IOSR Journal of Mathematics (IOSR-JM)
e-ISSN: 2278-5728, p-ISSN: 2319-765X. Volume 18, Issue 4 Ser. III (Jul. – Aug. 2022), PP 01-09
www.iosrjournals.org

A Coupled Mathematical Model for Cervical Cancer Incorporating Diffusion and Diagnosis

JacintaM.Mutwiwa[1*],Joyce K. Nthiiri[2], Boniface O. Kwach[3],Barack O. Abonyo[4]

[1*,3]*Department of Mathematics Kibabii University*
[2]*Departmentof Mathematics MasindeMuliro University of Science and Technology*
[4]*SchoolofMedicineUzimaCollege*

Abstract
In this paper a coupled cervical cancer model incorporating diffusion and diagnosis was formulated. Two transmission subsystems were coupled in which the transmission rate at the population was expressed as a function of the viral load, while the within-host infection rates were modelled as functions of the number of infectives. The basic reproduction number ,$R_{0C}$of the coupled model was found to be a maximum of the two reproduction numbers $R_{0B}$and R_{0w}corresponding to the between host and within host subsystems respectively. Stability analysis revealed that the disease free equilibrium is globally asymptotically stable whenever$R_{0B} < 1$ and R_{0w}<1. Theoretically this means that the disease is wiped out. Using the center manifold Theorem, the endemic equilibrium was found to be locally asymptotically stable if $R_{0C} > 1$and unstable otherwise. This reveals that the high transmissibility of the high viral load at the within host level which causes cervical cancer will lead to disease persistence in the population. Numerical simulation shows that an increase in viral load at the within host level leads to proportional increase in the number of infectives at the population level. In addition numerical simulations revealed that early diagnosis has remarkable effect on cervical cancer management and HPV transmission. Early diagnosis leads to significant reduction of the number infected cells and the viral load within a short period of time and space leading to much reduction of the number of infected and cervical cancer individuals at the population level.

Keywords: *Coupled model, Diagnosis, Human papilloma Virus, Reproduction Number, Stability Analysis.*

Date of Submission: 15-07-2022 Date of Acceptance: 31-07-2022

I. Introduction

Human papilloma Virus (HPV) is transmitted sexually through skin-to-skin genital contact. Cervical cancer is mainly due to the infections of HPV though the risk due to the various HPV types has been given little attention. Over one hundred dissimilar strains of HPV being identified and classified with HPV types 16, 18, 31 and 45 been classified as ''high-risk''. Approximately 85 percentage cancer of the cervix are reported to be as a result of these four strains alone [3]. There is no treatment for HPV but in most cases it disappears naturally. However, with persistent infections the high risk strains may become chronic and shed HPV virions.

Early stage diagnosis of cervical cancer makes it curable. Coupling brings in a new dimension which incorporates what happens inside the cell and what happens outside the cell. That is, the interaction between cell to cell and human to human. Coupled dynamics factor the spread of cervical cancer dynamics considering the population level to be a function of within-host immune viral responses at the individual level. The transmission potential between cervical cancer individuals to susceptibles can be affected by the viral load of infected hosts [1]. The transmission rate of between hosts is proportional to within-host viral load and the equilibrium of the within-host model is used to calculate the transmission rate.

II. The model

A coupled cervical cancer model linking both the within- host and between- host transmission subsystems is constructed. The coupled model consist of two processes, one for the between-host processes at the population level and the other for the viral dynamics within an individual host.

III. Within-Host model

We formulate a model composed of three variables, namely, the uninfected cells $T(t)$, cells infected with higher risk Human Papillomavirus types (viruses which leads to cervical cancer infection) $T^*(t)$,and free virus particles $V(t)$. The within - host model can be represented mathematically as follows

$$\frac{dT(t,x)}{dt} = \gamma T\left(1 - \frac{T}{T_{max}}\right) - \beta TV - \omega TT^* - \mu_w - \frac{D_2 d^2T}{dx^2}$$

$$\frac{dT^*(t,x)}{dt} = \beta TV + \omega TT^* - \sigma T^* - \frac{D_3 d^2T^*}{dx^2}$$

$$\frac{dV(t,x)}{dt} = \delta\sigma T^* - \epsilon V - \frac{D_1 d^2V}{dx^2} \quad (1)$$

ThebasicreproductionnumberR_{0w}isgivenas

$$R_{0w} = T_{max}\left(1 - \frac{\mu_w}{\gamma}\right)\frac{\omega}{\sigma} + T_{max}\left(1 - \frac{\mu_w}{\gamma}\right)\frac{\beta\delta}{\epsilon} \quad (2)$$

IV. Between-Host model

We formulate a model in which the total human population at any time t denoted by N is subdivided into classes, $S(t)$the class of individuals susceptible to cervical cancer infection. The class$I_h(t)$consists of individuals who are infected with higher risk Human papilloma virus. Individuals progress to cervical cancer $C(t)$class due to persistence of the HPV infection. The dynamics described can be represented mathematically as:

$$\dot{S}(t) = \Lambda + \alpha I_h(t) - \left(\frac{\kappa\tau\pi I_h}{N} + \mu\right)S(t)$$

$$\dot{I_h}(t) = \frac{\kappa\tau\pi I_h}{N}S(t) - (\alpha + \rho + \mu)I_h(t)$$

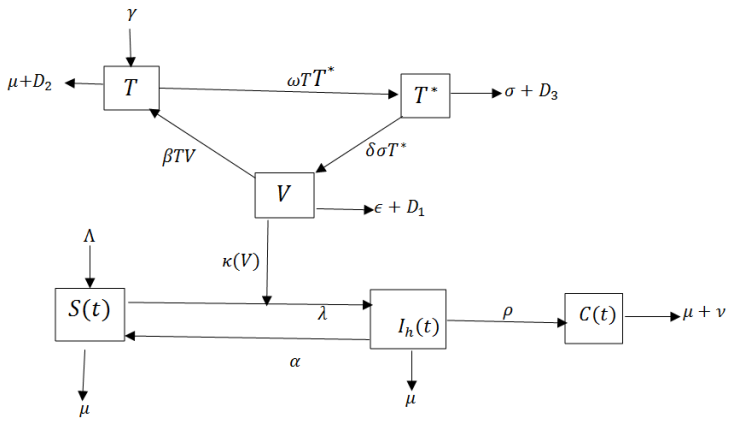
$$\dot{C}(t) = \rho I_h(t) - (\nu + \mu)C(t) \quad (3)$$

The basicre production numberR_{0B}isgivenas

$$R_{0B} = \frac{\pi\kappa\tau}{\mu+\alpha+\rho} \quad (4)$$

V. Coupling the subsystems

Coupled dynamics factor the spread of cervical cancer dynamics considering the population level to be a function of within-host immune viral responses at the individual level. In order to link the two processes, we examine the relationship between the two subsystems (3) and (1),by employing the method used by [6]. From system (3), it can be established that the host viral load has significant effect on Human Papilloma Virus transmission rate in the population. From subsystems (3) and (1)for the between- and within-host dynamics respectively, we obtain the coupled model linking between- and within-host dynamics of cervical cancer.



The dynamics described can be represented mathematically as:

$$\frac{dT(t,x)}{dt} = \gamma T\left(1-\frac{T}{T_{max}}\right) - \beta T I_h V - \omega T I_h T^* - \mu_w T - \frac{D_2 d^2 T}{dx^2}$$

$$\frac{dT^*(t,x)}{dt} = \beta T I_h V + \omega T I_h T^* - \sigma T^* - \frac{D_3 d^2 T^*}{dx^2}$$

$$\frac{dV(t,x)}{dt} = \delta\sigma T^* - \epsilon V - \frac{D_1 d^2 V}{dx^2}$$

$$\frac{dS(t)}{dt} = \Lambda + \alpha I_h(t) - \left(\frac{\kappa\tau\pi V I_h}{N} + \mu\right) S(t)$$

$$\frac{dI_h(\dot{t})}{dt} I_h(t) = \frac{\kappa\tau\pi V I_h}{N} S(t) - (\alpha+\rho+\mu) I_h(t)$$

$$\frac{dC(t)}{dt} = \rho I_h(t) - (\nu+\mu) C(t) \qquad (5)$$

Since the rate of transmission of HPV in the human population is considered as a function of the number of free viruses, then the viral load (V)at the between-host compartments can be considered as a parameter value and can therefore be denoted as θ_1. Similarly, the infectives(I_h)at the within host can also be taken as a parameter and denoted as θ_2. Hence model (5)becomes

$$\frac{dT(t,x)}{dt} = \gamma T\left(1-\frac{T}{T_{max}}\right) - \beta T \theta_2 V - \omega T \theta_2 T^* - \mu_w T - \frac{D_2 d^2 T}{dx^2}$$

$$\frac{dT^*(t,x)}{dt} = \beta T \theta_2 V + \omega T \theta_2 T^* - \sigma T^* - \frac{D_3 d^2 T^*}{dx^2}$$

$$\frac{dV(t,x)}{dt} = \delta\sigma T^* - \epsilon V - \frac{D_1 d^2 T}{dx^2}$$

$$\frac{dS(t)}{dt} = \Lambda + \alpha I_h(t) - \left(\frac{\kappa\tau\pi\theta_1 I_h}{N} + \mu\right) S(t)$$

$$\frac{dI_h(\dot{t})}{dt} I_h(t) = \frac{\kappa\tau\pi\theta_1 I_h}{N} S(t) - (\alpha+\rho+\mu) I_h(t)$$

$$\frac{dC(t)}{dt} = \rho I_h(t) - (\nu+\mu) C(t) \qquad (6)$$

VI. Basic Reproductive Ratio

The local stability of the model (6)is governed by the basic reproduction Number $R_{0C} = Max(R_{0B}, R_{0w})$, where $R_{0w}$and R_{0B} are the basic reproduction numbers for within-host and between-host subsystems respectively. Using the next generation matrix approach Diekmann [4], at diffusion free state $(D = 0)$ the basic reproduction number is given by

$$R_{0C} = Max\left\{\frac{\pi\kappa\tau\,\theta_1}{\mu+\alpha+\rho}, T_{max}\left(1-\frac{\mu_w}{\gamma}\right)\frac{\omega\,\theta_2}{\sigma} + T_{max}\left(1-\frac{\mu_w}{\gamma}\right)\frac{\beta\,\theta_2\delta}{\epsilon}\right\} \qquad (7)$$

Fromequations(2)and(4),equation(7)canbeexpressedas

$$R_{0C} = Max(R_{0B}, R_{0w}) \qquad (8)$$

$R_{0w}$is a measure of the average number of secondary viral and cellular infections within host caused by a single virion and infectious cells introducedinto an entirely susceptible cell population. $R_{0B}$is a measure of the average number of secondary Human Papilloma Virus infections in human population caused by a single infectious individual introduced into an entirely susceptible population.

VII. Local stability of Disease-free Equilibrium point

The system (6) always has a disease free equilibrium (DFE),), $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, T_{max}\left(1-\frac{\mu_w}{\gamma}\right), 0, 0\right)$.The local stability of the DFE obtained by analysing the eigenvalues of the Jacobian matrix of system (6) at the DFE with $D1 = D2 = D3 = 0$.

The Jacobian matrix of system (6) is as follows;

$$J_c = \begin{pmatrix} \frac{-\kappa\tau\pi\theta_1 I_h}{N} - \mu & \frac{-\kappa\tau\pi\theta_1 S}{N} & 0 & 0 & 0 & 0 \\ \frac{\kappa\tau\pi\theta_1 I_h}{N} & D & 0 & 0 & 0 & 0 \\ 0 & \rho & -(\nu+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma - \frac{2\gamma T}{T_{max}} - A - \mu_w & -B & -C \\ 0 & 0 & 0 & A & B-\sigma & C \\ 0 & 0 & 0 & 0 & \delta\sigma & -\epsilon \end{pmatrix} \tag{9}$$

Where

$$A = \beta\theta_2 V + \omega\theta_2 T^*$$
$$B = \omega\theta_2 T$$
$$C = \beta\theta_2 T$$
$$D = \frac{\kappa\tau\pi\theta_1 S}{N} - (\alpha+\rho+\mu)$$

At disease free equilibrium (DFE), $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, T_{max}\left(1-\frac{\mu_w}{\gamma}\right), 0, 0\right)$ the Jacobian matrix J_c will be;

$$J_c = \begin{pmatrix} -\mu & -\kappa\tau\pi\theta_1 & 0 & 0 & 0 & 0 \\ 0 & (\alpha+\rho+\mu)(R_{0B}-1) & 0 & 0 & 0 & 0 \\ 0 & \rho & -(\nu+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma - \frac{2\gamma T}{T_{max}} - \mu_w & -E & -F \\ 0 & 0 & 0 & 0 & E-\sigma & F \\ 0 & 0 & 0 & 0 & \delta\sigma & -\epsilon \end{pmatrix} \tag{10}$$

Where $E = \omega\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right)$ and

$$F = \beta\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right)$$

Since at DFE, $T_0 = T_{max}$, then $\gamma - \frac{2\gamma T}{T_{max}} - \mu_w$ reduces to $-\gamma - \mu_w$. The eigenvalues of the Jacobian matrix $J_c(10)$ are

$\lambda_1 = -\mu$ (11)
$\lambda_2 = (\alpha+\rho+\mu)(R_{0B}-1)$ (12)
$\lambda_3 = -(\nu+\mu)$ (13)
$\lambda_4 = -\gamma - \mu_w$ (14)

We analyze the reduced matrix

$$J_c = \begin{pmatrix} \omega\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right) - \sigma & \beta\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right) \\ \sigma\delta & -\epsilon \end{pmatrix} \tag{15}$$

Using Routh-Hurwitz criterion [7], the trace of Equation (15) is

$tr(J_c) = \omega\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right) - \sigma - \epsilon < 0$ (16)

Provided that $\omega\theta_2 T_{max}\left(1-\frac{\mu_w}{\gamma}\right) < 0$

And $\det J_c = -\frac{\beta\theta_2\delta}{\epsilon} T_{max}\left(1-\frac{\mu_w}{\gamma}\right) - \frac{\omega\theta_2}{\delta} T_{max}\left(1-\frac{\mu_w}{\gamma}\right) + 1$ (17)

Which simplifies to

$$\det J_c = (1 - \theta_2 R_{0w}) > 0 \qquad (18)$$

Equation(18)holds provided that$R_{0w} < 1$.Thus the Disease Free EquilibriumDFEislocallyasymptoticallystablewhenever$R_{0B} < 1$and$R_{0w} < 1$. This means that introduction of an infected individual into the populationwouldnotleadtonewtransmissionandthediseaseiswipedout.

VIII. Local stability of Endemic Equilibrium

Attheendemicequilibrium,persistenceofinfectionoccursatthepopulation.The endemic equilibrium of system (6) is obtained by means of the CentreManifoldTheorem[2]

Theorem8.1.*Considerthefollowinggeneralsystemofordinarydifferentialequationswithaparameter*a^*

Proof

$$\frac{dx}{dt} = f(x, a^*), f: \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \quad and\ f \epsilon\ C^2\ (\mathbb{R} \to \mathbb{R}^n)$$

Thefollowingassumptionshold

(i) Zeroisanequilibriumpointforsystem(6)forallvaluesoftheparameter a^*,thatis$f(0, a^*) \equiv 0, \forall\ a^*$.

(ii) Zeroisasimpleeigenvectorof$B$andallothereigenvaluesof$B$havenegativerealparts.

(iii) Matrix$B$hasarighteigenvector$w$andalefteigenvector$v$correspondingtothezeroeigenvalue .

(iv) $B = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_i}\ (0,0)\right)$ is the linearized matrix of the system (6) around the equilibrium 0 with a^* evaluated at zero

Let f_k be the k^{th} component of f and

$$s^* = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$r^* = \sum_{k,i=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial a^*}(0,0),$$

Weusethesignsofs^*andr^*todeterminethelocaldynamicsofthesystem aroundtheequilibriumpoint0

(i) In the case where $s^* > 0, r^* > 0$ when $\varphi < 0$, with $|\varphi| \ll 1, (0,0)$ islocally asymptotically stable and there exist a positive unstable equilibrium;when$0 < a^* \ll 1, (0,0)$isunstableandthereexistsanegativeandlocallyasymptoticallystableequilibrium.

(ii) In the case where$s^* < 0, r^* < 0$, when$a^* < 0$with$|a^*| \ll 1, (0,0)$ isunstableandthereexistapositiveunstableequilibrium,when$0 < a^* \ll 1, (0,0)$islocallyasymptoticallystable.

(iii) In the case where $s^* > 0, r^* < 0$, when $a^* < 0$ with $|a^*| \ll 1, (0,0)$is unstable and there exists a negative and locally asymptotically stableequilibrium, when $0 < a^* \ll 1, (0,0)$is stable and there exists a positiveunstableequilibrium.

(iv) Inthecasewhere$s^* > 0, r^* < 0$,when$a^* < 0$changesfromnegative to positive, $(0,0)$changes its stability from stable to unstable.Correspondingly, a negative unstable equilibrium becomes positive andlocallyasymptoticallystable.

Thefollowingsimplificationandchangeofvariablesaremadeonthesystem(6). Let $S = x_1, I_h = x_2, C = x_3, T = x_4, T^* = x_5$and $V = x_6$.so that$N_B = x_1 + x_2 + x_3$and$N_W = x_4 + x_5 + x_6$.Then the system(6)can bewrittenas

$$\frac{dx}{dt} = F(X)$$

Where $X = (x_1, x_2, x_3, x_4, x_5, x_6)$ and $F = (f_1, f_2, f_3, f_4, f_5, f_6)$

Thus

$$\frac{dx_4}{dt} = f_4 = \gamma x_4\left(1 - \frac{x_4}{T_{max}}\right) - \beta x_4\theta_2 x_6 - \omega x_4\theta_2 x_5 - \mu_w x_4 - \frac{D_2 d^2 x_4}{dx^2}$$

$$\frac{dx_5}{dt} = f_5 = \beta x_4\theta_2 x_6 + \omega x_4\theta_2 x_5 - \sigma x_5 - \frac{D_3 d^2 x_5}{dx^2}$$

$$\frac{dx_6}{dt} = f_6 = \delta\sigma x_5 - \epsilon x_6 - \frac{D_1 d^2 x_6}{dx^2}$$

$$\frac{dx_1}{dt} = f_1 = \Lambda + \alpha x_2 - \left(\frac{\kappa\tau\pi\theta_1 x_2}{N} + \mu\right)x_1$$

$$\frac{dx_2}{dt} = f_2 = \frac{\kappa\tau\pi\theta_1 x_2}{N}x_1 - (\alpha + \rho + \mu)x_2$$

$$\frac{dx_3}{dt} = f_3 = \rho x_2 - (\nu + \mu)x_3 \qquad (19)$$

TheJacobianmatrixofsystem(6)atdiseasefreeequilibrium (DFE) $E_0 = \left(\frac{\Lambda}{\mu}, 0,0, T_{max}\left(1 - \frac{\mu_w}{\gamma}\right), 0,0\right)$ and with $D_1 = D_2 = D_3 = 0$ is given by;

$$J_c = \begin{pmatrix} -\mu & -\kappa\tau\pi\theta_1 & 0 & 0 & 0 & 0 \\ 0 & (\alpha+\rho+\mu)(R_{0B}-1) & 0 & 0 & 0 & 0 \\ 0 & \rho & -(\nu+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & -\gamma-\mu_w & -G & -H \\ 0 & 0 & 0 & 0 & G-\sigma & H \\ 0 & 0 & 0 & 0 & \delta\sigma & -\epsilon \end{pmatrix} \qquad (20)$$

Where $G = \omega\theta_2 T_{max}\left(1 - \frac{\mu_w}{\gamma}\right)$ and $H = \beta\theta_2 T_{max}\left(1 - \frac{\mu_w}{\gamma}\right)$.The Jacobian matrix (20) has a right eigenvector given by

$W = (w_1, w_2, w_3, w_4, w_5, w_6)^T$ where $w_{1=0},\ w_2 = 0,\ w_{3=0}, w_4 = \frac{w_5\left(G - H\frac{\delta\sigma}{\epsilon}\right)}{(\gamma+\mu_w)}, w_5 = w_5 > 0, w_6 = \frac{w_5\delta\sigma}{\epsilon}$

Thecomponentsofthelefteigenvectoroftheabovejacobianmatrix(20)denotedby

$V = (v_1, v_2, v_3, v_4, v_5, v_6)^T$ given by $v_1 = 0, v_2 = 0, v_3 = 0, v_4 = 0, v_5 = v_5 > 0$ and $v_6 = \frac{Hv_5}{\epsilon}$

Let$a$and$b$bethecoefficientsdefinedintheorem(8.1).Thuswecancalculate$s^*$for the transformed system(20), the associated nonzero partial differentialsof$f$evaluatedattheDFE,E_0aregivenby;

$$\sum_{k,i,j}^{6} v_2 w_1 w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j}(0,0) = 2v_5\omega_5^2(G - H)\frac{\delta\sigma}{\epsilon}\left\{\omega\theta_2 + \frac{\delta\theta_2\beta\sigma}{\epsilon}\right\} > 0$$

Considerthecasewhen $R_{0C} = 1$ and assuming $R_{0B} < R_{0w}$ we choose $\theta_2 = \varphi$asabifurcationparameter.Solvingfor θ_2 from $R_{0C} = R_{0w} = 1$ gives

$$\theta_2 = \varphi = \frac{1}{T_{max}\left(1 - \frac{\mu_w}{\gamma}\right)\left(\frac{\delta\beta}{\epsilon} + \frac{\omega}{\sigma}\right)} \qquad (21)$$

And r^* is given by

$$r^* = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \varphi}(0,0)$$

$$= 2v_5 w_5 w\, T_{max} \left(1 - \frac{\mu_w}{\gamma}\right) > 0 \qquad (22)$$

Since $s^* > 0$ and $r^* > 0$,thentheorem(8.1)holdsandthussystem(6)has auniqueendemicequilibriumwhichislocallyasymptoticallystablewhenever $R_{0C} > 1$andunstablewhen $R_{0C} < 1$.

IX. Numerical simulation

Numerical simulations were carried out to graphically illustrate the coupled of cervical cancer.

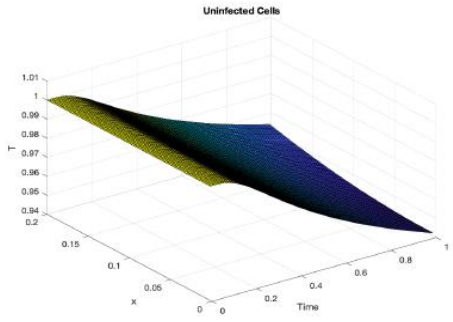


Figure 2: *Graph of the coupled uninfected cells at late diagnosis*

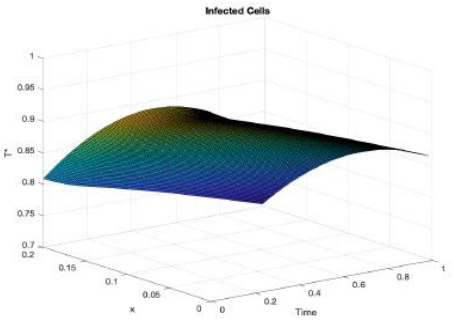


Figure 3: *Graph of the coupled infected cells at late diagnosis.*

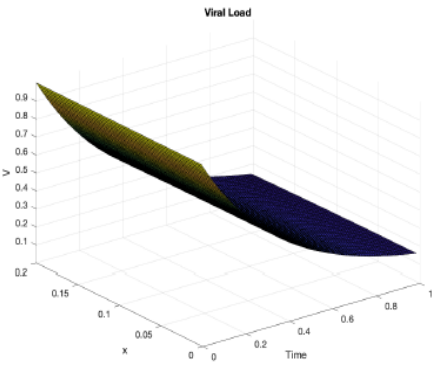


Figure 4: *Graph of the coupled viral load at late diagnosis.*

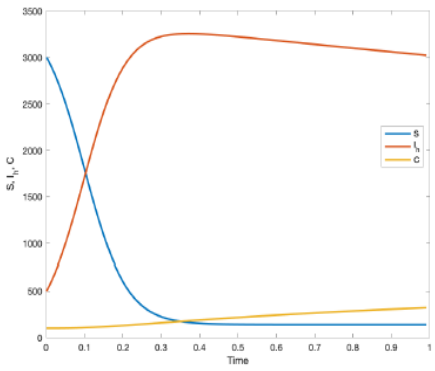


Figure 5: *Graph of the coupled model at the population level.*

The viral load decreases exponentially both in space and time, $figure$ (4). This is attributed to immune response, the natural death of virions and/or exhaustion of uninfected cells or the slow process of viral replication as a result of latency or treatment after diagnosis is done. The uninfected cells decreases, $figure(2)$.On the other hand, the infected cells increase considerably and then decrease with the passage of time and with the increase in distance from the reference cell $figure$ (3). This behavior is brought about by the coupling due to $I_h(t)$shown by $figure(5)$, which increases sharply before plateaus and then decreases slowly. The decrease in uninfected cells is an indication that more cells are recruited into the infected compartment, brought about by theincrease in $I_h(t)$. This explains why the infected cells are increasing.

It can also be deduced that the decline in the viral load at the within- host may not necessarily lead to a decline in the number of infectives at the population level. This is attributed to the fact that infectivity at the

population is highly dependent on the contact rate between infected and susceptible individuals. Even with low viral load transmission at the population level can persist as long as the contact rate is kept high.

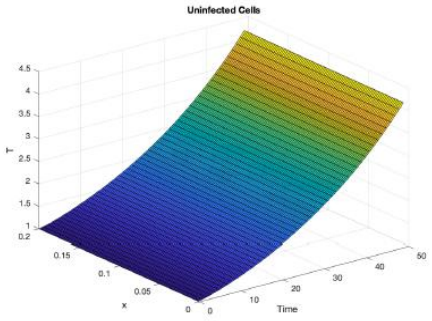


Figure 6: *Graph of the coupled uninfected cells at early diagnosis*

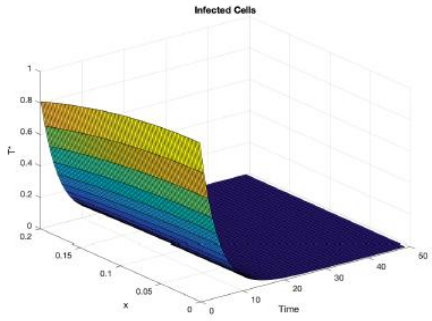


Figure 7: *Graph of the coupled infected cells at early diagnosis.*

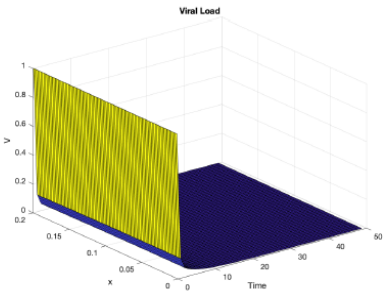


Figure 8: *Graph of the coupled viral load at early diagnosis.*

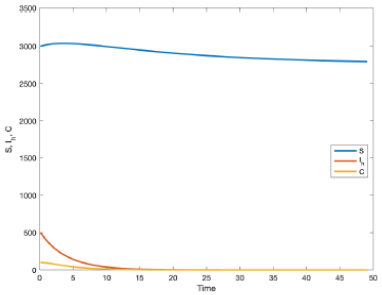


Figure 9: *Graph of the coupled model at the population level.*

$Figure$ (6) illustrates exponential increase in the number of uninfected cells increase with the passage of time and space, while the infected cells decrease exponentially, $figure$ (7). Correspondingly, the viral load decreases sharply with increase in time and space, $figure$ (8). The decrease in viral load leads to a corresponding but at a lower rate decrease in the number of infected cells both in space and time. This agrees with reality, in that at early diagnosis, the infected cells and infected areas are removed from the body before cancer spreads to other organs and thus the patient recover from the infection. Therefore, the decrease in viral load has a corresponding decrease in infected cells and increase in uninfected cells. This is also brought about by the coupling where at early diagnosis, $I_h(t)$ reduces and then tends to zero $figure$ (9) . The decrease in infected cells and the viral load is due to the removal of the infected areas, that is the cervix and the uterus, brought about by the decrease in $I_h(t)$. This explains why the uninfected cells are increasing.

Furthermore, the graphs show that with early diagnosis, the rate of increase in the number of infected cells is decreased while late diagnosis corresponds to an increase in the number of infected cells. Hence, the stage of diagnosis is crucial in combating and managing the cervical cancer infection.

X. Discussion

In this study we have formulated and analysed a model framework linking the two subsystems of within-and between-host cervical cancer dynamics. The newness in this study is in deriving the coupled model by expressing the transmission rate as a function of the viral load at the between host level, while expressing the infection rate at within host as a function of the infectivesat the population level. This was based on the approach by [5]. The six compartments model obtained remained mathematically and computationally tractable. Hence a detailed mathematical analysis was conducted, this involved determining the basic reproduction number for the coupled model. This wasfound to be a maximum of the two reproduction numbers for the

between-and within-host subsystems, that is$R_{0C} = Max(R_{0B},R_{0w})$. The analysis of the DFE was done using the Routh-Hurwiz criteria and was found to be asymptotically stable whenever$R_{0B} < 1$ and R_{0w} <1. This has both within and between-host significance, in that the introduction of an infected individual into the population would not lead to new transmission and the disease is wiped out.

The centre manifold theorem was used to show that the coupled model has a unique endemic equilibrium. This was found to be locally asymptotically stable whenever$R_{0C} > 1$andunstablewhen$R_{0C} < 1$.From the numericalsimulations, it was deduced that an increase in viral load has a corresponding increase in the number of infectives at the population level. This means that, movement of the virus makes the disease persist in the population. However,a decline in the viral load at the within- host may not necessarily lead to a decline in the number of infectives at the population level. This is because transmissibility is highly dependent on the rate of contact between the infectives and the susceptibles.

In addition numerical simulations revealed that early diagnosis has remarkableeffect on cervical cancer management and HPV transmission. Early diagnosis leads to significant reduction of the viral load and the number infected cellswithin a short period of time and space.

XI. Conclusion

Early diagnosis contributes to low viral replication, since it prevents successful infection of new cells and infected cells from maturing into actively infectious virions. This is likely to result into low transmission of HPV at the population level. Hence the small number of infected individuals at the population when diagnosed early, treatment is done and the patients gain full recovery from cervical cancer infection. This is in agreement with Bungoma district report where, those diagnosed early, fully recovered from the infection unlike late diagnosis.

References

[1]. **Attia S., Egger M., Mu¨ller M., Zwahlen M., Low N. 2009**. Sex- ual transmission of HIV according to viral load and antiretroviral ther- apy: systematic review and metaanalysis. AIDS 23(11):1397-1404 DOI 10.1097/QAD.0b013e32832b7dca.

[2]. **Carr Jack (1981**), Applications of Centre Manifold Theory, Applied Mathematical Sciences, Vol.35, Springer-Verlag, New York.

[3]. **Clifford G. M., Smith, J. S., Plummer, M., Munoz, N., and Franceschi, S. (2003**). Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. British journal of cancer, 88(1), 63-73.

[4]. **Diekmann, O., Heesterbeek, J., Metz J.A. (1990**). On the definition and the computation of the basic reproduction ratio in models for infectious diseases in heterogenious populations. Journal of Mathematical Biology. 167, 67-78.

[5]. **Feng Z., Velasco-Hernandez J., Tapia-Santos B. and Leite A.C M. (2011**).A model for coupling within-host and between-host dynamics in an infectious disease. Springer Science+Business Media B.V. 2011

[6]. **Mobisa B., Lawi G. O. and Nthiiri J. K. (2019**) . An Immuno- Epidemiological Model for HIV/AIDS Incorporating Viral and Cellular Transmission with Antiretroviral Treatment. Applied Mathematical Sci- ences, Vol. 13, no. 23, 1129 - 1145. HIKARI Ltd, www.m-hikari.com

[7]. **Routh E.,(1977**) A Treatise on the Stability of a Given State of Motion: Particularly Steady Motion, Macmillan Publishers.