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Mathematical Modeling of Antimicrobial Resistance of Typhoid Fever Incorporating Public Health Education

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Abstract

The rise of Antimicrobial Resistance (AMR) in typhoid fever has led to increased disease severity, prolonged infectious periods, higher treatment costs, and elevated mortality rates, making it a critical public health challenge. In this study, we develop and analyze a deterministic two-strain model to investigate the transmission dynamics of AMR of typhoid fever. The results from analytical analyses indicate that with mutation, typhoid-free equilibrium exists and is Locally Asymptotically Stable (LAS) when both $R_{er} < 1$ and $R_{es} < 1$. Further analysis showed that the drug-resistant dominance equilibrium exists and is Globally Asymptotically Stable (GAS) if $R_{er} > 1$. Furthermore, it was shown that coexistence equilibrium exists if both $R_{es} > 1$ and $R_{er} > 1$. Global sensitivity analysis using the Elementary Effect (EE) approach, identifies public health education as the most influential parameter in controlling AMR spread. Numerical simulation shows the impacts of mutation on the persistence of resistant-strain cases. The results further show that, higher mutation rates alone do not certainly lead to increased resistance, but in the absence of adequate education, resistance spreads more quickly. Further results from numerical simulations demonstrate that improving sanitation, treatment, and public health education reduces the reproduction number, with public health education playing a pivotal role. Our findings suggest that integrating public health education into control strategies is essential for effectively mitigating the spread of AMR in typhoid fever.

Keywords: Typhoid fever; Disease control; Antimicrobial resistance; Epidemiological; Sensitivity analysis.

Introduction

Typhoid fever is a life-threatening infectious disease caused by salmonella bacterium (*S. Typhi*). The pathogens are transmitted to humans through the consumption of contaminated food or water (Edward 2017, Tilahun et al. 2017, Irunde et al. 2023). As of 2019 estimates, there are 9 million cases of typhoid fever annually, resulting in about 110,000 deaths per year worldwide (WHO 2023). As to available data, Sub-Saharan Africa experiences a significant burden of typhoid cases, with estimates suggesting over 1.2 million cases and 29 thousand deaths annually (Kariuki and Onsare 2024). The global burden of disease study estimates that, 79,334 cases of typhoid fever and 1,671 typhoid-related deaths were estimated to have occurred in Tanzania in 2019 (WHO 2023).

Antibiotic treatment is the primary means of reducing infections. On the other hand,

improper use of antibiotics may lead to an AMR outbreak (Kaufhold et al. 2019). The emergence of AMR is mainly promoted by inappropriate use of antibiotics which includes; poor diagnosis of new cases, improper prescription of antibiotics, poor drug administration and the use of antibiotics in agricultural practices (Shah et al. 2020). AMR of typhoid fever has increased the severity and duration of the infectious period which has resulted in significant expenses (Shah et al. 2020).

According to the global estimate of the burden of AMR, 4.95 million deaths in 2019 were associated with AMR, making it a growing threat to the global health (WHO 2024). The number of people dying due to (AMR) is expected to reach 10 million annually by 2050 if effective measures will not be taken into account (O'Neill 2016). AMR of typhoid fever is a growing burden in Tanzania, regionally, and across the globe. The study conducted by Mahende et al. (2015) in rural Korogwe District (Tanga), found that 88% of typhoid isolates were resistant to a first-line treatment. Moreover, the study by Park et al. (2018) in rural and urban Moshi, Tanzania showed that 36% of samples from rural sites and 0.1% of samples from urban sites were mult-drug resistance. Because AMR is among top global health threat (Mapunjo et al. 2025) improved surveillances on the prevalence of AMR is of paramount. Motivated by the aforementioned facts about the existing situation of AMR, this study aims to use a mathematical model incorporating public health education to evaluate the impact of interventions on the dynamics of AMR in typhoid fever.

Numerous studies have been conducted to explore the dynamics of typhoid fever associated with drug resistance as pointed out by studies of Kaufhold et al. (2019), Irena and Gakkhar (2021) and Momoh et al. (2023), just to mention a few. These studies have certainly produced several important insights. For example, Kaufhold et al. (2019) conducted a study to predict the impact of typhoid conjugate vaccine on antimicrobial resistance. The results revealed that, vaccination has positive impacts in reducing the number of antimicrobial-sensitive and antimicrobial-resistance typhoid cases. Nevertheless, the element of environmental transmission, treatment-induced acquired resistance (mutation) and public health education were not captured. Momoh et al. (2023) analyzed a mathematical model which takes into account vaccine, treatment and drug resistance effects. Their results showed that, the combination of multiple interventions gives better results in controlling the spread of the disease. Nevertheless, the concept of treatment-induced acquired resistance was disregarded. In addition to that, their study presumed environmental transmission only. Furthermore, the aspects of both modes of transmissions was captured in the study of Irena and Gakkhar (2021) which explored the effects of treatment and vaccination on the dynamics of AMR of typhoid fever. The authors suggested that, proper hygiene practice and improved sanitation can slow the spread of AMR. Nevertheless, the aspect of public health education was not considered.

Additionally, few studies on typhoid fever have considered the aspect of global sensitivity analysis in the dynamics and control of the disease. For example, the study conducted by Nyerere et al. (2024) examined the influence of the model parameters using global sensitivity analysis techniques, specifically Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC). While PRCC is a valuable tool for global sensitivity analysis, EE offers advantages in simplicity, efficiency, and directness, particularly when model complexity and computational resources are concerns.

Despite these efforts, however, little attention has been devoted to quantify the impacts of treatment- induced acquired resistance on the prevalence of AMR of typhoid fever. Additionally, the aspect of global sensitivity analysis using EE is not captured in most of the studies. Furthermore, the significance of public health education in tackling the problem of treatment-induced acquired resistance remains poorly understood. Inappropriate uses of antibiotics

have been identified as the key factor contributing to the treatment-induced acquired resistance (Kaufhold et al. 2019). Establishing conditions under which the prevalence of AMR of typhoid fever is reduced under the existing mitigation approaches is an issue that demands immediate consideration.

The novelty of this study lies in incorporating both transmission modes and emphasizing public health education to raise AMR awareness to the community. Which also emphasize accurate typhoid diagnosis, proper antibiotic prescription, and sales regulations to combat antibiotics misuse.

Materials and Methods

A deterministic compartmental model for investigating the impacts of public health education on the dynamics of antimicrobial resistance to typhoid fever was formulated. The model considered two populations; human beings and pathogens. The human population N_h is divided into sub-populations of susceptible individuals $S(t)$, individuals infected with drug-sensitive strain $I_s(t)$, infected individuals with drug-resistant strain $I_r(t)$, and recovered individuals, $R(t)$. The pathogen population is divided into sub-populations of pathogens with drug-resistant strain $P_r(t)$ and pathogens with drug-sensitive strain, $P_s(t)$. This model considered direct and indirect modes of transmission. Susceptible humans are recruited into the population at a constant rate π. A newly infected individual progresses to infectious class with drug-sensitive strain and drug-resistant strain at the rates of $\varepsilon\lambda_s$ and $\varepsilon\lambda_r$, respectively, where $\varepsilon = 1-\varepsilon_e$, and $\varepsilon_e \in [0,1]$ is the efficacy of public health education. The forces of infections associated with the drug-sensitive and the drug-resistant strains are given as $\lambda_s = \frac{\beta_s I_s}{N_h} + \frac{\beta P_s}{c+P_s}$ and $\lambda_r = \frac{\beta_r I_r}{N_h} + \frac{\beta P_r}{c+P_r}$, respectively. Individuals infected with sensitive strain and resistant strain contribute to pathogen population enhancement through excretion at the rates of α_s and α_r, respectively. The total size of humans and pathogens at any time $t > 0$ are given by $N_h = S + I_s + I_r + R$ and $N_p = P_s + P_r$, respectively. Individuals infected with sensitive and resistant strains are treated at the rates τ_2 and τ_3, respectively. However, they can also recover as the result of one's natural immune at the rates γ_1 and γ_2, respectively. All individuals in different subgroups of humans, experience natural mortality rates at a rate μ. The disease-induced mortality occurs in two compartments, $I_s(t)$ and $I_r(t)$ at rates of ω_1 and ω_2, respectively. Typhoid pathogens in the aquatic environment decay at a rate μ_0. The pathogens infected with drug-sensitive and drug-resistant strains die at the rates of δ_1 and δ_2, respectively after proper environmental sanitation.

Model Assumptions

i) Drug resistance can emerge either through primary infection with strains of resistant pathogens or as a result of mutation at the rate, θ.

ii) Due to waning immunity in the recovered compartment, recovered individuals may become susceptible again at the rate, σ.

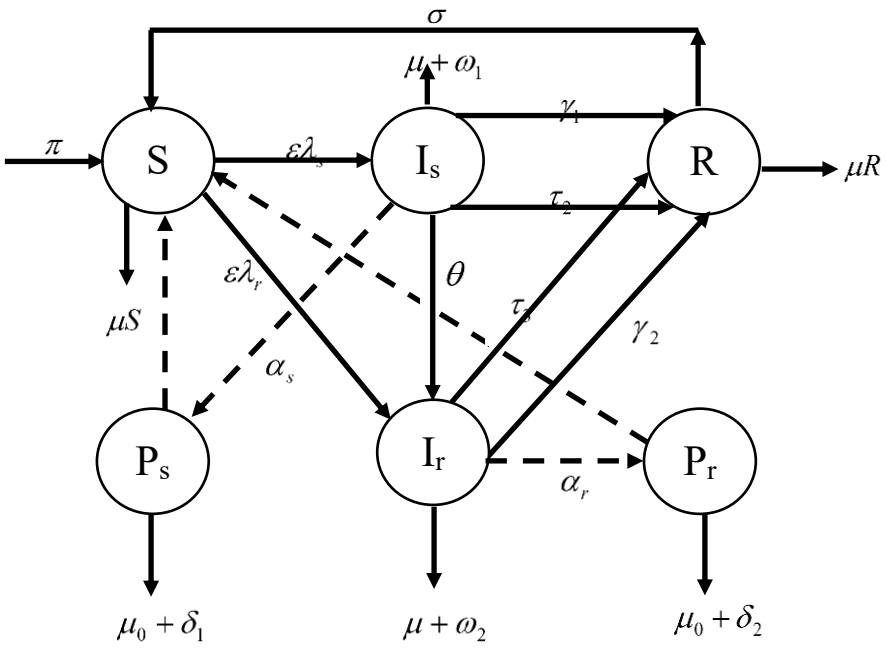


Figure 1: The schematic presentation of the transmission dynamics of a two-strain typhoid fever model.

Model Equations

$$\begin{aligned}
\dot{S} &= \pi + \sigma R - \varepsilon(\lambda_s + \lambda_r)S - \mu S,\\
\dot{I}_s &= \varepsilon\lambda_s S - (\mu + \gamma_1 + \tau_2 + \omega_1 + \theta)I_s,\\
\dot{I}_r &= \varepsilon\lambda_r S - (\mu + \gamma_2 + \tau_3 + \omega_2)I_r + \theta I_s,\\
\dot{R} &= (\gamma_1 + \tau_2)I_s + (\gamma_2 + \tau_3)I_r - (\mu + \sigma)R,\\
\dot{P}_s &= \alpha_s I_s - (\mu_0 + \delta_1)P_s,\\
\dot{P}_r &= \alpha_r I_r - (\mu_0 + \delta_2)P_r.
\end{aligned} \tag{1}$$

The initial conditions of the model system (1) are $S(0) > 0$, $I_s(0) \geq 0$, $I_r(0) \geq 0$, $P_s(0) \geq 0$, and $P_r(0) \geq 0.$

Invariant region

The model system (1) is biologically meaningful and mathematically well-posed in the invariant domain $\Phi = \Phi_h \times \Phi_p$, where

$$\Phi_h = \left\{(S, I_s, I_r R) \in R_+^4 : N_h \leq \frac{\pi}{\mu}\right\}$$ and

$$\Phi_P = \left\{(P_s, P_r) \in R_+^2 : N_P \leq (\alpha_s + \alpha_r)\frac{\pi}{\mu\mu_0}\right\}$$ is any solution of the system of equations in

(1) with non-negative variables. Therefore, the solution for human beings and the pathogen population inters the invariant region;

$$\Phi = \left\{ (S, I_s, I_r, R, P_s, P_r) \geq 0, (S, I_s, I_r, R, P_s, P_r) \in R_+^6 : N_h \leq \frac{\pi}{\mu}; N_P \leq (\alpha_s + \alpha_r)\frac{\pi}{\mu\mu_0} \right\}$$

, which is the positive invariant set under the flow. Therefore, the solutions in the model system (1) are positive and are attracted to the domain $\Phi \ \forall t > 0.$ Thus, the model is meaningful to allow further analysis.

Model Analysis

In this section, the model system (1) is qualitatively analyzed to obtain conditions necessary for the existence of equilibrium points and their stabilities. Since the drug-sensitive strain mutates into the drug-resistant strain, there are three possibilities namely; disease-free, drug-resistant, and co-existence equilibrium points.

Disease-Free Equilibrium

At the disease-free state, there are no typhoid fever pathogens and the human population is free from typhoid fever infections. The disease-free equilibrium of the model system (1) is given by

$$E_0 = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0 \right).$$

Effective Reproduction Number

According to Diekmann et al. (1990), the basic reproduction number R_0 is defined as the number of secondary infection cases produced when a single infectious individual is introduced in a completely susceptible population during its entire period of infectiousness. Adopting the technique of next-generation matrix method employed by Van den Driessche and Watmough (2002), Ndendya et al. (2023) we have

$$F = \Delta F_i = \begin{pmatrix} \varepsilon\beta_s & 0 & \frac{\varepsilon\beta\pi}{c\mu} & 0 \\ 0 & \varepsilon\beta_r & 0 & \frac{\varepsilon\beta\pi}{c\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and}$$

$$V = \Delta V_i = \begin{pmatrix} (\mu + \gamma_1 + \tau_2 + \omega_1 + \theta) & 0 & 0 & 0 \\ -\theta & (\mu + \gamma_2 + \tau_3 + \omega_2) & 0 & 0 \\ -\alpha_s & 0 & \mu_0 + \delta_1 & 0 \\ 0 & -\alpha_r & 0 & \mu_0 + \delta_2 \end{pmatrix},$$

where F_i is the rate of new infections in compartment *j* and V_i is the rate of transfer of infections from one compartment to another.

The effective reproduction number, R_e which is the spectral radius of the matrix, FV^{-1} is given by

$$R_e = \rho\left(FV^{-1}\right) = Max\left(R_{es}, R_{er}\right).$$

Hence,

$$R_e = Max\left(\frac{\varepsilon\left(c\mu\left(\mu_0+\delta_1\right)\beta_s + \alpha_s\beta\pi\right)}{c\mu(\mu_0+\delta_1)\left(\mu+\omega_1+\gamma_1+\tau_2+\theta\right)}, \frac{\varepsilon\left(c\mu(\mu_0+\delta_2)\beta_r + \alpha_r\beta\pi\right)}{c\mu(\mu_0+\delta_2)\left(\mu+\omega_2+\gamma_2+\tau_3\right)} \right). \quad (6)$$

In this case, R_{es} and R_{er} represent thresholds associated with drug-sensitive and drug-resistant strains, respectively.

The basic reproduction number, R_0 which is the threshold quantity in the absence of interventions, is deduced from the effective reproduction in equation (6) by setting $\delta_1 = \delta_2 = \tau_2 = \tau_3 = \varepsilon_e = \theta = 0$. Thus, the basic reproduction number is given by

$$R_0 = \max\left(\frac{(c\mu\mu_0\beta_s + \alpha_s\beta\pi)}{c\mu\mu_0(\gamma_1+\mu+\omega_1)}, \frac{(c\mu\mu_0\beta_r + \alpha_r\beta\pi)}{c\mu\mu_0(\gamma_2+\mu+\omega_2)} \right).$$

The Impacts of Public Health Education on Antimicrobial Resistance

In this section, the contribution of the public health education strategy is perceived by relating the reproduction numbers. The effective reproduction number for the drug-resistance in equation (6) is re-written as

$$R_{er} = \varepsilon\left(\frac{\left(c\mu\left(\mu_0+\delta_2\right)\beta_r + \alpha_r\beta\pi\right)}{c\mu\mu_0\beta_r + \alpha_r\beta\pi} \right)\left(\frac{\mu+\omega_2+\gamma_2}{\mu+\omega_2+\gamma_2+\tau_3} \right)\left(\frac{\mu_0}{\mu_0+\delta_2} \right) R_{0r} = \varepsilon k_2 R_{0r}, \quad (7)$$

where $k_2 = \left(\frac{\left(c\mu\left(\mu_0+\delta_2\right)\beta_r + \alpha_r\beta\pi\right)}{c\mu\mu_0\beta_r + \alpha_r\beta\pi} \right)\left(\frac{\mu+\omega_2+\gamma_2}{\mu+\omega_2+\gamma_2+\tau_3} \right)\left(\frac{\mu_0}{\mu_0+\delta_2} \right)$

Since all parameters are positive, $0 \le \varepsilon \le 1$, it follows that $\varepsilon k_2 < 1$ implying that $R_{er} < R_{0r}$. The factor εk_2 presents the contribution of public health education, sanitation and treatment interventions in reducing the initial transmission of AMR and epidemic.

Local Stability of the Disease-Free Equilibrium

The model system (1) is analyzed in order to investigate the stability of the DFE.

Theorem 2. *The disease-free equilibrium* E_{01} *is locally asymptotically stable if and only if* $R_{er} < 1$, $R_{es} < 1$, *and it is said to be unstable if at least one of these quantities is reversed.*

Proof.

The Jacobian matrix is evaluated at the disease free-equilibrium $\left(E_{01}\right)$ to get

$$J(E_{01}) = \begin{pmatrix} -\mu & -\varepsilon\beta_s & -\varepsilon\beta_r & \sigma & \frac{-\varepsilon\beta\pi}{c\mu} & \frac{-\varepsilon\beta\pi}{c\mu} \\ 0 & b & 0 & 0 & \frac{\varepsilon\beta\pi}{c\mu} & 0 \\ 0 & \theta & d & 0 & 0 & \frac{\varepsilon\beta\pi}{c\mu} \\ 0 & (\gamma_1+\tau_2) & (\gamma_2+\tau_3) & -(\mu+\delta) & 0 & 0 \\ 0 & \alpha_S & 0 & 0 & -(\mu_0+\delta_1) & 0 \\ 0 & 0 & \alpha_r & 0 & 0 & -(\mu_0+\delta_2) \end{pmatrix}, \tag{8}$$

where

$b = \varepsilon\beta_s - (\mu + \omega_1 + \gamma_1 + \theta + \tau_2)$

and $d = \varepsilon\beta_r - (\mu + \omega_2 + \gamma_2 + \tau_3)$.

From (8), it can be seen that the first two eigenvalues are $\lambda_1 = -\mu$ and $\lambda_2 = -(\mu + \delta)$. The remain four eigenvalues can be computed from the reduced matrix below.

$$J_1 = \begin{pmatrix} b & 0 & \frac{\varepsilon\beta\pi}{c\mu} & 0 \\ \theta & d & 0 & \frac{\varepsilon\beta\pi}{c\mu} \\ \alpha_s & 0 & -(\mu_0+\delta_1) & 0 \\ 0 & \alpha_r & 0 & -(\mu_0+\delta_2) \end{pmatrix}. \tag{9}$$

The characteristics polynomial equation corresponding to the reduced matrix in (9) is given by

$$a_0\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{10}$$

where $a_0 = 1$, $a_1 = c\mu(2\mu_0 + \delta_1 + \delta_2) + \varepsilon\pi\beta(\alpha_s + \alpha_r) + (1 - R_{es}) + (1 - R_{er})$,

$$a_2 = \left[2\mu_0 + \delta_1 + \delta_2 + \frac{\varepsilon\pi\beta}{\mu_0}\alpha_r + (1 - R_{er})\right]\left[\frac{\varepsilon\pi\beta}{c\mu}\alpha_s + (1 - R_{es})\right] + \alpha_s + \frac{\varepsilon\pi\beta}{c\mu}\alpha_r +$$

$$(\mu_0 + \delta_1)\left[\frac{\varepsilon\pi\beta}{\mu_0}\alpha_r + (1 - R_{er})\right],$$

$$a_3 = \left[\left(\frac{\varepsilon\pi\beta}{\mu_0}\right)^2 \alpha_r\alpha_s + \frac{\varepsilon\pi\beta\alpha_s}{\mu_0}(1 - R_{er}) + \frac{\varepsilon\pi\beta\alpha_r}{\mu_0}(1 - R_{es}) + (1 - R_{es})(1 - R_{er})\right](\mu_0 + \delta_1) +$$

$$(\mu_0 + \delta_2)\left[\frac{\varepsilon\pi\beta\alpha_s}{\mu_0} + (1 - R_{es})\right]\left[(\mu_0 + \delta_1) + \frac{\varepsilon\pi\beta\alpha_r}{\mu_0} + (1 - R_{er}) + (\mu_0 + \delta_1)(\mu_0 + \delta_2)\left[\frac{\varepsilon\pi\beta\alpha_r}{\mu_0} + (1 - R_{er})\right]\right] +$$

$$\frac{\varepsilon\pi\beta\alpha_r}{c\mu}(\mu_0 + \delta_1 + b) + \frac{\varepsilon\pi\beta_s\alpha_s}{c\mu}(d - (\mu_0 + \delta_2)),$$

$$a_4 = c\mu(\mu_0+\delta_1)\beta_s + c\mu(\mu_0+\delta_2)\beta_r + \frac{\varepsilon\pi(\mu_0+\delta_1)\alpha_s(\beta_r-\gamma_2)}{c\mu} + \frac{\varepsilon\pi(\mu_0+\delta_2)\alpha_r(\beta_s-\gamma_1)}{c\mu} +$$
$$\frac{\varepsilon\pi\beta}{c\mu}\left[\frac{\alpha_s\alpha_r\varepsilon\pi}{c\mu} - \mu(\mu_0+\delta_1)(\mu_0+\delta_2)(\mu(\alpha_s+\alpha_r)+\omega_1+\omega_2)\right] + (\mu_0+\delta_1)(\mu_0+\delta_2)[2\beta_s\beta_r+\gamma_1\gamma_2+\gamma_1\omega_2+\omega_1\omega_2] +$$
$$(1-R_{es})+(1-R_{er}).$$

Employing Routh Array criteria following the study by Sivanandam and Deepa (2007). The disease-free equilibrium of the model system (1) is LAS if $d < (\mu_0+\delta_2)$, $\beta_r < \gamma_2$, $\beta_s < \gamma_1$, $\frac{\alpha_s\alpha_r\varepsilon\pi}{c\mu} < \mu(\mu_0+\delta_1)(\mu_0+\delta_2)(\mu(\alpha_s+\alpha_r)+\omega_1+\omega_2)$ and both $R_{es}<1$ and $R_{er}<1$ as it was expected. This completes the proof. #

Existence of the Drug-Resistant Dominance Equilibrium

The drug-sensitive strain will not exist if the classes $I_s = P_s = 0$. Thus, the drug-resistant dominance equilibrium of the model system (1) under this condition is computed to get

$$\overset{*}{E}_r = \left(\overset{*}{S}, 0, \overset{*}{I}_r, \overset{*}{R}, 0, \overset{*}{P}_r\right),$$

where

$$\overset{*}{S} = \frac{\pi+\sigma R^*}{\varepsilon\lambda_r+\mu},\ \overset{*}{I}_r = \left(\frac{(\mu+\sigma)(\mu_0+\delta_2)\pi(R_{er}-1)}{R_{er}[(\mu+\sigma)\varepsilon(\beta_r+\beta\alpha_r)+\sigma(\mu_0+\delta_2)(\gamma_2+\tau_3)]}\right),$$

$$\overset{*}{R} = \left(\frac{\gamma_2+\tau_3}{\mu+\sigma}\right)\overset{*}{I}_r \text{ and } \overset{*}{P}_r = \left(\frac{\alpha_r \overset{*}{I}_r}{\mu_0+\delta_2}\right).$$

It can be seen that $I_r > 0$ if $R_{er} > 1$. Therefore, the drug-resistant dominance equilibrium exists if and only if $R_{er} > 1$.

Global Stability of the Drug-Resistant Dominance Equilibrium

Theorem 3. *The drug-resistant dominance equilibrium of the model system (1) is said to be GAS on* Φ *if* $R_{er} > 1$.

Proof. We use the approach by Oswald et al. (2025) to define the Lyapunov function V for the model system (1) as

$$V = k_1\left\{S - S^* - S^*\ln\frac{S^*}{S}\right\} + k_2\left\{I_r - I_r^* - I_r^*\ln\frac{I_r^*}{I_r}\right\} + k_3\left\{R - R^* - R^*\ln\frac{R^*}{R}\right\} + k_4\left\{P_r - P_r^* - P_r^*\ln\frac{P_r^*}{P_r}\right\}.$$

By taking the derivatives of V with respect to time along the solution of the model (1) and undergoing further algebraic manipulations one gets

$$\frac{dV}{dt} = k_1\left[\varepsilon\left[\lambda_r^*\left(1-\frac{S^*}{S}\right)+\lambda_r\left(1-\frac{S}{S^*}\right)\right]+a\left(2-\frac{S^*}{S}-\frac{S}{S^*}\right)\right]S^* + k_2(\mu+\omega_2+\gamma_2+\tau_3)\left(2-\frac{I_r^*}{I_r}-\frac{I_r}{I_r^*}\right)I_r^*$$
$$k_3(\gamma_2+\tau_3)\left[\left(2-\frac{R^*}{R}-\frac{R}{R^*}\right)\right]R^* + k_4(\mu_0+\gamma_2)\left(2-\frac{P_r^*}{P_r}-\frac{P_r}{P_r^*}\right)P_r^*.$$

Since the arithmetic mean is greater than the geometric mean, it follows that

$$\left(2-\frac{S^*}{S}-\frac{S}{S^*}\right)<0,\left(2-\frac{I_r^*}{I_r}-\frac{I_r}{I_r^*}\right)<0,\left(2-\frac{R^*}{R}-\frac{R}{R^*}\right)<0 \text{ and } \left(2-\frac{P_r^*}{P_r}-\frac{P_r}{P_r^*}\right)<0.$$

$$\frac{dV}{dt}\le k_1\varepsilon\left[\lambda_r^*\left(1-\frac{S^*}{S}\right)+\lambda_r\left(1-\frac{S}{S^*}\right)\right]S^*.$$

By using the inequality $1-x\le -\ln x$, it follows that

$$\frac{dV}{dt}\le -k_1\varepsilon\left[\lambda_r^*\ln\frac{S^*}{S}+\lambda_r\ln\frac{S}{S^*}\right]S^*\le 0.$$

The strict condition holds if and only if $S=S^*$, $I_r^*=I_r$, $R^*=R$, $P_r^*=P_r$. Consequently, V serves as a Lyapunov function on Φ, and E^* is the largest invariant set for which $\frac{dV}{dt}=0.$ According to LaSalle (1976), E^* is globally stable on Φ.

Epidemiologically, based on the above analysis, it is obvious that the drug resistance of typhoid fever will spread and prevail within the population if the value of R_{er} exceeds unity. The uncontrolled spread of AMR of typhoid fever increases severity leading to significant mortality. The burden of AMR will continue to rise if measures are not taken.

Existence of the Coexistence Equilibrium

A coexistence equilibrium is an equilibrium in which both sensitive strains and resistant strains are present, that is $I_s\neq 0$ and $I_r\neq 0$. The Co-existence equilibrium is determined by setting

$$\frac{dS}{dt}=\frac{dI_s}{dt}=\frac{dI_r}{dt}=\frac{dR}{dt}=\frac{dP_s}{dt}=\frac{dP_r}{dt}=0$$

and computing, to get

$$S^{**}=\frac{\pi}{\mu R_{es}},\ I_s^{**}=\left(1-\frac{R_{er}}{R_{es}}\right)\left(\frac{\mu+\gamma_2+\omega_2+\tau_3}{\theta}\right)I_r^{**},\ I_r^{**}=\frac{\pi(R_{er}-1)d_3}{d_1d_2(R_{es}-R_{er})+d_4}$$

$$R^{**}=\frac{(\gamma_1+\tau_2)I_s^{**}+(\gamma_2+\tau_3)I^{**}{}_r}{\mu+\sigma},\ P_s^{**}=\left(\frac{\alpha_s I_s^{**}}{\mu_0+\delta_1}\right),\text{ and }P_r^{**}=\left(\frac{\alpha_r I_r^{**}}{\mu_0+\delta_2}\right).$$

Therefore, the coexistence equilibrium $E^{**}=\left(S^{**},I_s^{**},I_r^{**},R^{**},P_s^{**},P_r^{**}\right)$, exists if $R_{es}>1$, $R_{er}>1$ and, $R_{es}>R_{er}$,

where

$$d_1=\frac{\mu+\gamma_2+\tau_3+\omega_3}{\theta},$$

$$d_2=\frac{\pi\varepsilon c\mu R_{es}(\mu_0+\delta_1)\beta_s+\beta\alpha_s\pi\varepsilon-(\mu R_{es}\delta(\gamma_1+\tau_2)(\mu_0+\delta_1))}{\theta},$$

$$d_3=c\mu R_{es}(\mu_0+\delta_1)(\mu_0+\delta_2),\text{ and}$$

$$d_4=R_{es}{}^2c\mu(\mu_0+\delta_1)[(\delta_2+\tau_3)(\mu_0+\delta_2)+\beta(\mu_0+\delta_2)+\beta_r\alpha_r].$$

Results and Discussion

Sensitivity Analysis

This section performs global sensitivity analysis using EE as described in Feng et al. (2020). EE offers quick and efficient ways of identifying the most influential inputs in complex models like models on AMR, without requiring a full-scale global sensitivity analysis for every parameter. In the context of AMR modelling, it is valuable for identifying critical factors driving resistance dynamics while accounting for model complexity and parameter interactions. The mean and the standard deviation are the two sensitivity measures of an output variable to a parameter. Mean measures the overall impact of a parameter on the model output, indicating its importance. On the other hand, Standard deviation reflects the non-linearity and interaction effects of the parameter with other parameters. Thus, the high value of the mean is an indication that a parameter has a strong effect on the output, and a large value of standard deviation implies that there is interaction between parameters. All parameters in the model system (1) are assumed to be uniformly distributed. Simulation is done by using parameter values and ranges as depicted in Table 1.

Table1: Parameter Descriptions and Values

Parameters	Descriptions	Ranges	Values	Sources
π	Recruitment rate	[1 - 50]	2 per day	Abboubakar and Racke R (2021)
ε_e	Education efficacy	[0 - 1]	0.81	Assumed
τ_2	Treatment rate for individuals infected with the drug-sensitive strain	[0 - 0.5]	0.02	Tilahun et al. (2017)
τ_3	Treatment rate for individuals infected with the drug-resistant strain	[0 - 0.6]	0.015	Irena and Gakkhar (2021)
θ	Mutation rate	[0 - 0.1]	0.05	Assumed
δ_1	Removal rate of drug-sensitive strain pathogens due to sanitation	[0 - 0.8]	0.2415	Mutua et al. (2015)
δ_2	Removal rate of drug-resistant strain pathogens due to sanitation	[0 - 0.6]	0.0018	Momoh et al. (2023)
σ	The rate of losing immunity	[0 - 0.4]	0.05	Momoh et al. (2023)
C	Carrying capacity for S. typhi	0-50,100	50,000	Momoh et al. (2023)
μ	The natural mortality rate for human	[0 - 0.02]	0.0005	Irena and Gakkhar (2021)
ω_1	The death rate due to disease for invectives with sensitive strain	[0 - 0.1]	0.012	Mushayabasa et al. (2013)
ω_2	Death rate due to disease for individuals infected with resistant strain	[0 - 0.1]	0.02	Mushayabasa et al. (2013)
γ_1	Natural recovery rate for individuals infected with sensitive strain	[0 - 0.01]	0.0005	Assumed

γ_2	Natural recovery rate for individuals infected with resistant strain	[0 - 0.01]	0.0004	Assumed
α_s	Shedding rate for individuals infected with drug-sensitive strain	[1 - 9]	9	Irena and Gakkhar (2021)
α_r	Shedding rate for individuals infected with the drug-resistant strain	[1 - 10]	0.4	Irena and Gakkhar (2021)
μ_0	Natural decay rate for pathogen population	[0 - 0.1]	0.2415	Mutua et al. (2015)
β_s	Effective contact rate for typhoid transmission for sensitive strain	[0 - 0.05]	0.006	Kaufhold et al. (2019)
β_r	Effective contact rate for typhoid transmission for resistant strain	[0 - 0.04]	0.0052	Kaufhold et al. (2019)
β	Indirect transmission rate	[0 - 0.2]	0.11	Edward (2017)

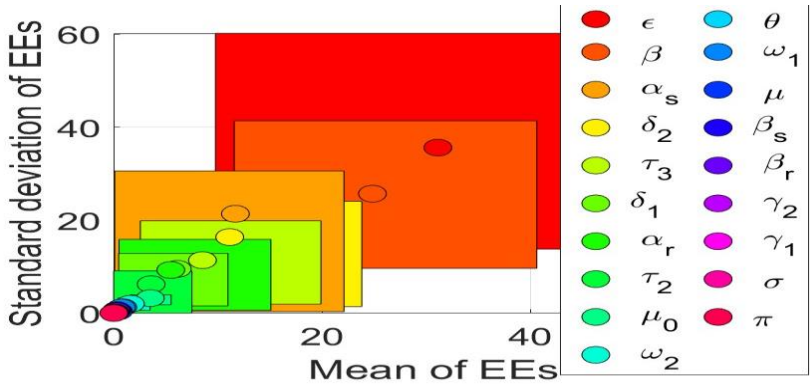


Figure 2: Global Sensitivity Analysis using Elementary Effects Approach for Model Parameters

Figure 2 illustrates the influence of model parameters on the output. The circles represent individual parameters, while the rectangular blocks likely group them based on their sensitivity and variability. Simulation results presented in Figure 2 shows that the most influential and interactive parameters is public health education ε, followed by indirect transmission rate β, shedding rate of sensitive-typhoid pathogens, α_s the removal rate of resistant- pathogens due to sanitation, τ_3 treatment rate for resistant strain, as it can be seen from the large values of their corresponding mean and standard deviation, respectively. The outputs in Figure 2 indicate that improving education consistently reduces the disease prevalence but with much interaction with other parameters. The results further indicates that reducing direct transmission rate through intervention such as sanitation and treatment can reduce the spread of the disease but its impact may vary under different conditions. We can also observe that the parameters with less influence and also less interactive are the recruitment rate and the natural recovery as it can be seen from their respective mean and standard deviation, respectively. This result indicates that, these parameters have less

impact on the model output and they interact less with other parameters, like mutation and treatment rates. Thus, it can be concluded that the power of typhoid fever to prevail is largely influenced by the public health education. However, its effectiveness in controlling the disease may depend on other factors like consideration of multiple interventions.

Numerical Results

In this section, the numerical simulation of the model system (1) is carried out to validate some of the analytic results using parameter values presented in Table 1. Simulation is done using MATLAB Package and the following initial conditions were considered: $S(0)=500$, $I_s(0)=10$, $I_r(0)=10$, $R(0)=1$, $P_s(0)=200$ and $P_r(0)=100$.

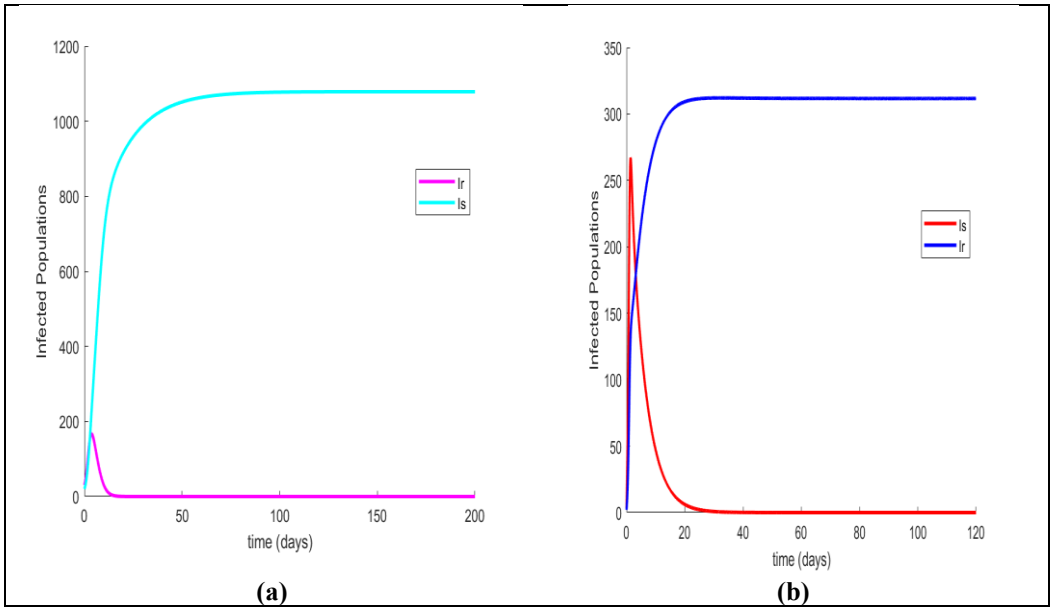


Figure 3: Competitive exclusion Principle when $\theta = 0$. (a) $R_{es} > R_{er} > 1$ and (b) $R_{er} > R_{es} > 1$.

Figure 3 illustrates the prevalence of typhoid fever in the absence of mutation. In Figure 3(a) Parameters are chosen such that $R_{er} > R_{es} > 1$. The results in Figure 3(a) show that the resistant strain will persist while the sensitive strain will die out after a short period of time. In Figure 3 (b) Parameters are also chosen such that $R_{es} > R_{er} > 1$. The results in Figure 3(b) indicates that the sensitive strain will persist while the resistant strain will be eliminated after a short period of time regardless of the initial value of the reproduction number. The results in Figure 3 indicate that in the absence of mutation, the strain with a large reproduction number is dominated while the other one dies out. This scenario agrees with the competitive exclusion principle employed in the study by Martcheva (2015). From these observations, it is suggested that, in the absence of mutation, targeting the strain with greater reproduction number may be ineffective because another strain can have a hidden advantage. Therefore, public health strategies should focus on comprehensive surveillance for early detection of the emerging strains.

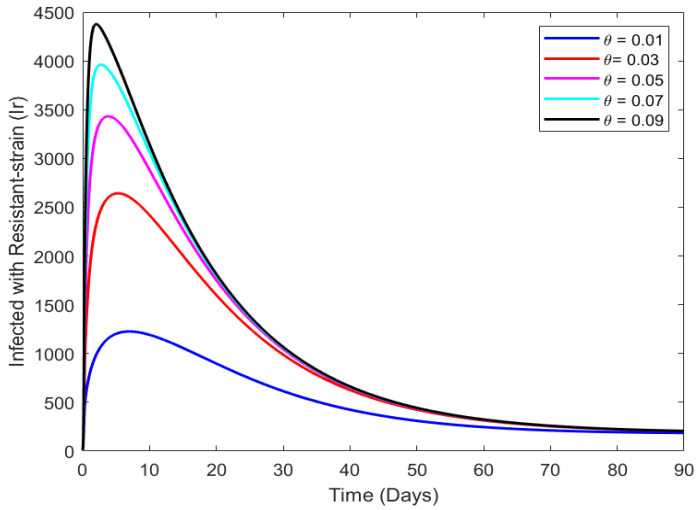


Figure 4: Impacts of mutation on individuals infected with the drug resistant strains.

Figure 4 illustrates the impacts of mutation on the dynamics of AMR of typhoid fever. The results in Figure 4 show that an increase in the mutation rate leads to a higher number of individuals infected with the drug-resistant strain. This occurs because some individuals initially infected with the sensitive strain acquire resistant pathogens and subsequently move to the compartment of those infected with the resistant strain. This suggests that mutation play a vital role in the persistence of AMR of typhoid fever. This result agrees with the results from the study by Irena and Gakkhar (2021), which suggested that, high prevalence of AMR was associated with an increase in mutation rate. The results in Figure 4 suggest that, to mitigate the persistence of AMR in typhoid fever, efforts should focus on reducing mutation rates. This can be achieved through the proper use of antibiotics.

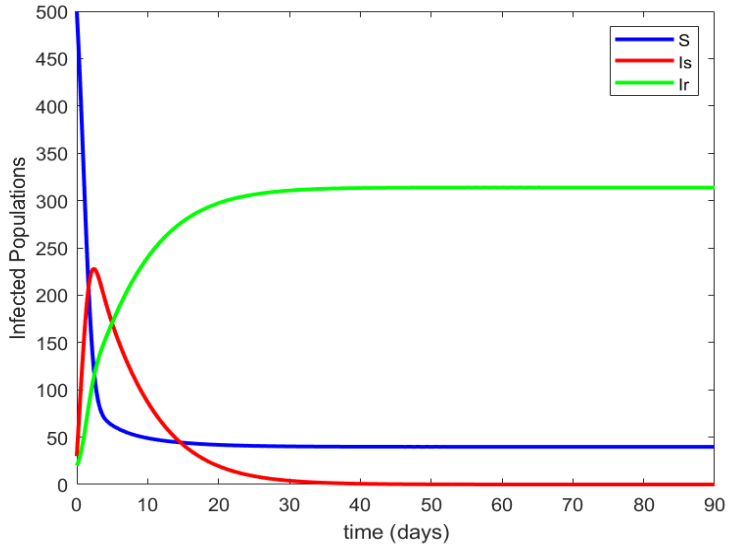


Figure 5: Permanence of Drug-resistant equilibrium when $\theta \neq 0$, and $R_{er} > R_{es} > 1$.

Figure 5 illustrates the disease dynamics in the presence of mutation. Parameters are chosen such that both reproduction numbers are greater than unity. The results show that under this situation, the individuals infected with sensitive strain will persist for a short period, and eventually will be led to extinction even if the reproduction number for sensitive strain is greater than unity. Thus, no sensitive strain equilibrium exists as shown analytically. On the other hand, it can be observed that individuals infected with the drug resistant strain will persist throughout the disease's duration. This suggests that in the presence of mutation, the drug resistant cases may outnumber cases of drug sensitive with time leading to the high prevalence of AMR of typhoid fever. Therefore, it is further suggested that, for effective control of typhoid fever, a close attention should be paid to the drug-resistant cases.

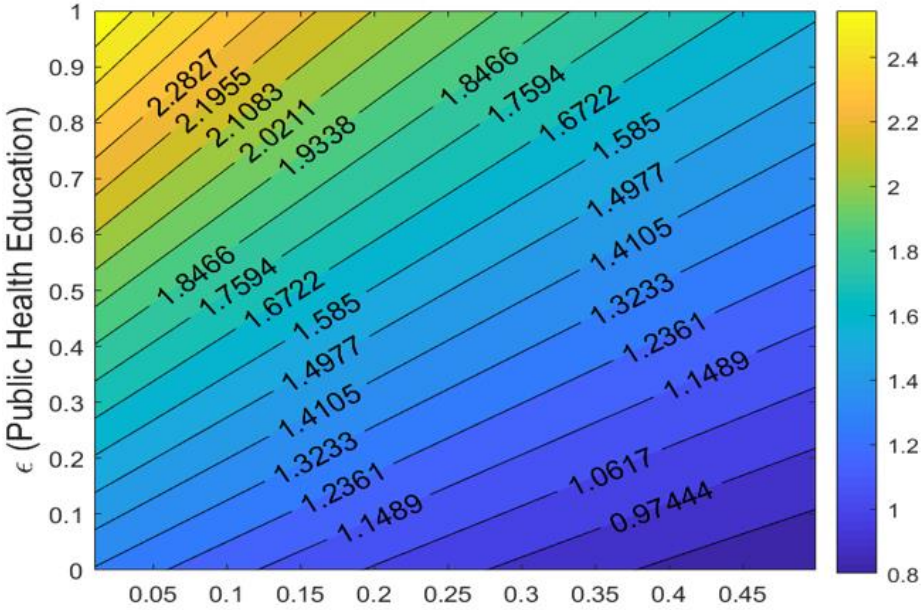


Figure 6: Contour plot showing the relationship between mutations rate (θ), public health education (ϵ) and the reproduction number for resistant typhoid Fever

The contour plot in Figure 6 illustrates the relationship between mutation rate (θ), public health education $\varepsilon = 1 - \varepsilon_e$ and the reproduction number for typhoid fever. It shows that as public health education increases, the reproduction number decreases significantly, highlighting the crucial role of public health education in controlling antimicrobial resistance. Higher mutation rates alone do not certainly lead to increased resistance, but in the absence of adequate education, resistance spreads more quickly, as shown by the yellow and green regions. Likewise, lower values of reproduction number (blue regions) occur where education efforts are strong, even at moderate mutation rates. This suggests that while mutation contributes to resistance, public health education is a key intervention in mitigating its impact and reducing the spread of drug-resistant infections.

Figure 7 presents the significance of public health education in reducing AMR of typhoid fever. The result indicates that, increasing the rate of education efficacy will have positive impacts in reducing the drug-resistant cases of typhoid fever. This is because public health education plays a role in reducing the

possibility of contacting with resistant-strain pathogens. This result is in line with the study of Edward and Nyerere (2016) on the significance of awareness campaign in controlling the disease. In addition to that, public health education plays a role in reducing the possibility of acquiring drug resistance due mutation. One can also observe that, with high education efficacy when $\varepsilon = 0.0025$, public health education is not sufficient enough to eradicate cases that are initially resistant to antibiotics. This result suggests the need for multiple interventions for the better results.

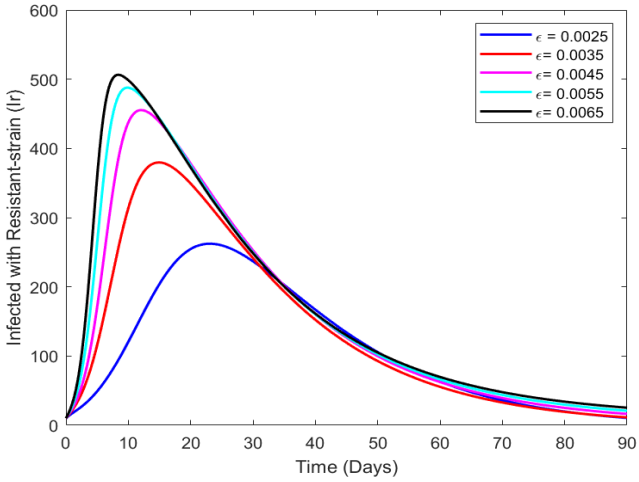
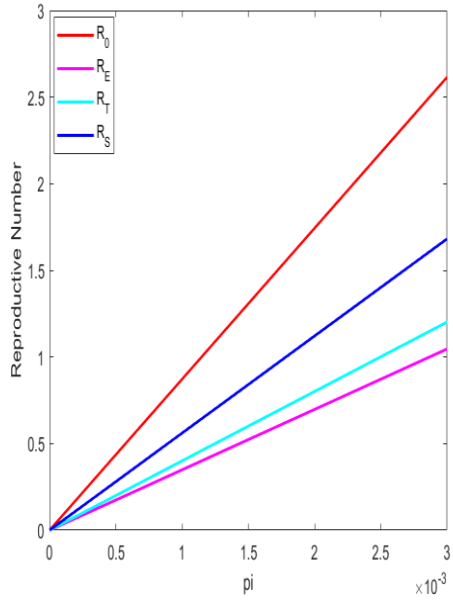
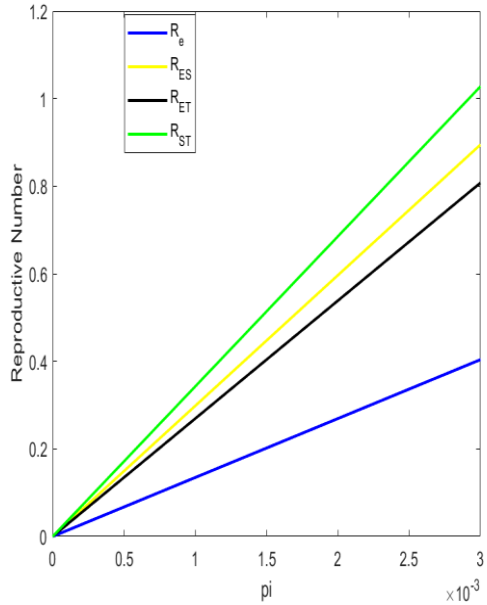


Figure: 7 Effect of Public Health Education on Individuals Infected with the drug-resistant strain.



(a)



(b)

Figure 8: The Impacts of interventions on the dynamics of antimicrobial resistance of typhoid fever.

Figure 8 illustrates the impacts of interventions on the reproduction numbers. Figure 8(a) illustrates the effects of a single intervention with four cases showing variation on the reproduction number with varying interventions. R_0 represents the basic reproduction number, R_E is the reproduction number for public health education alone, R_T is the reproduction number for treatment alone and R_S is the reproduction number for sanitation alone. The results in Figure 8(a) indicates that, the basic reproduction number R_0 decreases as interventions are incorporate, as expected. That is, $R_0 > R_S > R_T > R_E$ implying that each intervention (sanitation, treatment and public health education) has positive impacts in reducing the burden of AMR of typhoid fever. However, in this scenario, public health education appears to play a great role.

Figure 8(b) illustrates the effects of multiple interventions on the reproduction number. R_{ST} is the reproduction number associated with the combination of sanitation and treatment, R_{ET} is associated with public health education and treatment, R_{ES} is associated with public health education and treatment and R_e is associated with the combination of sanitation, treatment and public health education. The results in Figure 8(b) show a significant improvement when the combination of two interventions is considered as it can be seen from the small values of the respective reproduction numbers. Furthermore, one can observe that the combination of sanitation and treatment is less effective compared to other multiple interventions as it can be seen from the relation $R_{ST} > R_{ES} > R_{ET} > R_e$. This observation revealed that incorporating sanitation and treatment alone may not be sufficient enough to tackle the problem of mutation. Thus, the observation in Figure 8(b) suggests that the effective control of AMR of typhoid fever will be attained when other interventions are combined with public health education. This is contrary to the study of Irena and Gakkhar (2021) which ignored the importance of public education. The results in Figure 8(b) have further shown that the combination of all three interventions is more effective compared to the combination of two interventions. In particular, this observation suggests the importance of multiple interventions in controlling the spread of the disease and epidemic.

Conclusion

Understanding the control and dynamics of AMR of typhoid fever requires identifying critical factors influencing infections. In this paper, a two-strain mathematical model for the transmission dynamics of AMR of typhoid fever that incorporates mutation was developed and analyzed. The key novelty is the consideration of public health education in curtailing the crisis of treatment-induced acquired resistance to typhoid fever. We derived the reproduction number and utilized it to investigate the stabilities of the model steady states. The results from analytical analyses showed that the disease will become extinct in the community whenever both reproduction numbers are less than unity. Furthermore, results also showed that the drug-resistant strain will dominate irrespective of the initial condition whenever the reproduction associated with the drug-resistant strain is greater than one. We performed global sensitivity analysis by using EE. Our findings showed that the most influential parameter is the public health education followed by indirect transmission rate. Numerical simulation shows the impacts of mutation on the persistence of resistant-strain cases. The results further show that, higher mutation rates alone do not certainly lead to increased resistance, but in the absence of adequate education, resistance spreads more quickly. In addition, we

observed that in the presence of mutation, if both reproduction numbers are greater than unity then the resistant strain may lead to the extinction of the sensitive strain. This finding is of concern regarding effective eradication of resistant-typhoid pathogens by setting effective control strategies.

Comprehensive numerical analysis of the model showed that each intervention (sanitation, treatment and public health education) play part in controlling the disease, with public health education playing a crucial role. Further analysis on the impacts of multiple interventions revealed the significance improvement when two interventions are combined, with public health education playing a crucial role. However, the combination of all three interventions yields the best outcome. Our findings suggest that integrating public health education into control strategies is essential for effectively mitigating the spread of AMR of typhoid fever.

It is therefore recommended that, the government should use multifaceted approach to address the problem of AMR to the community, health stakeholders and other policymakers. This may, includes enforcing antibiotics sales regulations, training health workers and strengthening laboratory networks to ensure accurate diagnosis of typhoid fever.

Although the proposed model focuses on symptomatic infectious individuals, an expansion of this work to incorporate screening for carriers in the dynamics of antimicrobial resistance of typhoid fever would provide a compressive understanding. Furthermore, vaccination intervention which is known to play part in reducing the prevalence of typhoid fever (Kaufhold et al. (2019)), was neglected in this study and could be considered in future works.

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Declaration

The authors declare that there is no conflict of interest.

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