

# *Mathematical Modeling of Drug Abuse as an Infectious Disease in Secondary Schools Incorporating Guidance and Counseling*

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*Abstract: Drug abuse is a major problem that has affected many young people in our society. In this study, we looked at drug abuse as an infectious disease in secondary schools. We developed a SEIGWR model which is a mathematical model of drug abuse as an infectious disease with six compartments; susceptible, exposed, infected, guided and counseled, rehabilitated and recovered. The model stability and the existence of equilibrium points was determined. From the quantitative analysis of the study, it was found out that the local stability existed when  $R_0 < 1$ . From the numerical analysis of the drug abuse model, we determined that guidance and counseling affects the dynamics of the model. We established that an increase in guidance and counseling leads to a decrease in the number of infections. This suggests that there is a need for all the relevant stakeholders in the secondary schools to increase the rate at which guidance and counseling is offered in the schools. The study suggested that guidance and counseling would serve as a control strategy if given at an early age when the students are still in the primary schools.*

**Keywords: Drug Abuse, Guidance and Counseling, Infectious, Local stability and Model.**

## I. Introduction

Drug abuse according to Alewu [1] is when one uses legal or illegal substances that they should not use. A report by the Centre for Disease Control and prevention (CDC) indicates that people abuse drugs so that they may feel good, ease stress or avoid the reality of life [2]. The abuse of drugs, if not managed early, may have serious ramifications on a persons physical health, mental health and generally the well being of a person.

According to findings by NACADA, Schools are no longer drug free environments [6]. The problem of substance abuse usually starts with smoking cigarettes at the toilets during school breaks. These adolescents would then proceed to use other drugs such as alcohol, cannabis and hard drugs. Youths use substances for various reasons and contributing factors include their developmental stage, peer group pressure, family problems and stress relief [5]. These youths seem not to be considering the long-term effect of these drugs on their lives. The students in the Secondary school level are in their

youthful stage with majority ranging from 14 years to 20 years of age. Students in secondary schools listen more to their peers. On the process they may influence or lure each other into drug abuse and the process becomes infectious. Sutanto et al (2017), found out that the increase and decrease on the number of drug abusers showed a pattern of spread that had the same characteristics with patterns of spread of infectious disease [11].

These reports on drug abuse formed the basis of this study on Mathematical modeling of drug abuse in Secondary schools incorporating guidance and counseling.

## II. Model Description and Formulation

The population model comprises a population size  $N(t)$  which is subdivided into six compartments at any time  $(t)$ . Students who are not abusing drugs but are at a high risk of taking drugs,  $S(t)$ , those exposed to drugs but have received education on drug abuse,  $E(t)$ , students already abusing drugs,  $I(t)$ , students who have received guidance and counseling,  $G(t)$ , those who are in rehabilitation,  $W(t)$  and the recovered individuals  $R(t)$ . The population model is expressed in the following equation:

$$N(t) = S(t) + E(t) + I(t) + G(t) + W(t) + R(t)$$

The following are the definitions of the parameters used in the model:

$\gamma$  - recruitment rate

$q$  - probability rate of students who have received education and guidance on drug abuse

$\mu$  - rate at which the susceptible are exposed to drug abuse education

$\beta_1$ - rate at which the susceptible get infected

$\beta_2$ - rate at which the exposed are infected

$\alpha$ - rate at which the infected undergo guidance and counseling

$\sigma$  -rate at which those who undergo guidance and counseling proceed to rehabilitation centers

$\omega$ -progression rate of the infected to complete recovery

$k$ - progression rate from rehabilitation to recovery

$m$ - progression rate from Guidance and counseling to complete recovery

$\delta$ - direct progression rate of the exposed to complete recovery

$d$ - natural death

The above model can be presented in a diagram as shown in the figure below:

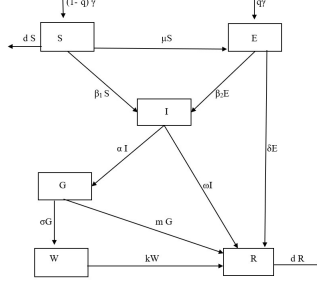


Figure 1: *Model flow*

The model is represented by the following system of non-linear ordinary differential equations :

$$\frac{dS}{dt} = (1 - q)\gamma - (d + \beta_1 + \mu)S \quad (1)$$

$$\frac{dE}{dt} = q\gamma + \mu S - (\beta_2 + \delta)E \quad (2)$$

$$\frac{dI}{dt} = \beta_1 S + \beta_2 E - (\alpha + \omega)I \quad (3)$$

$$\frac{dG}{dt} = \alpha I - (m + \sigma)G \quad (4)$$

$$\frac{dW}{dt} = \sigma G - kW \quad (5)$$

$$\frac{dR}{dt} = kW + mG + \omega I + \delta E - dR \quad (6)$$

### III. Results and Analysis

#### A. Drug Free Equilibrium

The drug-free equilibrium (DFE) is defined as the point at which no drugs are present in the population. At the DFE, we set the values of the infected, those who have gone through guidance and counselling, Rehabilitated individuals and the Recovered to be zero. i.e  $I^* = G^* = W^* = R^* = 0$

The system of equations simplifies to:

$$\frac{dR}{dt} = kW + mG + \omega I + \delta E - dR = 0$$

$$\delta E = 0$$

Therefore,  $E = 0$

$$\text{Since } \frac{dI}{dt} = \beta_1 S + \beta_2 E - (\alpha + \omega)I = 0,$$

Then  $\beta_1 = 0$

From equation (2) we have:

$$\frac{dE}{dt} = q\gamma + \mu S - (\beta_2 + \delta)E = 0$$

$$q\gamma + S\mu = 0$$

Therefore

$$\mu = -\frac{(q\gamma)}{S} \quad (7)$$

From equation (1),

$$\frac{dS}{dt} = (1 - q)\gamma - (d + \beta_1 + \mu)S = 0$$

But  $\beta_1 = 0$

Then,

$$(1 - q)\gamma = (d + \mu)S \quad (8)$$

Substituting (7) in equation (8) and simplifying we have:

$$S = \frac{\gamma}{d}$$

Thus the DFE will be given by

$$(S^*, E^*, I^*, G^*, W^*, R^*) = \left(\frac{\gamma}{d}, 0, 0, 0, 0, 0\right)$$

### B. Local Stability of Drug Free Equilibrium

The DFE is locally asymptotically stable if  $R_0 < 1$  and unstable if  $R_0 > 1$ .

The Jacobian matrix of the model system equations at J(SEIGWR) is given by:

$$J = \begin{bmatrix} -(d + \beta_1 + \mu) & 0 & 0 & 0 & 0 & 0 \\ \mu & -(\beta_2 + \delta) & 0 & 0 & 0 & 0 \\ \beta_1 & \beta_2 & -(\alpha + \omega) & 0 & 0 & 0 \\ 0 & 0 & \alpha & -(m + \sigma) & 0 & 0 \\ 0 & 0 & 0 & \sigma & -k & 0 \\ 0 & \delta & \omega & m & k & -d \end{bmatrix}$$

Finding the determinant of the Jacobian matrix of the drug free equilibrium gives:

$$\begin{vmatrix} -(d + \beta_1 + \mu) - \lambda & 0 & 0 & 0 & 0 & 0 \\ \mu & -(\beta_2 + \delta) - \lambda & 0 & 0 & 0 & 0 \\ \beta_1 & \beta_2 & -(\alpha + \omega) - \lambda & 0 & 0 & 0 \\ 0 & 0 & \alpha & -(m + \sigma) - \lambda & 0 & 0 \\ 0 & 0 & 0 & \sigma & -k - \lambda & 0 \\ 0 & \delta & \omega & m & k & -d - \lambda \end{vmatrix}$$

Where  $\lambda$  is the eigenvalue.

Since all the eigenvalues are negative, the Drug Free Equilibrium is locally asymptotically stable.

### C. Drug Endemic Equilibrium

An endemic equilibrium exists if and only if the value of S given by this condition is less than N, and this is equivalent to  $R_0 > 1$ . [10]

Drug endemic equilibrium, is the point where drug abuse exists within the susceptible. We therefore equate the equations obtained from our model to zero. Making I the subject in equation (3) gives:

$$I = \frac{\beta_1 S + \beta_2 E}{\alpha + \omega} \quad (9)$$

Making E the subject in equation (2) above by equating to zero

$$q\gamma + \mu S - (\beta_2 + \delta)E = 0$$

By simplifying the equation we obtain:

$$E = \frac{q\gamma + \mu S}{\beta_2 + \delta} \quad (10)$$

Making S the subject in (1) above

$$S = \frac{(1-q)\gamma}{(d + \beta_1 + \mu)} \quad (11)$$

Substituting S in equation (10) and simplifying we have:

$$E = \frac{\gamma q(d + \beta_1 + \mu) + \mu\gamma(1-q)}{(d + \beta_1 + \mu)(\beta_2 + \delta)} \quad (12)$$

Substituting S and E in (9) and simplifying we obtain:

$$I = \frac{(\beta_2 + \delta)(\beta_1\gamma)(1-q) + \beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1-q)}{(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \quad (13)$$

Substituting I in (4) gives

$$G = \frac{\alpha}{m + \sigma} \left( \frac{(\beta_2 + \delta)(\beta_1\gamma)(1-q) + \beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1-q)}{(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right)$$

$$G = \frac{\alpha(\beta_2 + \delta)(\beta_1\gamma)(1-q) + \alpha\beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1-q)}{(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \quad (14)$$

Substituting G in (5) above and simplifying

$$W = \frac{\gamma\alpha(\beta_2 + \delta)(\beta_1\gamma)(1-q) + \alpha\beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1-q)}{k(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \quad (15)$$

Making R the subject in (6) above

$$R = \frac{kW + mG + \omega I + \delta E}{d}$$

Substituting W, G, I and E and simplifying thus,

$$R = \left[ \left( \frac{\gamma\alpha k(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma kq(d + \beta_1 + \mu) + \beta_2\mu\gamma k(1 - q)}{kd(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\alpha m(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma m q(d + \beta_1 + \mu) + \beta_2\mu\gamma m(1 - q)}{d(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\omega(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \omega\beta_2\gamma q(d + \beta_1 + \mu) + \omega\beta_2\mu\gamma(1 - q)}{d(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\delta\gamma q(d + \beta_1 + \mu) + \delta\mu\gamma(1 - q)}{d(d + \beta_1 + \mu)(\beta_2 + \delta)} \right) \right]$$

Endemic equilibrium ( $S^*, E^*, I^*, G^*, W^*, R^*$ ) is given by:

$$\left[ \frac{(1 - q)\gamma}{(d + \beta_1 + \mu)}, \frac{\gamma q(d + \beta_1 + \mu) + \mu\gamma(1 - q)}{(d + \beta_1 + \mu)(\beta_2 + \delta)}, \frac{(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1 - q)}{(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)}, \frac{\alpha(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1 - q)}{(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)}, \frac{\gamma\alpha(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma q(d + \beta_1 + \mu) + \beta_2\mu\gamma(1 - q)}{k(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)}, \left( \frac{\gamma\alpha k(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma kq(d + \beta_1 + \mu) + \beta_2\mu\gamma k(1 - q)}{kd(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\alpha m(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \alpha\beta_2\gamma m q(d + \beta_1 + \mu) + \beta_2\mu\gamma m(1 - q)}{d(m + \sigma)(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\omega(\beta_2 + \delta)(\beta_1\gamma)(1 - q) + \omega\beta_2\gamma q(d + \beta_1 + \mu) + \omega\beta_2\mu\gamma(1 - q)}{d(d + \beta_1 + \mu)(\beta_2 + \delta)(\alpha + \omega)} \right) + \left( \frac{\delta\gamma q(d + \beta_1 + \mu) + \delta\mu\gamma(1 - q)}{d(d + \beta_1 + \mu)(\beta_2 + \delta)} \right) \right]$$

#### D. Stability of drug endemic equilibrium

If  $R_0 > 1$ , then the drug endemic equilibrium is globally asymptotically

stable [3]. We shall prove this using the lyapunov function as shown below:

$$\begin{aligned} L(S^*, E^*, I^*, G^*, W^*, R^*) = & (S - S^* - S^* \ln \left( \frac{S^*}{S} \right)) + (E - E^* - E^* \ln \left( \frac{E^*}{E} \right)) + \\ & (I - I^* - I^* \ln \left( \frac{I^*}{I} \right)) + (G - G^* - E^* \ln \left( \frac{G^*}{G} \right)) + \\ & (W - W^* - W^* \ln \left( \frac{W^*}{W} \right)) + (R - R^* - R^* \ln \left( \frac{R^*}{R} \right)) \end{aligned}$$

By computing the derivative of L:

$$\begin{aligned} \frac{dL}{dt} = & \left( \frac{S - S^*}{S} \right) \frac{dS}{dt} + \left( \frac{E - E^*}{E} \right) \frac{dE}{dt} + \left( \frac{I - I^*}{I} \right) \frac{dI}{dt} + \\ & \left( \frac{G - G^*}{G} \right) \frac{dG}{dt} + \left( \frac{W - W^*}{W} \right) \frac{dW}{dt} + \left( \frac{R - R^*}{R} \right) \frac{dR}{dt} \quad (16) \end{aligned}$$

Substituting the system model ODE's in (16) above:

$$\begin{aligned} \frac{dL}{dt} = & \left[ \left( \frac{S - S^*}{S} \right) [(1-q)\gamma - (d + \beta_1 + \mu)S] + \left( \frac{E - E^*}{E} \right) [q\gamma + \mu S - (\beta_2 + \delta)E] + \right. \\ & \left. \left( \frac{I - I^*}{I} \right) [\beta_1 S + \beta_2 E - (\alpha + \omega)I] + \left( \frac{G - G^*}{G} \right) [\alpha I - (m + \sigma)G] + \right. \\ & \left. \left( \frac{W - W^*}{W} \right) [\sigma G - kW] + \left( \frac{R - R^*}{R} \right) [kW + mG + \omega I + \delta E - dR] \right] \quad (17) \end{aligned}$$

Expanding and simplifying equation (17):

$$\begin{aligned} \frac{dL}{dt} = & \gamma - dS - (1-q)\frac{\gamma S^*}{S} + (d + \beta_1 + \mu)S^* + (\beta_2 + \delta)E^* - \\ & (q\gamma + \mu S)\frac{E^*}{E} - \frac{\beta_1 S I^*}{I} - \frac{\beta_2 E I^*}{I} + \alpha I^* + \omega I^* - \frac{\alpha I G^*}{G} + mG^* + \sigma G^* - \\ & \frac{\sigma G W^*}{W} + kW^* - dR - \frac{kW R^*}{R} - \frac{mG R^*}{R} - \frac{\delta E R^*}{R} + dR^* \end{aligned}$$

We let P be the positive terms and Q be the negative terms thus

$$\frac{dL}{dt} = P - Q$$

$$P = \gamma + (d + \beta_1 + \mu)S^* + (\beta_2 + \delta)E^* + \alpha I^* + \omega I^* + mG^* + \sigma G^* + kW^* + dR^*$$

$$\begin{aligned} Q = & dS + (r - q)\frac{\gamma S^*}{S} + (q\gamma + \mu S)\frac{E^*}{E} + \frac{\beta_1 S I^*}{I} + \frac{\beta_2 E I^*}{I} + \\ & \frac{\alpha I G^*}{G} + \frac{\sigma G W^*}{W} + dR + \frac{kW R^*}{R} + \frac{mG R^*}{R} + \frac{\delta E R^*}{R} \end{aligned}$$

If  $P < Q$ , then  $\frac{dL}{dt} \leq 0$ ,  $\frac{dL}{dt} = 0$ , if and only if  $S = S^*, E = E^*, I = I^*, G = G^*, W = W^*$  and  $R = R^*$ .

The largest invariant set in  $((S, E, I, G, W, R) \in \psi : \frac{dL}{dt} = 0)$  is  $E^*$ , where  $E^*$  is the endemic point.

Hence, the proof that the endemic equilibrium is asymptotically stable[3].

#### *E. Basic Reproduction Number*

We define the basic reproductive number  $R_0$  as the number of secondary infections that one infective individual would create over the duration of the infectious period provided that everyone else is susceptible [8]. The Basic Reproduction Rate( $R_0$ ) according to [9], depends on three parameters:

1. The contact rate
2. The duration of the infectious period and
3. The probability that a contact between an infected and a susceptible individual leads to an infection.

The  $R_0$  in this section, is derived using the next-generation matrix (NGM) approach. We are considering the compartments with the infected individuals (the I and G compartments)

$$\begin{aligned}\frac{dI}{dt} &= \beta_1 S + \beta_2 E - (\alpha + \omega)I \\ \frac{dG}{dt} &= \alpha I - (m + \sigma)G\end{aligned}$$

We let  $x = (SEIGWR)^T$ ,  $F(x)$  be the number of new infections coming into the system and  $V(x)$  to be the number of new infections coming out of the system, then the model can be written as

$$\frac{dx}{dt} = F(x) - V(x)$$

The above equations then in matrix form can be written thus;

$$F(x) = \begin{bmatrix} \beta_1 S + \beta_2 E \\ \alpha I \end{bmatrix} \text{ and } V(x) = \begin{bmatrix} (\alpha + \omega)I \\ (m + \sigma)G \end{bmatrix}$$

Differentiating the matrices above in respect to I and G respectively gives

$$F = \begin{bmatrix} 0 & 0 \\ \alpha & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (\alpha + \omega) & 0 \\ 0 & (m + \sigma) \end{bmatrix}$$

The matrix  $FV^{-1}$  gives the expected number of secondary infections produced by an infected individual.



Thus,

$$\begin{aligned}
 V^{-1} &= \frac{1}{(\alpha + \omega)(m + \sigma)} \begin{bmatrix} (m + \sigma) & 0 \\ 0 & (\alpha + \omega) \end{bmatrix} \\
 FV^{-1} &= \begin{bmatrix} 0 & 0 \\ \alpha & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\alpha + \omega} & 0 \\ 0 & \frac{1}{m + \sigma} \end{bmatrix} \\
 FV^{-1} &= \begin{bmatrix} 0 & 0 \\ \frac{\alpha}{\alpha + \omega} & 0 \end{bmatrix}
 \end{aligned}$$

Thus  $FV^{-1}$  is the NGM and  $R_0 = \rho(FV^{-1})$  where,  $\rho$  denotes the spectral radius. Therefore,  $R_0 = \frac{\alpha}{\alpha + \omega}$

#### IV. Numerical Solutions of the Model

In this section, we performed qualitative analysis of the system of differential equations of the model using Runge-Kutta fourth order scheme through the Matlab software. The duration of the spread of the abuse of drugs through interaction between students at risk of abusing drugs and the drug abusers was taken to be four years. The period was assumed to be the duration at which peer influence can have impact on the susceptible population during the four years study course in high school. We start by estimating the parameters to be used in calculations based on the existing literature.

Table 1: **Parameter Estimations**

Symbol	Description	Value	Source
$\gamma$	Recruitment rate	0.5	[4]
$q$	Probability rate of the exposed	0.03	estimate
$\mu$	Rate at which the susceptible remain exposed	0.02	estimate
$\beta_1$	Rate at which the susceptible get infected	0.9	estimate
$\beta_2$	Rate at which the exposed are infected	0.0045	estimate
$\alpha$	Rate for Guidance and counseling(G & C)	0.098	estimate
$\sigma$	Rate to rehabilitation centers	0.0068	estimate
$\omega$	Rate of the infected to complete recovery	0.00024	estimate
$k$	Rate from rehabilitation to recovery	0.23	estimate
$m$	Rate from G & C to complete recovery	0.03	[4]
$\delta$	Rate of the exposed to complete recovery	0.24	estimate
$d$	Natural death	0.0056	[4]

##### A. Drug Abuse and the total Population with time

Figure 2 shows dynamics of drug abuse in the total population comprising of Susceptible, Exposed, Infected, Guided and counseled, Rehabilitated and Recovered. The number of susceptible students decreases with time as well

as the exposed in the population. The infected in the population increases exponentially in the beginning but after one year, the number starts decreasing due to the guidance and counseling given in the schools. The number of those who have received guidance and counseling increases exponentially with time hence by the end of the four years of secondary level, the number gets closer to the total population indicating that almost all the students get sessions of guidance and counseling. Those who go to rehabilitation centres reduce with time due to the guidance and counseling sessions received. The recovered drug abusers increase with time hence by the end of the high school level, there are more recoveries than the infected. The total population remains constant because this is determined by the number of students being admitted each year in the secondary schools. The graph of the drug abuse dynamics is shown in figure 2 below:

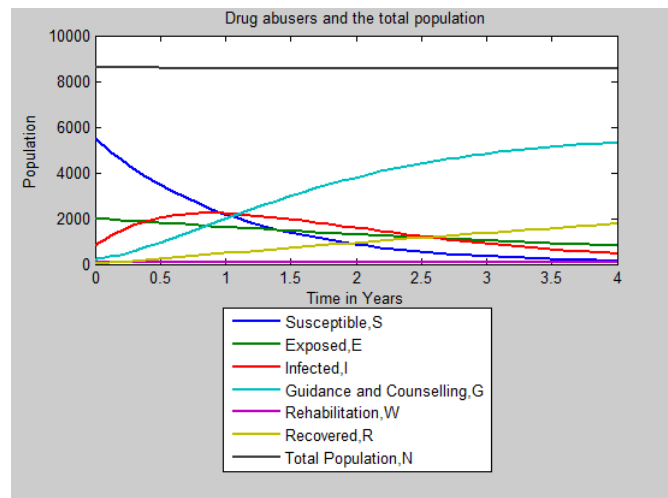


Figure 2: *Drug abuse dynamics graph*

*B. Susceptible Drug abusers with time*

Figure 3 below shows the susceptible drug abusers with time. The number of susceptible drug abusers reduces with time as compared to the total population which from figure 2 remains constant. This may be due to the impact of guidance and counseling and any other sensitization practices that students are given in the secondary schools. Towards the end of the four years, the graph seems to be constant indicating that there are still a number of susceptible drug abusers as they finish their studies in secondary school.

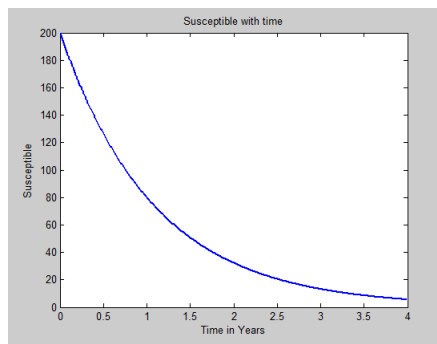


Figure 3: *Susceptible drug abusers with time*

*C. Infected drug abusers who undergo Guidance and Counseling*

From our model, infected individuals may recover naturally or are taken through guidance and counseling. From figure 4 below, the number of those who undergo the process of guidance and counseling is directly proportional to the time taken in the secondary schools. This implies that the more the learners stay in the school the deeper the sensitization on drug abuse through guidance and counseling.

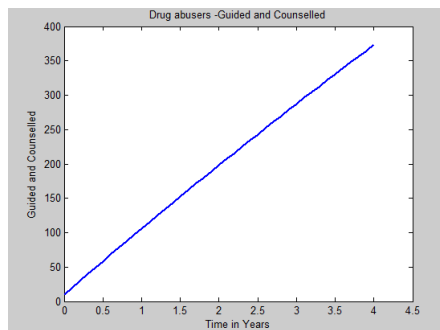


Figure 4: *Infected- Guided and Counseled*

## V. Conclusions

In our research, we have developed a Mathematical model of drug abuse as an infectious disease that incorporates guidance and counseling in Secondary schools. Through the developed model, guidance and counseling seems to affect the number of students who are susceptible, exposed, infected, rehabilitated and those who recover. In figure 2, we found out that the more students become susceptible to the abuse of drugs, the more the abuse but as the susceptibility rate decreases, the abuse of drugs among students decreases. Increase in guidance and counseling causes a decrease in infection and rehabilitation rates. This is an indication that guidance and counseling may be used as a control strategy for the abuse of drugs in secondary schools.

From the analytical solution, the basic reproductive number ( $R_0$ ) is less than or equal to one, the Disease Free Equilibrium and the endemic equilibrium are asymptotically stable. This implies that drug abuse will eventually die out of the system. This is similar to what we found out from the numerical solution which showed that as guidance and counseling increases with time, infection rate decreases thus the stability of the system.

## VI. Data Availability

The data used in the analysis of the drug abuse model was obtained from previously published articles which have been cited accordingly. Some of the parameter values are taken from published articles and others have been assumed. These articles are cited at relevant places within the text as references.

## VII. Conflict of Interest

The authors of this publication declare that there is no conflict of interest regarding the publication of this manuscript

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