DYNAMICAL ANALYSIS OF DIPHTHERIA AND PERTUSIS CO-INFECTION WITH OPTIMAL CONTROL.

Presented by: Dr. EDOGBANYA Helen Olaronke

At

INTERNATIONAL CONFERENCE AND ADVANCED WORKSHOP ON MODELLING AND SIMULATION OF COMPLEX SYSTEMS

o be held at: AFRIGIST Conference Hall, off Road 1, Obafemi Awolowo University Campus, Ile – Ife, Osun State, Nigeria

Under the auspices of

IEMATICAL MODELLING OF COMPLEX SYSTEMS RESEARCH GROUP, DEPARTMENT OF MATHEMATICS, FACULTY OF SCIENCE, OBAFEMI AWOLOWO UNIVERSITY (OAU), ILE IFE, NIGERIA

OUTLINE

- ABSTRACT
- INTRODUCTION
- BACKGROUND OF STUDY
- PROBLEM STATEMENT
- AIMS AND OBJECTIVES
- MODEL FORMULATION
- RESULTS
- CONCLUSION
- REFERENCES

ABSTRACT

Due to post COVID-19 pandemic aftermath, the resurgence of vaccine-preventable respiratory diseases like Diphtheria and Pertussis poses as public health challenge particularly in infants and children who missed out of routine vaccination programs during outbreak.

This study hinges on the fact that pathogens can coexist in a host, therefore we propose a non-optimal and optimal control intervention strategy to check the transmission co-dynamics of diphtheria and pertussis. The SIR-type model was utilized and modified into 8 compartments with Vaccination at birth, Maternal derived immunity and partial quarantine as non-optimal control disease controller. Our research work first established that the model is both epidemiologically and mathematically sound.

The next generation matrix was used to derive the co-infection of the basic reproduction number, after which stability analysis was done. The formulated model exhibits four equilibria points, which are; diphtheria-free equilibrium, pertussis-free equilibrium, co-infection-free equilibrium and co-infection endemic equilibrium. The sensitivity analysis was manually calculated to know the effects and magnitude of each parameter on the basic reproduction number.

Furthermore, the existence of an optimal control was established, The Hamilton and Pontryagin principles for optimal control was employed to provide insights on control input interventions such as disease awareness campaigns, vaccination programs, provision of personal protective equipment (PPE) for health workers, cocooning and intensified diagnosis efforts.

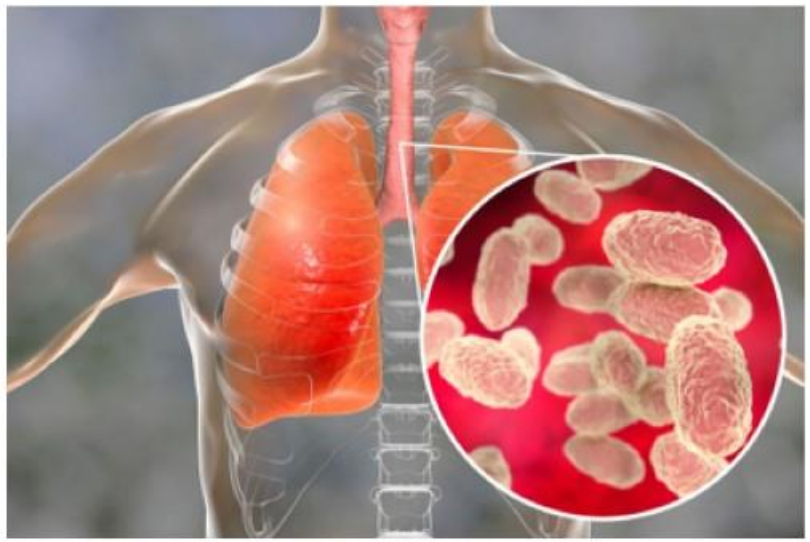
The accuracy of the pertussis-diphtheria co-infection model was validated through theoretical and Numerical simulation and relevant results are graphically displayed.

INTROD UCTION

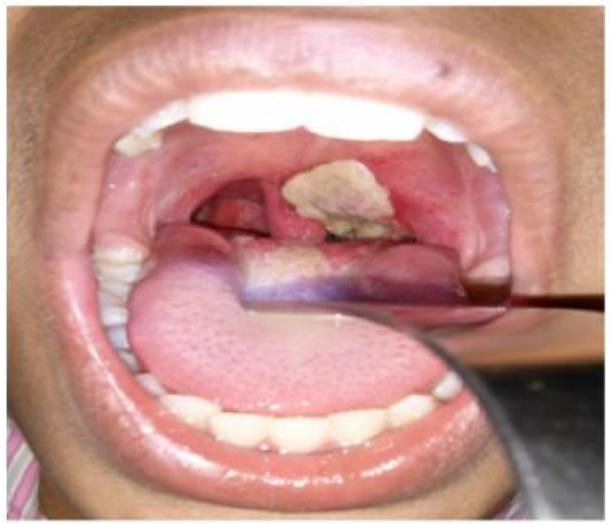
Emergence and resurgence of vaccine-preventable infectious diseases such as diphtheria and pertussis continues to pose formidable challenges to public health, particularly due to disruptions in basic immunization programs induced by the recent COVID-19 Pandemic. As of January 14, 2024, the World Health Organization (WHO) reports concern in the surge of suspected and fatality cases of diphtheria across African countries, with Nigeria bearing the brunt of outbreak. Recently, Wales in the first few weeks of January, 2024 recorded rapid rise in Whooping cough cases with 135 notifications compared to 200 in the whole of 2023. Public Health Wales (PHW) expert said BBC. (2024) *"With rates suppressed during the lockdowns of the pandemic we are naturally seeing a resurgence this year."* The consultant epidemiologist said "*whooping cough has waves of increased infection every three to four years*". Urging pregnant women, parents, children and all care givers to get vaccinated as quickly as possible. To tackle pertussis disease, Mathematicians around the globe has formulated several models to this effect. For example, [15] considered the Analytical and Numerical study of whooping cough (pertussis) using the SEIR model and concluded that the implicit numerical integration scheme is best fit for studying pertussis epidemic. Also [16] considered pertussis resurgence despite huge vaccination interventions and formulated a model for the transmission behavior of pertussis with maternal derived immunity. The transmission dynamics of pertussis is influenced by vaccine wanning and natural booster of pertussis immunity, [17] developed a model SIVRWS (Susceptible-Infected-Vaccinated-Recovered-Waned-Susceptible) in a stationary homogeneous population setting. For instance, \cite{j}, \cite{k}, \cite{l}, \cite{m} focused on diphtheria transmission in Indonesia, \cite{j} proposed a five (5) compartmental model that captures natural immunity alongside low vaccination coverage as a major concern. Stability analysis of the model was done, results show that reducing the basic reproduction number $ R_0 $ to less than 1 via high vaccination and natural immunity is crucial to mitigating outbreaks. \cite{k} proposed an optimal control for diphtheria outbreaks using the Pontryagin Minimum Principle and numerical methods on SEIQR (Susceptible-Exposed-Infected-Quarantined-Recovered) model of \cite{j}. The optimal control strategy was essential in determining the most effective intervention combination for minimizing both the outbreak size and associated costs.

INTRODUCTION CONT.

The fig.1(a) below shows diphtheria infection: grey pseudo membrane covering the tonsils. Also fig.1(b) shows Whooping cough also known as pertussis a lung or breathing tube infection, which is contagious. a diagram of inhaled bordetella bacteria through droplets pertussis infection. fig.1(c) shows the disease preventive vaccine for Diphtheria, Tetanus and Pertussis (whooping cough).



a. Pertussis Infection



b. Diphtheria infection

c. DTAP Vaccine

Fig.1. Images showing Diphtheria, Perussis and recommended routine vaccine

PROBLEM STATEMENT

The resurgence of diphtheria and Pertussis, exacerbated by gaps in immunization and healthcare strain post-COVID-19, poses a significant public health threat. This study aims to address the lack of optimal control measures for co-infections like diphtheria and pertussis in developing countries, where routine vaccinations were disrupted during the pandemic. Through mathematical modelling and analysis, we seek to provide actionable insights to mitigate the impact of these diseases and strengthen healthcare systems.. This study intends to fill this gap.

AIM OF STUDY

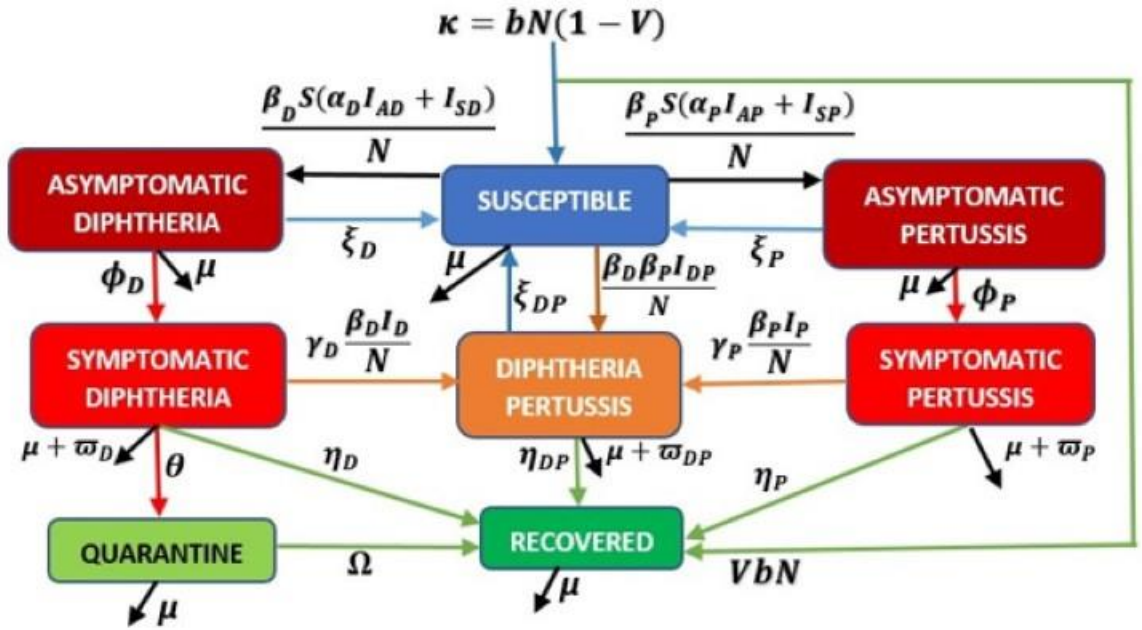
The main aim of this study is to propose an optimal and non optimal control model to mitigate diphtheria-pertussis disease co-infection. Also, to develop an implementable control strategy to aid developing countries towards minimizing the total cost of disease outbreak in the post COVID-19 pandemic.

MODEL FORMULATION

The diphtheria-pertussis co-infection model comprises of eight different compartments, where, the total population at time (t) denoted as $N(t)$ is given by

$$N(t) = S(t) + I_{AD}(t) + I_{SD}(t) + I_{AP}(t) + I_{SP}(t) + I_{SDP}(t) + Q(t) + R(t)$$

the eight sub-divided compartments are Susceptible or vulnerable individuals $S(t)$, the infected individuals with diphtheria in asymptomatic stage $I_{AD}(t)$the infected individuals with diphtheria in symptomatic stage $I_{SD}(t)$ the infected individuals with pertussis in asymptomatic $I_{AP}(t)$, the infected individuals with pertussis in symptomatic stage $I_{SP}(t)$ the infected individuals with both diphtheria and pertussis in there symptomatic stage $I_{SDP}(t)$ individuals who has recovered from diphtheria, pertussis or dual infection. $R(t)$ Quarantine of individuals showing clinical symptoms of diphtheria $Q(t)$. Schematic diagram and The equation Governing the formulated model is given by



MODEL FORMULATION CONTINUE

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= bN(1-V) + \xi_D I_{AD} + \xi_P I_{AP} + \xi_{DP} I_{DP} + \left(\frac{\beta_D(\alpha_D I_{AD} + I_{SD})}{N} + \frac{\beta_P(\alpha_P I_{AP} + I_{SP})}{N} + \frac{\beta_{DP} I_{SDP}}{N} \right) S - \mu S \\
\frac{dI_{AD}}{dt} &= \frac{\beta_D(\alpha_D I_{AD} + I_{SD})}{N} S - (\phi_D + \mu + \xi_D) I_{AD} \\
\frac{dI_{SD}}{dt} &= \phi_D I_{AD} - (\theta + \eta_D + \varpi_D + \mu) I_{SD} - \gamma_1 \frac{\beta_P(\alpha_D I_{AP} + I_{SP})}{N} I_{SD} \\
\frac{dI_{AP}}{dt} &= \frac{\beta_P(\alpha_P I_{AP} + I_{SP})}{N} S - (\phi_P + \mu) I_{AP} \\
\frac{dI_{SP}}{dt} &= \phi_P I_{AP} - (\eta_P + \varpi_P + \mu) I_{SP} - \gamma_2 \frac{\beta_D(\alpha_D I_{AD} + I_{SD})}{N} I_{SP} \\
\frac{dI_{SDP}}{dt} &= \frac{\beta_{DP} I_{SDP}}{N} S + \gamma_1 \frac{\beta_P(\alpha_P I_{AP} + I_{SP})}{N} I_{SD} + \gamma_2 \frac{\beta_D(\alpha_D I_{AD} + I_{SD})}{N} I_{SP} - (\eta_{PD} + \varpi_{PD} + \mu) I_{SDP} \\
\frac{dQ}{dt} &= \theta - (\Omega + \mu) Q \\
\frac{dR}{dt} &= \eta_P I_{SD} + \eta_D I_{SP} + \eta_{SDP} - \mu R
\end{aligned}
\right\}
$$

$$S(0) > 0, I_{AD} > 0, I_{SD} > 0, I_{AP} > 0, I_{SP} > 0, I_{SDP} > 0, Q > 0, R > 0,$$

The following assumptions is also considered in model formulation:

1. We assumed that $\kappa = bN(1-V)$ is the total proportion of zero vaccinated individuals where b is the birth rate and V is the vaccinated at birth.

2. We also assume that due to vaccination during pregnancy, the mother would have passed on strong immunity to the infant via placenta at foetus stage. Therefore, the Susceptible or Vulnerable compartment S increases by the influx of non-vaccinated.

MODEL PARAMETER'S

S\N	PARAMETER	DESCRIPTION	VALUES
1	β_D	Effective contact rate for Diphtheria	0.57/day
2	β_P	Effective contact rate for Pertussis	0.5-1/day
3	β_{DP}	Effective contact rate for Diphtheria-Pertussis dual transmission	0.2/day
4	ξ_D	Maternally Derived Immunity against Diphtheria infection	0.35
5	ξ_P	Maternally Derived Immunity against Diphtheria infection	0.35
6	ξ_{DP}	Maternally Derived Immunity against Diphtheria-Pertussis	0.35
7	Ω	Recovery rate of Quarantine	0.1-0.9
8	η_D	Recovery rate of symptomatically infected with Diphtheria	0.5
9	η_P	Recovery rate of symptomatically infected with pertussis	0.026
10	η_{DP}	Recovery rate of symptomatic infected with Diphtheria-Pertussis	0.15
11	ϖ_D	Disease induced death rate of Diphtheria	0.05
12	ϖ_P	Disease induced death rate of Pertussis	0.0309
13	ϖ_{DP}	Disease induced death rate of Diphtheria-Pertussis	0.005/day
14	μ	Natural death rate	0.006
15	θ	Quarantined rate of symptomatically infected with Diphtheria	0.1/day
16	b	Birth rate	0.019
17	V	Vaccination	0.1-1.2
18	α_D, α_P	Modification Parameters	0.5
19	ϕ_D, ϕ_P	Progression to symptomatic infected stage	1

MODEL FORMULATION CONTINUE

The Basic reproduction number which is the average number of secondary infections produced by an index case of completely uninfected population (Diekmann & Heesterbeek 2000; Diekmann et al. 1990) was determined using the next Generation Matrix $R_0 = \rho FV^{-1}$, where ρ is the spectral radius, F is the infective class, and V is the transmission class. The reproduction number represents three terms which are Diphtheria, pertussis and there co-infection respectively.

$$R_0 = \max\left\{\frac{b(1-V)}{\mu}\left(\frac{\beta_D(\alpha_D(\theta_D+\eta_D+\varpi_D+\mu)+\phi_D}{(\phi_D+\xi_D+\mu)(\theta_D+\eta_D+\varpi_D+\mu)}, \frac{\beta_p(\alpha_p(\eta_p+\varpi_p+\mu)+\phi_p}{(\phi_p+\xi_p+\mu)(\eta_p+\varpi_p+\mu)}, \frac{\beta_{DP}}{\eta_{DP}+\varpi_{DP}+\mu}\right)\right\}$$

Where,

$$S_0 = \frac{b(1-V)}{\mu}$$

$$R_{0\,diphtheria} = \frac{\beta_D(\alpha_D(\theta_D+\eta_D+\varpi_D+\mu)+\phi_D}{(\phi_D+\xi_D+\mu)(\theta_D+\eta_D+\varpi_D+\mu)}$$

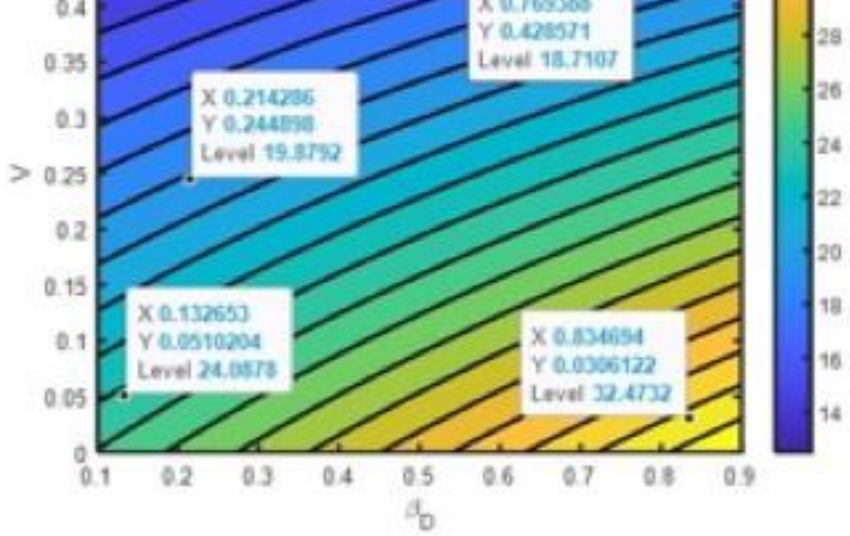
$$R_{0\,pertussis} = \frac{\beta_p(\alpha_p(\eta_p+\varpi_p+\mu)+\phi_p}{(\phi_p+\xi_p+\mu)(\eta_p+\varpi_p+\mu)}$$

$$R_{0\,coinfection} = \frac{\beta_{DP}}{\eta_{DP}+\varpi_{DP}+\mu}$$

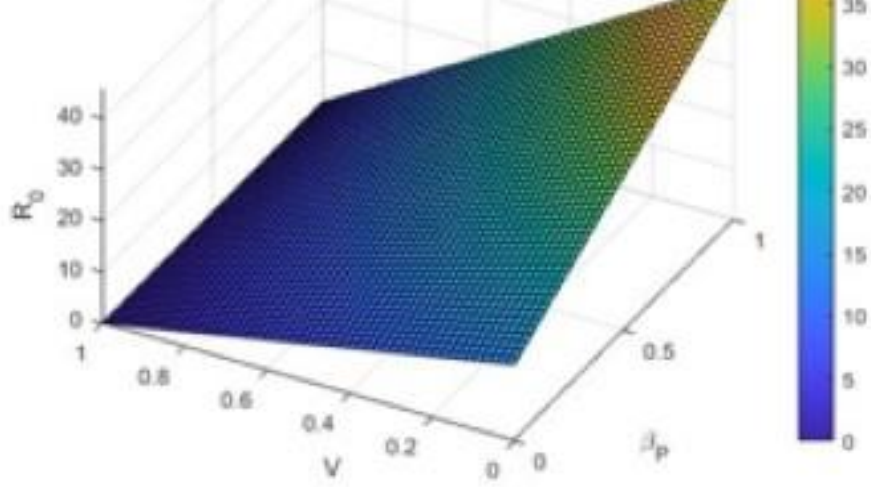
OPTIMAL CONTROL DESIGN

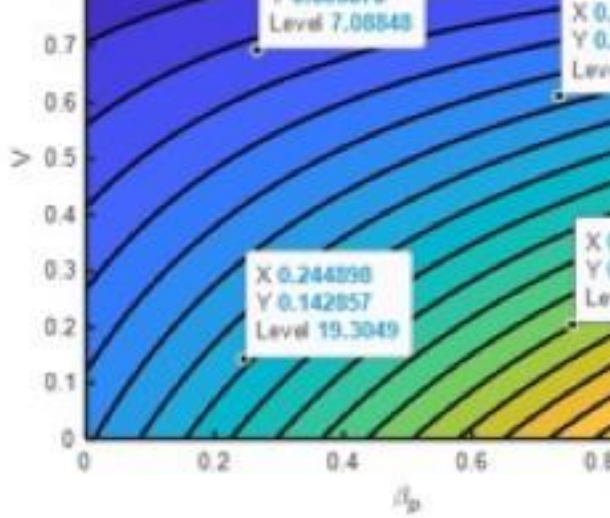
Introducing optimal control measures u_1, u_2, u_3 and u_4, to determine the best co-Infection intervention strategy. $\boldsymbol{u_1(t)}$: for Diphtheria represents vaccination and use of personal protective equipment's (PPE). $\boldsymbol{u_2(t)}$: for pertussis represents vaccination and cocooning. $\boldsymbol{u_3(t)}$: represents tackling dual infection since same vaccination DTaP is effective for both diseases then $u_3(t)$ is a combination of $u_1(t)$ and $u_2(t)$. $\boldsymbol{u_4(t)}$: prevention strategies against second infection by individuals singly infected with Diphtheria or pertussis in there symptomatic stage.

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \Gamma-(1-u_1)\frac{\beta_1(\alpha I_{AD}+I_{SD})}{N}S-(1-u_2)\frac{\beta_2(\varepsilon I_{AP}+I_{SP})}{N}S-(1-u_3)+\frac{\beta_{12}I_{SDP}}{N}S-\mu S\\
\frac{dI_{AD}}{dt} &= (1-u_1)\frac{\beta_1(\alpha I_{AD}+I_{SD})}{N}S-(\phi_1+\mu)I_{AD}\\
\frac{dI_{SD}}{dt} &= \phi_1 I_{AD}-(\Omega_D+\eta_D+\varpi_D+\mu)I_{SD}-(1-u_4)\gamma_1\frac{\beta_2(\varepsilon I_{AP}+I_{SP})}{N}I_{SD}\\
\frac{dI_{AP}}{dt} &= (1-u_2)\frac{\beta_2(\varepsilon I_{AP}+I_{SP})}{N}S-(\phi_2+\mu)I_{AP}\\
\frac{dI_{SP}}{dt} &= \phi_2 I_{AP}-(\eta_P+\varpi_P+\mu)I_{SP}+(1-u_4)\gamma_2\frac{\beta_1(\alpha I_{AD}+I_{SD})}{N}I_{SP}\\
\frac{dI_{SPD}}{dt} &= (1-u_3)\frac{\beta_{12}I_{SDP}}{N}S+(1-u_4)\gamma_1\frac{\beta_2(\varepsilon I_{AP}+I_{SP})}{N}I_{SD}+(1-u_4)\gamma_2\frac{\beta_1(\alpha I_{AD}+I_{SD})}{N}I_{SP}-(\eta_{PD}+\varpi_{PD}+\mu)I_{SDP}\\
\frac{dQ_{SD}}{dt} &= \Omega_{il}-(\theta+\varpi_D+\mu)Q\\
\frac{dR}{dt} &= \eta_P I_{SD}+\eta_D I_{SP}+\eta_{SDP}-\mu R
\end{aligned}
\right\}
$$

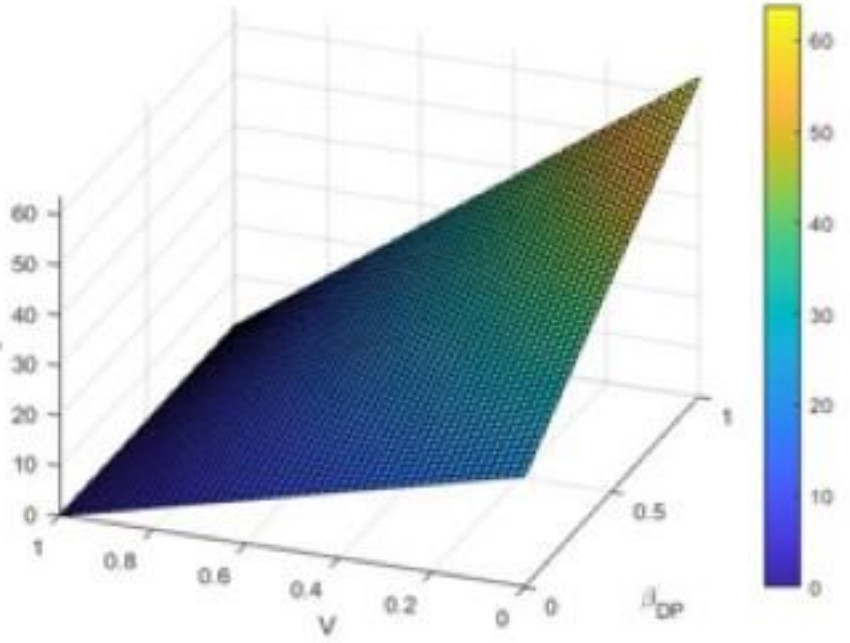


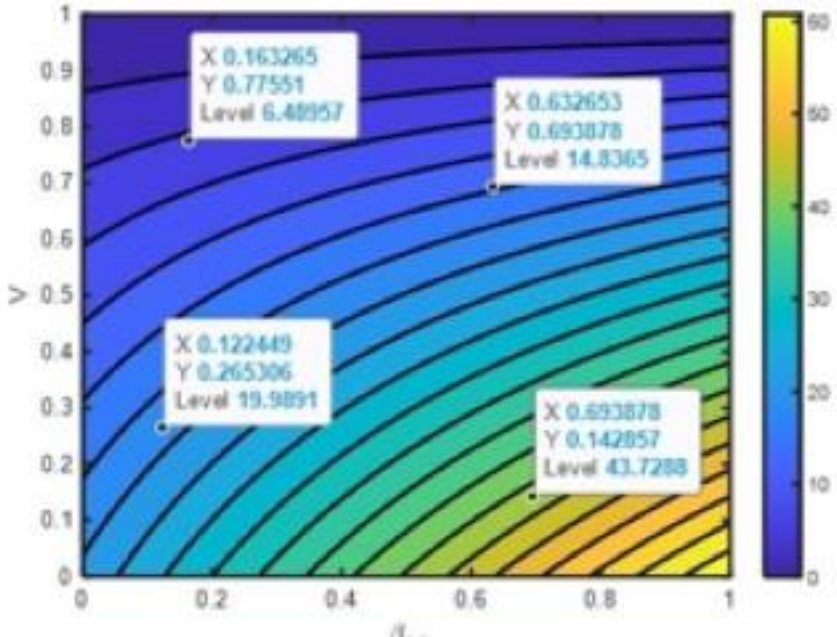
Diphtheria on R_0 with Contour Plot.





(b) Effect of Vaccination V and contact rate β_P of Diphtheria on R_0 with Contou





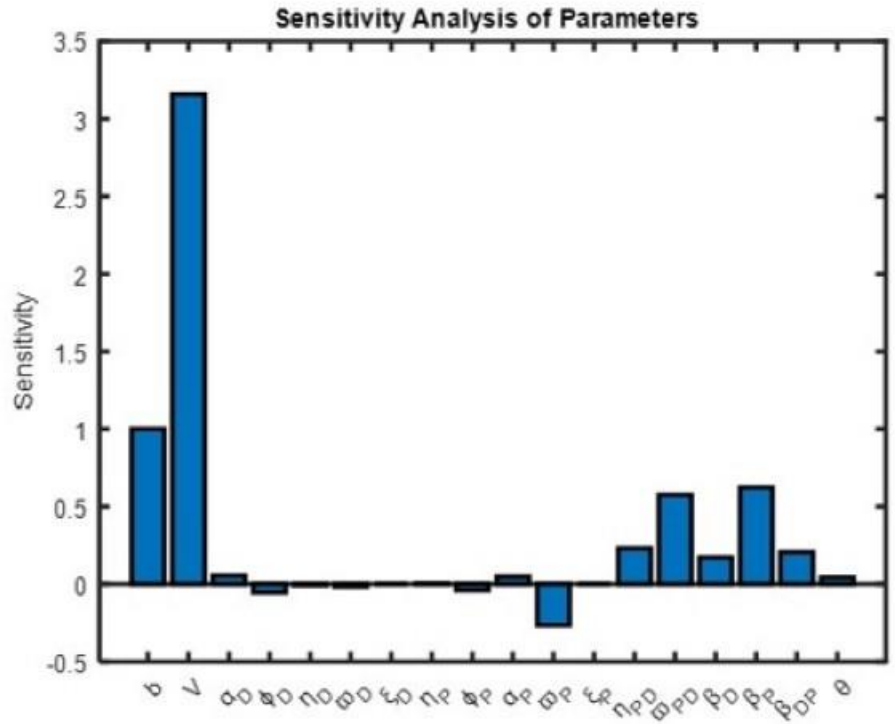
RESULTS CONT.

The normalized forward sensitivity index of the reproduction number was explored to determine the strength and weakness of each parameter in the models prediction.

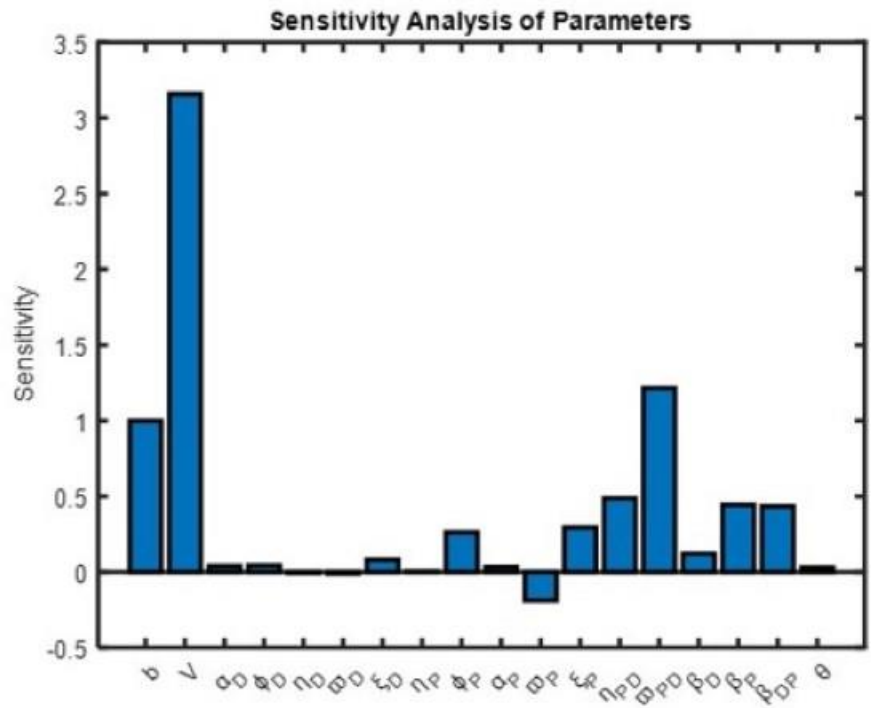
The magnitude of each parameter on R_0 was manually calculated and represented in bar chats below.

For instance, The Normalized forward sensitivity index of R_0 differentiable with respect to a given parameter β_D is defined as

$$\Upsilon_{\beta_D}^{R_0} = \frac{\beta_D}{R_0}\frac{\partial R_0}{\partial \beta_D}$$



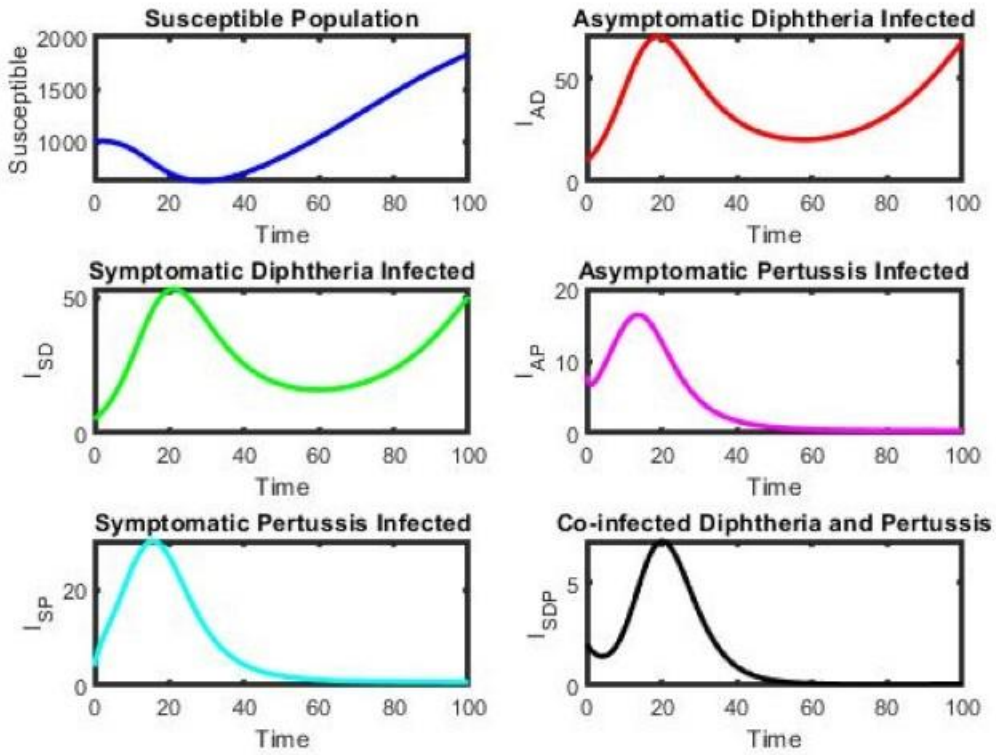
(g) V = 0.06, θ =0.3, $\xi_D = \xi_P = 0$



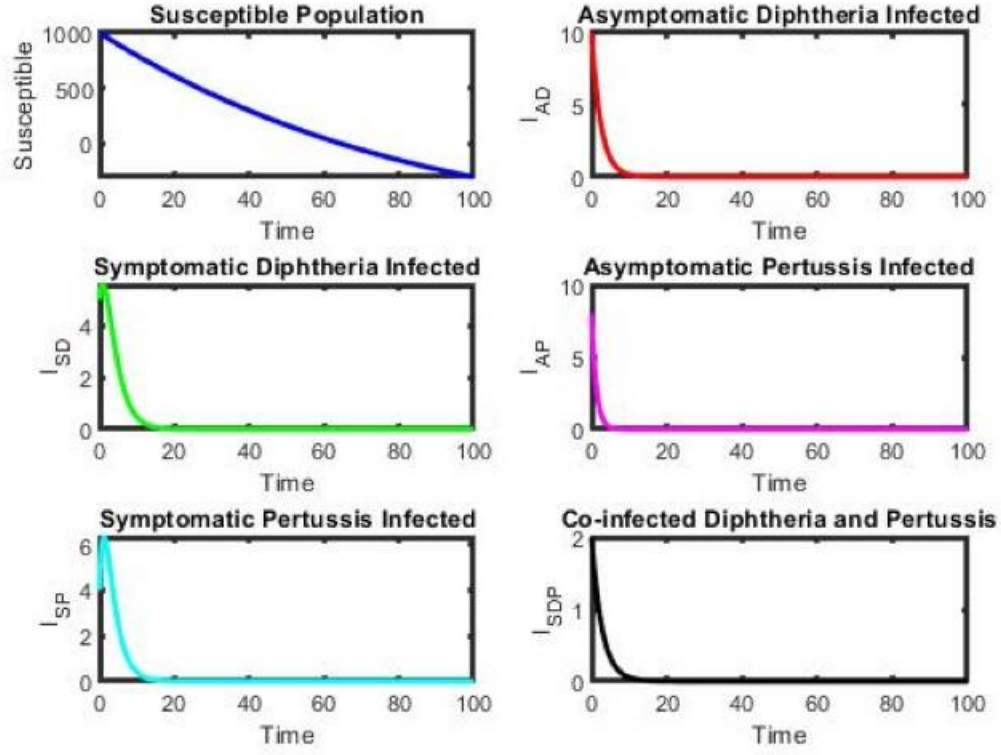
(h) V = 0.06, θ = 0.6, = $\xi_D = \xi_P = 0.8$

RESULTS CONT.

The sub-plots Fig a. bellow shows the effect of No Optimal control that is $u_1 = u_2 = u_3 = u_4 = u_5 = 0$. Also, Fig. b $u_1 = u_2 = u_3 = u_4 = u_5 = 1$ shows the effects of optimal control.



a. Formulated Model without optimal control



b. Formulated Model with optimal control

CONCLUSION

In this study, a mathematical model for transmission dynamics of Diphtheria and pertussis (whooping cough) is developed. The basic reproduction number R_0 was derived and the forward sensitivity analysis on R_0 was carried out to determine the impact of each parameter in disease threshold. It was observed that Vaccination at birth and pregnant women played significant role in mitigating Diphtheria-pertussis co-infection.

Furthermore, results shows that increase in key intervention parameter like vaccination and maternaly derived immunity, reduced R_0.

Also, Based on graphical experiments performed on the Optimal control system, Results shows that the combination of the four diaseas controllers did not only eradicate diphther and pertussis but drastically reduced its co-infection.

In a nutshell, the combination of the four optimal intervention strategies will lower or eradicate Diphtheria and Pertussis (whooping cough) reproduction number, increase recovery rate and completely end co-infection if the strategies are well implemented by policy makers.

REFERENCES

- BBC News. (2024, March 1). 'A wake-up call': Food bank use up 30% in Wales in a year. BBC News. https://www.bbc.com/news/uk-wales-68067829
- Brauer, F. (2017). Mathematical epidemiology: Past, present, and future. *Infectious Disease Modelling*, *2*(2), 113-127.
- Deressa, C. T., Mussa, Y. O., & Duressa, G. F. (2020). Optimal control and sensitivity analysis for transmission dynamics of Coronavirus. *Results in Physics*, *19*, 103642.
- Edogbanya, H. O., & Oladipupo, J. (2024). Mathematical Modeling for Mitigating Pertussis Resurgence in the Post-COVID-19 Era: A Sensitivity Analysis and Intervention Strategies. Federal University Lokoja. DOI: 10.5281/zenodo.10721146
- Gavi, the Vaccine Alliance. (2021, April). The Zero Dose Children: Explained. Retrieved January 25, 2023, from https://www.gavi.org/vaccineswork/zero-dose-child-explained
- Inayaturohmat, F., Anggriani, N., Supriatna, A. K. (2022). A mathematical model of tuberculosis and COVID-19 coinfection with the effect of isolation and treatment. Frontiers in Applied Mathematics and Statistics, 8, 958081.
- Izzati, N., & Andriani, A. (2021). Dynamical analysis of diphtheria epidemic model with natural immunity rate on exposed individuals. In *Journal of Physics: Conference Series* (Vol. 1869, No. 1, p. 012117). IOP Publishing.

- Johnson, O. S., Edogbanya, H. O., Emmanuel, J., & Olukanni, S. E. (2023). Stability Analysis of COVID-19 Model with Quarantine. *International Journal of Mathematical Sciences and Computing*, *9*(3), 26-45.
- Kanchanarat, S., Chinviriyasit, S., & Chinviriyasit, W. (2022). Mathematical Assessment of the Impact of the Imperfect Vaccination on Diphtheria Transmission Dynamics. Symmetry, 14(10), 2000.
- Kermack, W. O., & McKendrick, A. G. (1927). A contribution to the mathematical theory of epidemics. *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character*, *115*(772), 700-721.
- NCDC. (n.d.). An update of Diphtheria Outbreak in Nigeria. Retrieved February 3, 2023, from https://ncdc.gov.ng/diseases/sitreps/?cat=18name=An
- P´erez, A. G. C., Oluyori, D. A. (2022). A model for COVID-19 and bacterial pneumonia coinfection with community- and hospital-acquired infections. Mathematical Modelling and Numerical Simulation with Applications, 2(4), 197-210.
- Teklu, S. W., Mekonnen, T. T. (2021). HIV/AIDS-pneumonia coinfection model with treatment at each infection stage: mathematical analysis and numerical simulation. Journal of Applied Mathematics, 2021, 1-21.
- Tilahun, G. T. (2019). Optimal control analysis of pneumonia and meningitis coinfection. Computational and Mathematical Methods in Medicine, 2019.

Thank You