A Humble offering

MODELLING AND OPTIMAL CONTROL OF TYPHOID FEVER DISEASE WITH COST-EFFECTIVE STRATEGIES

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INTRODUCTION

- Typhoid is a bacterial infection.
- It is caused by Salmonella paratyphi A,B,C.
- This bacterium is gram negative,rod shaped, flagellated.It's only reservoir is human body.
- It can be transmitted through contaminated food and drinking water
- It can be spread through flies.
- Symptoms are fever,headache,weakness, abdominal pain and diarrhea.
- It can be treated by antibiotics(Ciprofloxacin and ofloxacin) and antipyretic drugs.
- It can be prevented by washing hands,drinking treated water,eating hot food etc.

- A mathematical model is a mathematical framework representing variables and their interrelationships to describe observed phenomena or predict future events.
- They are quick and easy to produce.
- They can simplify a complex situation.
- Mathematical techniques can explain how the world works and make it better.
- Mathematical models can be used to link the biological process.
- They have great benefits for describing the dynamics of the disease.
- They help to take decisions faster and more accurately.
- In this paper the investigation has been done in typhoid fever dynamics with the application of optimal control methods and cost-effectiveness analysis of the applied control strategies.

MODEL DESCRIPTION AND FORMULATION

- This model considers human population(N) as well as bacteria population(B_c).
- The human population at time t is divided into four subclasses:
- Susceptible(S):This class includes all individuals who are more likely to catch infection.
- Infected(I):This class includes all individuals who show symptoms of the infection.
- Carrier(C):This class includes all who don't show any symptoms but they infect others.
- Recovered(R):This class includes all who have recovered from disease and got temporary immunity.
- Λ is the rate at which susceptible class is increased by birth or emigration.
- The susceptible class is increased from recovered class by losing temporary immunity with δ rate.
- The force of infection of the model is $\lambda = B_c\nu/k+B_c$.
- ν is the ingestion rate.

- K is the concentration of salmonella bacteria in foods or waters.
- $B_c/k+B_c$ is the probability of individuals in consuming contaminated food which has bacteria.
- ρ is the rate at which susceptible individuals join carriers.
- 1- ρ is the rate at which susceptible individuals join infected.
- The infected subclass is increased from carrier subclass by θ rate.
- The infected subclass joins recovered subclass by β rate after getting treatment.
- The individuals in carrier subclass joins recovered subclass by ϕ rate after getting natural immunity.
- μ is the natural death rate.
- In the infective class α is the disease causing death rate.
- Carriers and infectives can contribute to increasing the bacteria population.
  with a discharge rate of σ_1 and σ_2 respectively.
- μ_b is the death rate of salmonella bacteria.

Model Formulation

$$\frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S,$$

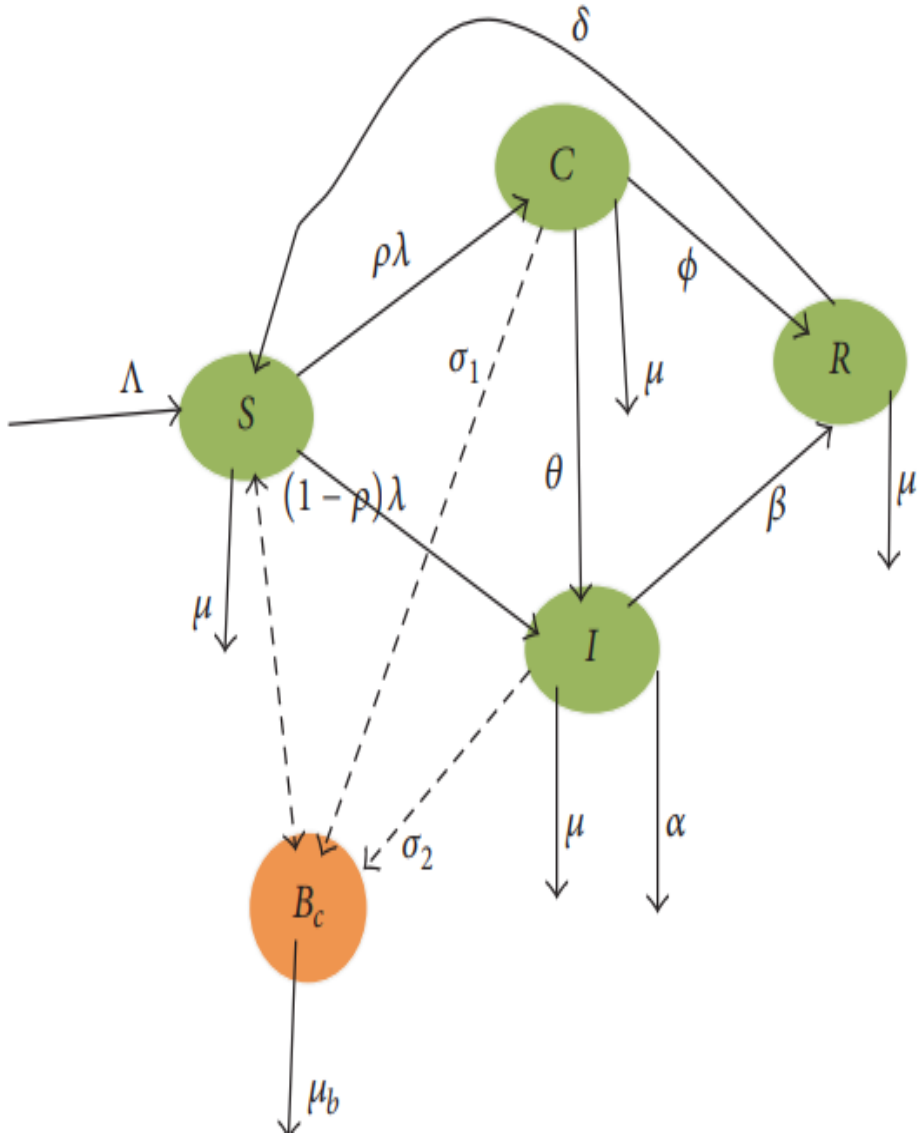
$$\frac{dC}{dt} = \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C,$$

$$\frac{dI}{dt} = (1-\rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I,$$

$$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R, \qquad \rightarrow (1)$$

$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c$$

Where $\lambda = B_c\nu/k+B_c$,with initial conditions $S(0)=S_0, C(0)=C_0, I(0) = I_0, R(0) = R_0$,and $B_c(0)=B_{c0}$.



The Model Analysis

- We obtain the region in which the model solution is bounded.
- Total human population (N)=S+C+I+R.

differentiating N on both sides with respect to t

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dC}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \qquad \rightarrow ②$$

By combining ① and ② we get

$$\frac{dN}{dt} = \Lambda - \mu(S + C + I + R) - \alpha I = \Lambda - \mu N - \alpha I$$

$$\frac{dN}{dt} \leq \Lambda - \mu N$$

Integrating on both sides

$$\int \frac{dN}{dt} \leq \int \Lambda - \ \mu N$$

$$\int \frac{dN}{\Lambda - \ \mu N} \leq \int dt$$

$\frac{-1}{\mu}\ln(\Lambda - \mu N) \leq$ t+c where c is constant of integration

$\ln(\Lambda - \mu N) \geq -\mu t - \mu c$

$\Lambda - \mu N \geq e^{-\mu(t+c)} = e^{-\mu t} * e^{-\mu c}$

Where A= $e^{-\mu c}$

$\Lambda - \mu N \geq A\, e^{-\mu t}$

Where A is a constant and by applying initial condition N(0)=N_0

We get A= $\Lambda - \mu N_0$

$\Lambda - \mu N \geq (\Lambda - \mu N_0)\, e^{-\mu t}$

$-\mu N \geq (\Lambda - \mu N_0)\, e^{-\mu t} - \Lambda$

$\mu N \leq -(\Lambda - \mu N_0)\, e^{-\mu t} + \Lambda$

$N \leq \frac{\Lambda}{\mu} - [\frac{\Lambda - \mu N_0}{\mu}]\, e^{-\mu t}$ As $t \to \infty$ the population size $N \to \frac{\Lambda}{\mu}$ which implies that $0 \leq N \leq \frac{\Lambda}{\mu}$.The feasible solution set of the set of equation of the model enters and remains in the region $\Omega = \{ (S,I,C,R) \in \mathfrak{R}_+^4 : N \leq \frac{\Lambda}{\mu}\}$

Positivity of the solutions

- Theorem: Let Ω={(S,C, I,R,B_c) ϵ $\mathfrak{R}_+^5$: S_0>0, I_0>0, C_0>0, R_0>0, B_{c0}>0};then the solutions of {S,C,I,R, B_c} are positive for t ≥ 0.

Proof : From the system of differential equation ① ,let us take the first equation

$$\frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S$$

$$\frac{dS(t)}{dt} \geq -(\mu + \lambda)S(t)$$

$$\frac{dS(t)}{S(t)} \geq -(\mu + \lambda)d(t)$$

$$\int \frac{dS(t)}{S(t)} \geq -\int(\mu + \lambda)d(t)$$

$lnS(t) \geq -(\mu + \lambda)t + c$, S(0)=$S_0$

and ln S_0=c

$lnS(t) \geq -(\mu + \lambda)t + \ln S_0$

$\ln S(t) - \ln S_0 \geq -(\mu + \lambda)t$

$\ln(\frac{S(t)}{S_0}) \geq -(\mu + \lambda)t$

$S(t) \geq S_0 e^{-(\mu+\lambda)t} \geq 0.$

$$\frac{dC}{dt} = \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C$$

$$\frac{dC}{dt} \geq -(\sigma_1 + \theta + \mu + \phi)C$$

$$\int \frac{dC}{C} \geq -\int (\sigma_1 + \theta + \mu + \phi)\ dt$$

$$\ln C(t) \geq -(\sigma_1 + \theta + \mu + \phi)t + c$$

By applying initial condition $C(0)=C_0$

So $c = \ln C_0$

$$C(t) \geq C_0 e^{-(\sigma_1+\theta+\mu+\phi)} \geq 0$$

We take third equation of ①

$$\frac{dI}{dt} = (1-\rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I$$

$$\frac{dI}{dt} \geq -(\sigma_2 + \beta + \mu + \alpha)I$$

$\int \frac{dI}{I} \geq \int -(\sigma_2 + \beta + \mu + \alpha)\,\mathrm{dt}$

By applying initial condition $I(0) = I_0$

We get I(t) $\geq I_0 e^{-(\sigma_2+\beta+\mu+\alpha)t} \geq 0$

We take the fourth equation from ①

$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R$

$\frac{dR}{dt} \geq -(\mu + \delta)R$

$\int \frac{dR}{R(t)} \geq -\int (\mu + \delta)\mathrm{dt}$

By applying initial condition $R(0) = R_0$

R(t) $\geq R_0 e^{-(\mu+\delta)t} \geq 0$

We take fifth equation of ①

$\frac{d\mathrm{B_c}}{dt} = \sigma_1 C + \sigma_2 \mathrm{I} - \mu_b \mathrm{B_c}$

$\frac{d\mathrm{B_c}}{dt} \geq -\ \mu_b \mathrm{B_c}$

$\int \frac{d\mathrm{B_c}}{\mathrm{B_c}} \geq -\int \mu_b \mathrm{dt}$

By Separation of variables method and by applying initial condition $B_c(0)=B_{c0}$

We get $B_c \geq B_{c0}e^{-\mu_B t} \geq 0$

Therefore the solution of the model is positive.

The Disease free equilibrium point(DFE) : The point at which no disease is present in the population.

DFE of this model should be evaluated at C=0,I=0.

We solve for noninfected and noncarrier state variables

$\frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S$

$\Lambda + \delta R - (\mu + \lambda)S = 0$

$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R$

$\beta I + \phi C - (\mu + \delta)R = 0$

implies R=0 since C=0,I=0

therefore S= $\frac{\Lambda}{\mu}$

So, DFE E_0 = ($\frac{\Lambda}{\mu}$,0,0,0,0).

Basic reproduction number

- Basic reproduction number of an infection is the expected number of cases directly generated by one case in a population where all the individuals are susceptible to infection.
- It is denoted by $\mathfrak{R}_0$
- We obtain basic reproduction number by using the next generation matrix method

We consider the stages where disease is present

$$\frac{dC}{dt} = \rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C,$$

$$\frac{dI}{dt} = (1-\rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I,$$

$$\frac{d\mathrm{B_c}}{dt} = \sigma_1 C + \sigma_2 \mathrm{I} - \mu_b \mathrm{B_c}$$

We construct matrices f and v

$$f = \begin{bmatrix} \rho(B_c\nu/k+Bc)S \\ (1-\rho)(B_c\nu/k+Bc)S \end{bmatrix}$$

$$V = \begin{bmatrix} (\sigma_1 + \theta + \mu + \phi)C \\ (\sigma_2 + \beta + \mu + \alpha)I - \theta C \\ -(\sigma_1 C + \sigma_2 I - \mu_b B_c) \end{bmatrix}$$

We Jacobian matrices of f and v

$f(C,I, B_c) = \rho(B_c\nu/k+Bc)S$

$g(C,I, B_c) = (1-\rho)(B_c\nu/k+Bc)S$

$$F = \begin{bmatrix} \frac{\partial f}{\partial C} & \frac{\partial f}{\partial I} & \frac{\partial f}{\partial B_c} \\ \frac{\partial g}{\partial C} & \frac{\partial g}{\partial I} & \frac{\partial g}{\partial B_c} \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & 0 & \frac{\rho\upsilon\Lambda}{\mu K} \\ 0 & 0 & \frac{(1-\rho)\Lambda\upsilon}{\mu K} \\ 0 & 0 & 0 \end{bmatrix}$$

$a(C,I,B_c) = (\sigma_1 + \theta + \mu + \phi)C$

$b(C,I,B_c) = (\sigma_2 + \beta + \mu + \alpha)I - \theta C$

$h(C,I,B_c) = -(\sigma_1 C + \sigma_2 I - \mu_b B_c)$

$$V = \begin{bmatrix} \frac{\partial a}{\partial C} & \frac{\partial a}{\partial I} & \frac{\partial h}{\partial B_c} \\ \frac{\partial b}{\partial C} & \frac{\partial b}{\partial I} & \frac{\partial h}{\partial B_c} \\ \frac{\partial h}{\partial C} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial B_c} \end{bmatrix} = \begin{bmatrix} (\sigma_1 + \theta + \mu + \phi) & 0 & 0 \\ -\theta & (\sigma_2 + \beta + \mu + \alpha) & 0 \\ -\sigma_1 & -\sigma_2 & \mu_b \end{bmatrix}$$

By using Augmented matrix method we get $V^{-1} = \begin{bmatrix} \frac{1}{k_1} & 0 & 0 \\ \frac{\theta}{k_1 k_2} & \frac{1}{k_2} & 0 \\ \frac{\theta\sigma_2 + \sigma_1 k_2}{k_1 k_2 \mu_b} & \frac{\sigma_2}{k_2 \mu_b} & \frac{1}{\mu_b} \end{bmatrix}$

Where $k_1 = (\sigma_1 + \theta + \mu + \phi)$ and $k_2 = (\sigma_2 + \beta + \mu + \alpha)$

We caluculate F V^{-1}

$$F\,V^{-1} = \begin{bmatrix} \frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu K k_1 k_2 \mu_b} & \frac{\rho\Lambda\nu\sigma_2}{\mu K k_2 \mu_b} & \frac{\rho\Lambda\nu}{\nu K \mu_b} \\ \frac{(1-\rho)\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu K k_1 k_2 \mu_b} & \frac{(1-\rho)\Lambda\nu\sigma_2}{\mu K k_2 \mu_b} & \frac{(1-\rho)\Lambda\nu}{\nu K \mu_b} \\ 0 & 0 & 0 \end{bmatrix}$$

The characteristic polynomial of F V^{-1} is obtained as

$$(\lambda^2-0)(\lambda - (\frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu K k_1 k_2 \mu_b}+\frac{(1-\rho)\Lambda\nu\sigma_2}{\mu K k_2 \mu_b})) =0$$

We get three Eigen values $\lambda_1 = 0, \lambda_2 = 0, \lambda_3 = (\frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu K k_1 k_2 \mu_b}+\frac{(1-\rho)\Lambda\nu\sigma_2}{\mu K k_2 \mu_b})$

The dominant Eigen value gives the basic reproduction number

$$\mathfrak{R}_0 = (\frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu K k_1 k_2 \mu_b}+\frac{(1-\rho)\Lambda\nu\sigma_2}{\mu K k_2 \mu_b}) = (\frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1(\sigma_2+\beta+\mu+\alpha))}{(\sigma_1+\theta+\mu+\phi)}+(1-\rho)\,\sigma_2)\,\frac{\Lambda\nu}{\mu K(\sigma_2+\beta+\mu+\alpha)\mu_b}$$

Proposition: The disease free equilibrium point is locally asymptotically stable if $\mathfrak{R}_0 < 1$and unstable if $\mathfrak{R}_0 > 1$.

Proof: We obtain Jacobian matrix of system ① at E_0

Let us take f(S,C,I,R,B_c) =$\Lambda + \delta R - (\mu + \lambda)S$

g(S,C,I,R,B_c)= $\rho\lambda S - (\sigma_1 + \theta + \mu + \phi)C$

h(S,C,I,R,B_c)= (1- ρ)$\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I$

a(S,C,I,R,B_c)= $\beta I + \phi C - (\mu + \delta)R$

b(S,C,I,R,B_c)= $\sigma_1 C + \sigma_2 \mathrm{I} - \mu_b B_c$

$$J = \begin{bmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial C} & \frac{\partial f}{\partial I} & \frac{\partial f}{\partial R} & \frac{\partial f}{\partial B_c} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial C} & \frac{\partial g}{\partial I} & \frac{\partial g}{\partial R} & \frac{\partial g}{\partial B_c} \\ \frac{\partial h}{\partial S} & \frac{\partial h}{\partial C} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial R} & \frac{\partial h}{\partial B_c} \\ \frac{\partial a}{\partial S} & \frac{\partial a}{\partial C} & \frac{\partial a}{\partial I} & \frac{\partial a}{\partial R} & \frac{\partial a}{\partial B_c} \\ \frac{\partial b}{\partial S} & \frac{\partial b}{\partial C} & \frac{\partial b}{\partial I} & \frac{\partial b}{\partial R} & \frac{\partial b}{\partial B_c} \end{bmatrix}$$

After doing partial derivation we get

$$J = \begin{bmatrix} -(\mu+\lambda) & 0 & 0 & \delta & \frac{\nu SK}{(K+B_c)^2} \\ \frac{\rho B_c \nu}{K+B_c} & -(\sigma_1+\theta+\mu+\phi) & 0 & 0 & \frac{\rho \nu SK}{(K+B_c)^2} \\ (1-\rho)\lambda & \theta & -(\sigma_2+\beta+\mu+\alpha) & 0 & \frac{(1-\rho)\nu SK}{(K+B_c)^2} \\ 0 & \phi & \beta & -(\mu+\delta) & 0 \\ 0 & \sigma_1 & \sigma_2 & 0 & -\mu_b \end{bmatrix}$$

After substituting E_0 = ($\frac{\Lambda}{\mu}$,0,0,0,0) in the Jacobian matrix

$$J_{E_0} = \begin{bmatrix} -\mu & 0 & 0 & \delta & \frac{\nu\Lambda}{K\mu} \\ 0 & -(\sigma_1 + \theta + \mu + \phi) & 0 & 0 & \frac{\rho\nu\Lambda}{\mu K} \\ 0 & \theta & -(\sigma_2 + \beta + \mu + \alpha) & 0 & \frac{(1-\rho)\nu\Lambda}{\mu K} \\ 0 & \phi & \beta & -(\mu + \delta) & 0 \\ 0 & \sigma_1 & \sigma_2 & 0 & -\mu_b \end{bmatrix}$$

The characteristic polynomial is $(-\lambda - \mu)(-\lambda - (\mu + \delta))(\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3) = 0$

Where L_1= σ_2+ β+2μ + α + σ_1+ϕ + θ + μ_b

L_2= μ_b(σ_2+ β+2μ + α + σ_1+ϕ + θ)+(σ_2+ β+ μ + α)(σ_1+ μ+ϕ + θ)-($\rho\sigma_1$+(1-ρ) σ_2)$\frac{\nu\lambda}{\mu K}$

L_3= μ_b(σ_2+ β+ μ + α)(σ_1+ μ+ϕ + θ)(1- $\mathfrak{R}_0$)

$-\lambda - \mu$ = 0 or $-\lambda - (\mu + \delta)$=0 or $\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3$=0

Implies $\lambda_1 = -\mu < 0, \lambda_2 = -(\mu + \delta) < 0$

Let us take the last expression $\lambda^3 + L_1\lambda^2 + L_2\lambda + L_3 = 0 \rightarrow ③$

By applying Routh-Hurwitz criteria to ③

$a_0 = 1, a_1 = L_1, a_2 = L_2, a_3 = L_3$

$\Delta_1 = a_1 = L_1 > 0$

$$\Delta_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = \begin{vmatrix} L_1 & 1 \\ L_3 & L_2 \end{vmatrix} = L_1L_2 - L_3 > 0$$

$\Delta_3 = a_3\ \Delta_2 = L_3(L_1L_2 - L_3) > 0$

So, $L_3 > 0$ and $L_1L_2 > L_3$

For L_3 to be positive (1- $\mathfrak{R}_0$) must be positive which leads to $\mathfrak{R}_0 < 1$.

Therefore,DFE will be locally asymptotically stable if and only if $\mathfrak{R}_0 < 1$

If $\mathfrak{R}_0 > 1$ the disease free equilibrium is unstable.

Theorem:The disease-free equilibrium is globally asymptotically stable in the feasible region Ω if $\mathfrak{R}_0$<1

Proof: We develop the Lyapunov function,technically

$$L = \left[\frac{\theta\sigma_2+\sigma_1 k_2}{k_1}\right] C + \sigma_2 I + k_2 B_c$$

Where $k_1 = (\sigma_1 + \theta + \mu + \phi)$ and $k_2 = (\sigma_2 + \beta + \mu + \alpha)$

Then differentiating L on both sides

$$\frac{dL}{dt} = \left[\frac{\theta\sigma_2+\sigma_1 k_2}{k_1}\right] \frac{dC}{dt} + \sigma_2 \frac{dI}{dt} + k_2 \frac{dB_c}{dt}$$

We substitute $\frac{dC}{dt}$, $\frac{dI}{dt}$,and $\frac{dB_c}{dt}$ from ①

$$\frac{dL}{dt} = \left[\frac{\theta\sigma_2+\sigma_1 k_2}{k_1}\right] (\rho\lambda s - (\sigma_1 + \theta + \mu + \phi)C) + \sigma_2((1-\rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I) + k_2(\sigma_1 C + \sigma_2 I - \mu_b B_c)$$

$\frac{dL}{dt}$=$\left[\rho\frac{\theta\sigma_2+\sigma_1k_2}{k_1}+(1-\rho)\sigma_2\right]\lambda S+(\theta\sigma_2-\theta\sigma_2-\sigma_1k_2)C-\sigma_2k_2I+k_2(\sigma_1C+\sigma_2I-\mu_bB_c)$

$\frac{dL}{dt}$= $\left[\rho\frac{\theta\sigma_2+\sigma_1k_2}{k_1}+(1-\rho)\sigma_2\right]\lambda S-k_2\,\mu_bB_c$

Since $\mathfrak{R}_0$= ($\frac{\rho\Lambda\nu(\theta\sigma_2+\sigma_1k_2)}{\mu Kk_1k_2\mu_b}$+$\frac{(1-\rho)\Lambda\nu\sigma_2}{\mu Kk_2\mu_b}$)

$\frac{dL}{dt}$= ($\mathfrak{R}_0\,\mu_b\,k_2\,\frac{\mu K}{\Lambda\nu}$) $\lambda S-k_2\,\mu_bB_c$

$\frac{dL}{dt}$= ($\mathfrak{R}_0\,\mu_b\,k_2\,\frac{\mu K}{\Lambda\nu}$)$\lambda\frac{\Lambda}{\mu}-k_2\,\mu_bB_c$

$\frac{dL}{dt}$=($\mathfrak{R}_0$ -1) $k_2\,\mu_bB_c$

$\frac{dL}{dt}$<0 if $\mathfrak{R}_0$ < 1

If there is a Lyapunov function L in the neighbourhood of DFE with a negative definite derivative then DFE is globally asymptotically stable.

Sensitivity analysis of model parameters

- On the basic parameters we carry out sensitivity analysis.
- This helps us to check and identify parameters that can impact basic reproductive Number.
- The sensitivity index of all basic parameters is defined as $\Delta_x^{\mathfrak{R}_0} = \left(\frac{\partial \mathfrak{R}_0}{\partial x}\right)\left(\frac{x}{\mathfrak{R}_0}\right)$.

  here x represents all the basic parameters.

For example the values of the parameters are taken as$\Lambda = 100, \phi = 0.0003, \sigma_1 = 0.9, \sigma_2$=0.8,$\beta = 0.0002, \rho = 0.3, \mu = 0.0247, \mu_b$=0.0001,$\alpha = 0.052, \theta = 0.2, \nu = 0.9$, and K=50,000.

- The sensitivity indices of $\mathfrak{R}_0$with respect to all basic parameters are $\Delta_\nu^{\mathfrak{R}_0}, \Delta_K^{\mathfrak{R}_0}, \Delta_{\sigma_1}^{\mathfrak{R}_0}, \Delta_{\sigma_2}^{\mathfrak{R}_0}, \Delta_\beta^{\mathfrak{R}_0}, \Delta_\rho^{\mathfrak{R}_0}, \Delta_\mu^{\mathfrak{R}_0}, \Delta_{\mu_b}^{\mathfrak{R}_0}, \Delta_\alpha^{\mathfrak{R}_0}, \Delta_\theta^{\mathfrak{R}_0}, \Delta_\phi^{\mathfrak{R}_0}$.

- The parameters(ν,k, σ_1, σ_2,and ρ) that have positive indices increases $\mathfrak{R}_0$ value if their values increase.

- The parameters($\mu, \mu_b, \alpha, \theta, \beta$, and ϕ) that have negative indices decreases $\mathfrak{R}_0$ value if their values increase.

Sensitivity indices table

Parameter symbol	Sensitivity indices
ν	1
K	0.999
σ_1	0.26
σ_2	0.03
ρ	0.00506
μ	-1.028
μ_b	-1
α	-0.0592
θ	0.009
β	-0.00017
ϕ	-0.000089

Extension of Model into Optimal control

- The basic model of typhoid fever is generalized by incorporating three control interventions.
- The controls are prevention(u_1)(Sanitation and proper hygiene controls),treatment(u_2),and screening of carriers(u_3)
- After incorporating the controls into basic model

$$\frac{dS}{dt} = \Lambda + \delta R - (1 - u_1)\,\lambda S - \mu S,$$

$$\frac{dC}{dt} = (1 - u_1)\rho\lambda S - (\theta + u_3)C - (\sigma_1 + \mu + \phi)C,$$

$$\frac{dI}{dt} = (1 - u_1)(1 - \rho)\lambda S + (1 - u_3)\theta C - (u_2 + \beta)I - (\sigma_2 + \mu + \alpha)I,$$

$$\frac{dR}{dt} = (u_2 + \beta)I + \phi C - (\mu + \delta)R,$$

$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c$$

Where $\lambda = B_c\nu/k+B_c$,{$0 \leq u_1 < 1, 0 \leq u_2 < 1, 0 \leq u_3 < 1, 0 \leq t < T$

- Our main objective is to obtain the optimal levels of the controls

that optimize the objective function.

- The objective function is taken as $J = \min_{u_1, u_2, u_3} \int_0^{t_f} (b_1 C + b_2 I + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2)\, dt.$

where b_1 and b_2 are coefficients of state variables and $\frac{1}{2} w_i u_i^2$ is the cost expression.

- We get an optimal triple (u_1^*, u_2^*, u_3^*) inorder to minimize the optimal function.

$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3) | u_i \epsilon U\}$,where $U = \{(u_1, u_2, u_3) | 0 \leq u_i < 1\}$

- We construct the function H

Hamiltonian(H)=$\frac{dJ}{dt} + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dC}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dR}{dt} + \lambda_5 \frac{dB_c}{dt}$.

$H(S,C,I,R, B_c) = L(C,I, u_1, u_2, u_3, t) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dC}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dR}{dt} + \lambda_5 \frac{dB_c}{dt}$

Where $L(C,I, u_1, u_2, u_3, t) = (b_1 C + b_2 I + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2)$, $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ are the adjoint variable functions.

We use Pontryagin's principle.

To get system of adjoint variables,We write state equations

$$\frac{dS}{dt} = \frac{dH}{d\lambda_1}, \frac{dC}{dt} = \frac{dH}{d\lambda_2}, \frac{dI}{dt} = \frac{dH}{d\lambda_3}, \frac{dR}{dt} = \frac{dH}{d\lambda_4}, \frac{dB_c}{dt} = \frac{dH}{d\lambda_5}$$

We write Co-state adjoint equations

$$\frac{d\lambda_1}{dt} = \frac{-dH}{ds}, \frac{d\lambda_2}{dt} = \frac{-dH}{dC}, \frac{d\lambda_3}{dt} = \frac{-dH}{dI}, \frac{d\lambda_4}{dt} = \frac{-dH}{dR}, \frac{d\lambda_5}{dt} = \frac{-dH}{dB_c}$$

$$\frac{d\lambda_1}{dt} = \frac{-dH}{ds} = -\lambda_1\left(-\mu - \frac{B_c\nu(1-u_1)}{K+B_c}\right) - \frac{\lambda_2(1-\rho)(1-u_1)B_c\nu}{K+B_c} - \frac{\lambda_3(1-u_1)\rho\nu B_c}{K+B_c}$$

$$\frac{d\lambda_2}{dt} = \frac{-dH}{dC} = -b_1 - \lambda_2(-\theta - u_3) - \lambda_3(1 - u_3)\,\theta - \lambda_4\phi - \lambda_5(\sigma_1 + \phi + \mu),$$

$$\frac{d\lambda_3}{dt} = \frac{-dH}{dI} = -b_2 - \lambda_3(-u_2 - \beta - \sigma_2) - \lambda_4(u_2 + \beta) - \lambda_5(\sigma_2 + \mu + \alpha),$$

$$\frac{d\lambda_4}{dt} = \frac{-dH}{dR} = -\lambda_1\delta - \lambda_4(-\mu - \delta),$$

$$\frac{d\lambda_5}{dt} = \frac{-dH}{dB_c} = -\frac{\lambda_1 B_c(1-u_1)S}{(K+B_c)^2} - \lambda_2\left(\frac{(1-u_1)\rho\nu S}{K+B_c} - \frac{(1-u_1)\rho\nu B_c S}{(K+B_c)^2}\right) -$$

$$\lambda_3\left(\frac{(1-\rho)(1-u_1)\nu S}{K+B_c} - \frac{(1-\rho)(1-u_1)B_c\nu S}{(K+B_c)^2}\right) + \lambda_5\,\mu_b$$

We find the optimal control set u_1, u_2, u_3 that minimizes J(u_1, u_2, u_3) over U

$\frac{\partial H}{\partial u_i} = 0 \ \ at \ \ \ u_i = u_i^*$, where i =1,2,3

For i =1

$\frac{\partial H}{\partial u_1} = 0 \ at \ u_1^* \quad \rightarrow u_1^* = \frac{S(\lambda_2 \rho \nu B_c - B_c \rho \nu \lambda_3 + B_c \nu \lambda_3 - \lambda_1 B_c \nu)}{(K + B_c) w_1}$

For i =2

$\frac{\partial H}{\partial u_2} = 0$ at $u_2^* \rightarrow u_2^* = \frac{I(\lambda_3 - \lambda_4)}{w_2}$

For i=3

$\frac{\partial H}{\partial u_3} = 0$ at $u_3^* \rightarrow u_3^* = \frac{C(\lambda_3 \theta + \lambda_2)}{w_3}$.

We can write in a compact notation

$$u_1^*=\max\left\{0,\min\left(1,\frac{S(\lambda_2\rho\nu B_c-B_c\rho\nu\lambda_3+B_c\nu\lambda_3-\lambda_1 B_c\nu)}{(K+B_c)w_1}\right)\right\},$$

$$u_2^*=\max\left\{0,\min\left(1,\frac{I(\lambda_3-\lambda_4)}{w_2}\right)\right\},$$

$$u_3^*=\max\left\{0,\min\left(1,\frac{C(\lambda_3\theta+\lambda_2)}{w_3}\right)\right\}.$$

Cost-Effectiveness Analysis

- We identify a strategy which is cost-effective compared to other strategies.
- We use incremental cost-effectiveness ratio(ICER)

$$\text{ICER} = \frac{difference\ of\ costs\ between\ two\ strategies}{difference\ of\ the\ total\ number\ of\ their\ infections\ averted}$$

- The cost of each strategy is obtained by their respective cost function $\frac{1}{2}w_1u_1^2$, $\frac{1}{2}w_2u_2^2$, $\frac{1}{2}w_3u_3^2$.
- We do not consider strategies that implement one intervention only.
- We incorporate more than one intervention

  i.e., strategy A (prevention and screening)

  Strategy B (treatment and screening)

  Strategy C (prevention and treatment)

  Strategy D (prevention,treatment, and screening)

We compare the cost-effectiveness of strategies

Cost-effectiveness of strategies A and B:

$$\text{ICER(A)}=\frac{733.07}{11,977}=0.06$$

$$\text{ICER(B)}=\frac{(733.07-800)}{(11,977-13,805)}=0.037$$

We exclude strategy A

Cost-effectiveness of strategies B and C

$$\text{ICER(B)}=\frac{800}{13,805}=0.058$$

$$\text{ICER(C)}=\frac{(800-573.19)}{(13,805-19,699)}=-0.039$$

We exclude strategy B

Cost-effectiveness of strategies C and D

Strategies	Description	Total infections averted	Total cost (USD)
A	Prevention and screening	11,977	733.07
B	Treatment and screening	13,805	800
C	Prevention and treatment	19,699	573.19
D	Prevention,tr-eatment,and screening	19,987	1104.5

ICER(C)=$\frac{\mathbf{573.19}}{\mathbf{19,699}} = 0.029$

ICER(D)= $\frac{573.19-1104.5}{19,699-19,987} = 1.845$

We exclude Strategy D.

So Strategy C(prevention and treatment)is the best strategy from all compared strategies due to it’s cost-effectiveness and healthy benefit.

Conclusion

- In this study, a deterministic model for the dynamics of typhoid fever disease is proposed.
- Free equilibrium point of the Model is obtained and it's local as well as global stability conditions are obtained.
- The basic reproduction number of the disease reveals the intensity of the spread of the disease.
- Sensitivity analysis of the basic reproductive number is done.
- The optimal control problem is formulated and the conditions for optimal control of the disease are analyzed.
- The results indicate that prevention and the cost put into treatment have a strong impact on the disease control.

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THANK YOU