps maintain a larger number of vaccinated individuals, contributing to the overall stability of immunity in the community. This condition supports ongoing efforts to achieve herd immunity and can reduce the frequency of required booster shots or additional vaccination drives. For the Vaccine-Induced Immunity (W) class, a high natural death rate can significantly reduce the proportion of the population with vaccine-induced immunity. This decrease could result in a higher risk of subsequent outbreaks and a greater need for continual vaccination programs to replace those who have passed away due to natural causes. It also points to a less stable level of immunity within the population, requiring ongoing public health efforts to sustain protection against the disease. In contrast, a lower natural death rate in the Vaccine-Induced Immunity class helps maintain a more robust and stable immune population. This stability contributes to the long-term control of the disease and reduces the need for constant vigilance or frequent vaccination campaigns.

The disease-induced death rate as shown in Figure 12 indicates the lethality of a disease and has a major impact on public health dynamics. A high disease-induced death rate leads to a quicker reduction in the

infected population, which can help contain outbreaks but also results in increased mortality and a strain on healthcare systems. This rate can create public concern due to its impact on society and healthcare resources. Conversely, a lower disease-induced death rate suggests that more infected individuals are likely to recover, potentially prolonging the duration of an outbreak. While this might reduce the immediate burden on healthcare from fatalities, it can increase the demand for treatment and extend the period of disease transmission. Understanding and managing the disease-induced death rate is crucial for public health planning, as it affects outbreak control, healthcare capacity, and the overall impact on society.

Waning immunity is the gradual loss of immunity over time, affecting both individuals with vaccine-induced immunity (as shown in Figure 3) and the broader population. For individuals in the Vaccine-Induced Immunity (W) class, waning immunity means they may eventually lose their protection and become susceptible again. This shift decreases the immune population and increases the risk of re-infection, contributing to the overall susceptible pool. As a result, there's a higher likelihood of disease resurgence and new outbreaks, especially in populations with a high disease transmission rate or low vaccine coverage. For the broader population, waning immunity results in an increase in the Susceptible (S) class as more individuals revert from the immune state. This expansion of the susceptible pool can destabilize herd immunity, requiring a higher proportion of the population to be vaccinated or have natural immunity to maintain a protective threshold. Consequently, there's a greater risk of outbreaks, which can strain healthcare systems and necessitate more aggressive public health measures. To mitigate the effects of waning immunity, public health officials may need to implement regular vaccination campaigns or booster programs to maintain a stable level of immunity. This approach helps to ensure a consistent immune population and reduce the risk of new outbreaks. Additionally, public health authorities must closely monitor immunity levels to determine the timing and frequency of booster shots.

Vaccinating infected individuals can affect both the Infected and Vaccinated populations as seen in Figure 5 and 6, leading to significant changes in disease dynamics and public health strategies. When infected individuals receive a vaccine, it can impact the severity of the disease, the potential for transmission, and overall recovery rates. In the Infected (I) population, vaccinating infected individuals may lead to a reduction in disease severity. The vaccine can stimulate the immune system, potentially resulting in fewer complications and faster recovery. This may ease the burden on healthcare systems, as individuals experience milder symptoms and require less intensive care. Additionally, if the vaccine reduces viral shedding or infectiousness, this can decrease the transmission risk to other susceptible individuals, thereby slowing the spread of the disease. However, there are also potential risks, such as adverse reactions, which need careful consideration, especially if the vaccine is administered during the infection's acute phase. For the Vaccinated (V) population, vaccinating infected individuals contributes to an increase in the total number of vaccinated people, enhancing the overall level of protection within the community. This could accelerate progress toward herd immunity, as more people acquire immunity, reducing the overall susceptible pool. The vaccine may also provide additional immunity beyond what is gained from natural infection, leading to stronger and longer-lasting immunity. This might affect public health strategies, requiring revised approaches to vaccination campaigns and monitoring for any side effects or unintended outcomes.

The recovery rate in epidemiological models represents the speed at which individuals recover from an infection and transition from the Infected (I) compartment to the Recovered (R) compartment as shown in Figure 7 and 8. This rate plays a critical role in determining the course and impact of an infectious disease on both the infected and recovered populations, influencing the healthcare system's capacity and the overall progression of an epidemic. A higher recovery rate in the Infected population leads to quicker recovery times, resulting in shorter infection durations. This can reduce the overall burden on healthcare systems, as patients require care for shorter periods. Additionally, shorter infection durations mean reduced transmission risks, contributing to a slower spread of the disease. This can be beneficial for managing healthcare resources, as a quicker recovery rate lessens the strain on hospitals and clinics, allowing them to allocate resources more efficiently. Conversely, a lower recovery rate prolongs the time infected individuals remain in the Infected compartment, increasing the risk of disease transmission and potentially placing greater pressure on healthcare systems due to extended care needs. The impact on the Recovered population is equally significant. A higher recovery rate results in faster growth of the Recovered class, contributing to a larger immune population, which can aid in achieving herd immunity and reducing the need for ongoing public health interventions. A slower recovery rate has the opposite effect, delaying the build-up of the immune population and prolonging the path to herd immunity, requiring extended public health measures to manage and control the disease. Thus, understanding and managing the recovery rate is critical for effective public health strategies and epidemic control.

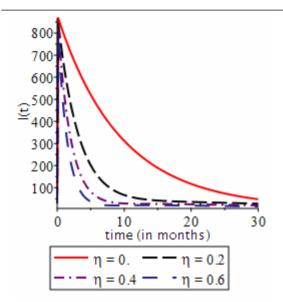


Figure 5: Effect of infected individuals getting vaccinated on the infected population.

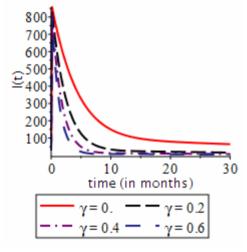


Figure 7: Effect of the recovery rate on the infected population.

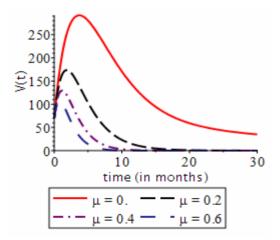


Figure 9: Effect of the natural mortality rate on the vaccinated population.

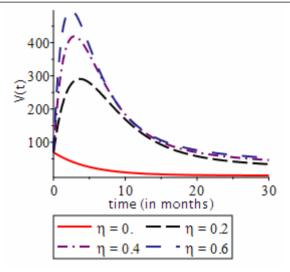


Figure 6: Effect of infected individuals getting vaccinated on the vaccinated population.

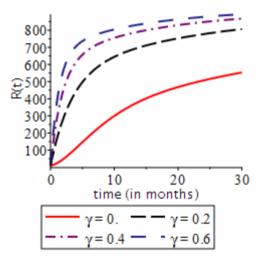


Figure 8: Effect of the recovery rate on the recovered population.

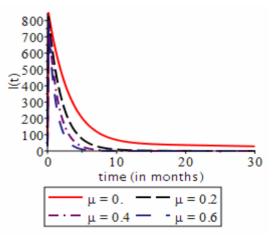
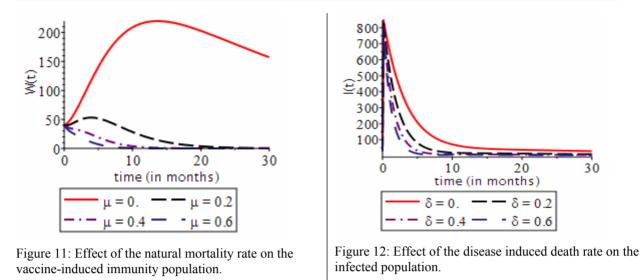


Figure 10: Effect of the natural mortality rate on the infected population.



V. Summary, Conclusion and Recommendation

In this section, we examined the impact of various factors on the proposed SIVWR, focusing on Infected (I), Vaccinated (V), Vaccine-Induced Immunity (W), and Recovered (R) compartments. Key consideration included the effects of the recovery rate, the transition rate from Vaccinated to other compartments, the natural death rate, disease-induced mortality, waning immunity, and the implications of vaccinating infected individuals. Higher recovery rates were associated with shorter infection durations, reduced healthcare system strain, and quicker growth of the Recovered population, potentially leading to earlier achievement of herd immunity. Conversely, slower recovery rates prolonged the duration of infection, increased healthcare demand, and delayed herd immunity. Vaccinating infected individuals could reduce disease severity and transmission, but also posed risks requiring careful consideration. Waning immunity emphasized the need for ongoing vaccination campaigns and booster programs to maintain a stable level of immunity, while the natural and disease-induced death rates significantly influenced overall disease dynamics and public health strategies.

The findings indicate that various factors play crucial roles in shaping the dynamics of infectious diseases and the effectiveness of public health interventions. Understanding these factors helps to develop targeted strategies for disease control, healthcare system management, and vaccination planning. The recovery rate emerged as a key determinant of infection duration, healthcare burden, and immunity build-up. The rate of transition from Vaccinated to other compartments, as well as the natural and disease-induced death rates, influenced disease spread and healthcare system capacity. Vaccination strategies must balance immediate benefits with potential risks, especially when vaccinating infected individuals or dealing with waning immunity.

To improve public health outcomes, focus should be placed on maximizing recovery rates through effective treatment and support to reduce infection duration and ease healthcare system strain. Adapt vaccination strategies to manage waning immunity, considering booster campaigns and careful risk assessment when vaccinating infected individuals. Plan for herd immunity while remaining flexible to accommodate changes in population dynamics and emerging health needs. Finally, raise public awareness about the importance of vaccination and preventive measures to maintain a robust public health infrastructure and reduce the risk of disease resurgence.

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