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Dynamical Analysis of Model Human Papillomavirus Transmission with Vaccination

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ABSTRACT

Cervical cancer is one of the most common diseases suffered by women around the world. One of the causes of cervical cancer is the Human Papillomavirus virus (HPV). This virus attacks the sexual organs of men and women. This study was conducted to analyze the dynamic of HPV transmission system when a vaccination treatment is applied. The constructed model that analyzed in this study was an extended SIR model. A group of women S is divided in two compartment; S_1 (denotes a group of 0 -10 years of age) and S_2 (denotes the group of above 10 years). The group S_2 represents the vulnerable age group to the HPV. Apart from compartments S_1S_2IR we also included the compartment C (cancer development) which resulted in the model became S_1S_2IRC. The analysis to the disease-free equilibrium point shows that it will be asymptotically stable for the reproduction number $R_0 < 1$ whereas for the endemic equilibrium point was achieved when $R_0 > 1$. We also conducted the sensitivity analysis to investigate which parameters influenced R_0 significantly. The results indicated that parameters population growth β and proportions of unvaccinated population x are related positively to R_0 while parameters natural birth μ inluenced negatively.

Keywords: dynamical analysis; equilibrium points, sensitivity analysis, human papillomavirus; cervical cancer

INTRODUCTION

Cervical cancer is one of the most frequent diseases suffered by women worldwide. Marth et al. [1] showed that more than 265 thousand women died of cervical cancer in 527 thousand cases annually in both developed and developing countries. Cervical cancer generally affects women between the ages of 15 and 25. However, 50% of sexually active women are more at risk of developing cervical cancer [2]. According to Made Boer [3], in 2006 there were 2686 cases of cervical cancer in Indonesia, which were divided into 880 cases in Jakarta, 919 cases in Tasikmalaya, and 887 cases in Bali.From 2015 to 2019, the number of women screened for cervical cancer was not constant, whereas in 2017, the cases increased rapidly with a total of 1,114,173 and decreased again in 2018 with a total of 611,645 cases. Then, in 2019, the number of

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cases increased again, with a total of 1,170,353[4]. In 2020, there were 36,633 cases with the number of deaths from cervical cancer as high as 21,003[5]. Cervical cancer can be caused by many viruses. One of the deadly viruses is HPV. This virus contains a group of more than 150 interconnected types. More than 40 virus types of HPV are known to infect the sexual organs of both males and females.

There were reports made that in order to reduce the number of people being exposed to HPV infections people can take some precautions such as getting HPV vaccine, only having one sex partner and avoiding having sex with people who have had many sex partners. Atkinson et al. [6] stated that in 2006 The Food and Drug Administration (FDA) in the US approved a vaccine that can prevent not only the 2 types of HPV (HPV 16 and 18) that cause 70% of the cervical cancers, but also the 2 types of HPV (HPV 11 and 16) that cause 90% of all genital warts or condylomata. This was a enourmous break through. There were also known about 40 types of HPV that can potentially cause diseases [7] but the above 4 types of HPV are the most common causes of cervical cancers and genital diseases in general

It is widely known that mathematical models and dynamical analysis have become essential tools in the study of diseases transmission. The study can lead to more effective strategies in order to reduce the spread of the contagious diseases such as HPV infections [8]. Research on HPV transmission and cervical cancers were mostly statistical to find what factors caused the infectious disease and how to intervene that. Without understanding the dynamic of the transmission system and how it happens in a particular period of time, such research will probably be of limited use [9]. This is worsened by the condition where data collection about genital diseases or genital warts such HPV are not always easy to obtain due to the consideration of being ashamed to be exposed about such a private life [2]

Research on mathematical modeling in HPV infections that lead to cervical cancers has been carried out by several authors. To name a few Lee and Tameru[2], Gamet et al.[10], and Sroczinsky et al. [11] applied the SI model to describe the transmission of HPV in cervical cancer. However, in this research, only a mathematical model was developed without conducting stability analysis which is an important part of the work. Another researcher was Asih et al [12], who discussed CUSP bifurcation in cervical cancer mathematical models that discuss how to find bifurcation phenomena with some parameters. Without discussing the treatment carried out to prevent cervical cancer, they did not move further in analysing the treatment for the disease to prevent the transmission of human papillomavirus.

Therefore, this current study is dedicated to analyze the dinamic of HPV transmission where vaccination is incorporated as one of the parameters in the system model. By doing so, we expect to understand how the transmission system works and we can also generate some numerical simulations to understand better all the dynamic subpopulations incorporated in the system as well as all the parameters we assummed to be involved. It is hoped that this will at least help the policy makers to intervene or overcome the emerging infectious diseases such as HPV infections.

METHODS

The dynamical analysis equipped with sensitivity analysis will help us understand the behaviour of the HPV transmission system in the long run as well as the understand of the paramaters that significantly influence the reproduction number R_0. This research was conducted using literature studies related to dynamic analysis, HPV transmission to

cervical cancer and vaccination. The study was carried out by first making assumptions related to the dynamic of HPV transmission with vaccination, followed by establishing a model of HPV transmission with vaccination, conducting dynamical analysis of the model including the determination and the stability analysis of the equilibrium points, then generating numerical simulation using Mathlab software and finally interpretating the results of the analysis.

RESULTS AND DISCUSSION

Assumptions

The constructed model used in this study is an extended of the model proposed by Kermack and MCKendrick [13] with women population S divided into two subpopulations; S_1 (population age 0–10 years who are not vulnerable to virus transmission) and S_2 (population age more 10 years who are vulnerable to virus transmission). Newborns are in group S_1, the birth rate is equal to the death rate which implies a constant population, there is no incubation period in HPV transmission, the recovered population is not susceptible, and the untreated population will move to group C (cancer) whereas the treated population is in the R (recovered) subpopulation. The vaccination program is applied in the model S_1S_2IRC. The vaccine is only applied to the susceptible population. The parameters employed in this research are:

$\boldsymbol{S_1}$	:	Subpopulation age 0-10 years
$\boldsymbol{S_2}$	:	Subpopulation age greater than 10 years
$\boldsymbol{I}$	:	HPV-infected subpopulation
$\boldsymbol{C}$	:	Cancer subpopulation
$\boldsymbol{R}$	:	Recovered subpopulation
$\boldsymbol{A}$	:	The number of natural births
$\boldsymbol{\delta}$	:	Population growth
$\boldsymbol{\beta}$	:	HPV-infected population growth
$\boldsymbol{n}$	:	Recovered population growth from a treatment
$\boldsymbol{1-n}$	:	Cancer-infected population from the infected group because of no treatment
$\boldsymbol{m}$	:	The proportion of the susceptible population that is vaccinated
$\boldsymbol{1-m}$	:	The proportion of the susceptible population that is unvaccinated
$\boldsymbol{\mu}$	:	The natural death rate

Model Construction

From the above assumptions we then constructed the HPV transmission model as follows:

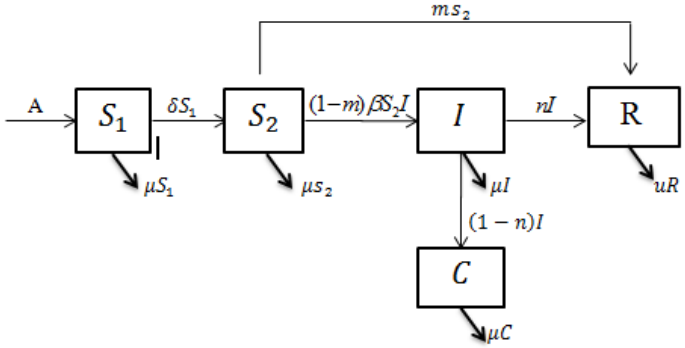

Figure 1. Transmission Diagram

which can be represented in the following system of differential equations:

$$\begin{aligned}
\frac{dS_1}{dt} &= A - \delta S_1 - \mu S_1 \\
\frac{dS_2}{dt} &= \delta S_1 - mS_2 - (1-m)\beta S_2 I - \mu S_2 \\
\frac{dI}{dt} &= (1-m)\,\beta S_2 I - (\mu - n)I - (1-n)I \\
\frac{dR}{dt} &= mS_2 + nI - \mu R \\
\frac{dC}{dt} &= (1-n)I - \mu C
\end{aligned} \tag{1}$$

The diagram in Figure 1 and the system of differential equations in equation 1 show that there are five (5) compartments in the model. They are S_1 (population of 0-10 years), S_2 (population over 10 years vulnerable to HPV), I (HPV infected before developed to cervical cancer population), C (cervical cancer population), R (recovered population). The population of S_1 grows due to the natural birth A but loose with death rate (μ) and move to S_2 with the rate of (δ). S_2 as a susceptible population can be treated with vaccination m so that they will not be exposed to HPV and move to group R (recovered). The population in S_2 who are not vaccinated is prone to be infected so that they will move to compartment I (HPV infected) with the number of $(1-m)$. Those who are in the I (infected) compartment and recovered beacuse of the vaccination will move to compartment R with the rate of n, wehereas $1-n$ population (who are untreated) will develop cervical cancer.

Equilibrium Points

The crucial aspect in dynamical analysis is to determine equilibrium points of a system where we are able to know the behaviour of the system in the long time period. From the system of equations (1), the equilibrium points are obtained by letting the right hand side of the equations equal zero i.e:

$$\frac{dS_1}{dt} = \frac{dS_1}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = \frac{dC}{dt} = 0$$

For the dynamical analysis of the diseases transmission such as HPV transmission above we know there are 2 types of equilibriums points; Disease free equilibrium point (E_0) where $I = C = 0$ and Endemic equilibrium point (E_1) where $I = C \neq 0$.

a. For the Disease-free equilibrium point (E_0), with $I = C = 0$, then we obtain $E_0(S_1^*, S_2^*, I^*, C^*, R^*)$ where

$$\frac{dS_1^*}{dt} = A - \delta S_1^* - \mu S_1^* = A - (\delta + \mu)S_1^* = 0$$

$$S_1^* = \frac{A}{\delta + \mu}$$

In the similar manner, we obtain

$$S_2^* = \frac{\delta A}{\mu^2 + \delta m + \delta\mu + \mu m}$$

$$I^* = 0$$

$$C^* = 0$$

$$R^* = \frac{m\delta A}{\mu(\mu^2 + \delta m + \delta\mu + \mu m)}$$

Thus the disease-free equilibrium point is as follows

$$E_0 = \left(\frac{A}{(\delta+\mu)}, \frac{\delta A}{\mu^2 + \delta m + \delta\mu + \mu m}, 0, \frac{m\delta A}{\mu(\mu^2 + \delta m + \delta\mu + \mu m)}, 0\right) \quad (2)$$

b.

For Endemic equilibrium point (E_1) which means the disease exists in the population with

$I = C \neq 0$, then we obtain $E_1(S_1^{**}, S_2^{**}, I^{**}, C^{**}, R^{**})$ where

For $\frac{dS_1^*}{dt} = 0$

$$A - \delta S_1^{**} - \mu S_1^{**} = 0$$

$$S_1^{**} = \frac{A}{(\delta+\mu)}$$

$$\frac{dS_2^*}{dt} = 0$$

$\delta S_1^* - mS_2^* - (1-m)\beta S_2^* I - \mu S_2^* = 0$ e.g $x = (1-m)$

We obtained

$$S_2^* = \frac{\delta A}{I(\mu x\beta + \delta x\beta) + m(\mu+\delta) + \mu(m+\delta)}$$

In the similar manner, we obtain

$$S_2^{**} = \frac{\delta A(\mu+n+\rho)}{x\beta\delta A}$$

$$I^{**} = \frac{x\beta\delta A - (\mu+n+\rho)\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)}{(\mu+n+\rho)(\mu x\beta + \delta x\beta)}$$

$$R^{**} = \frac{m(\mu+n+\rho)^2(\mu x\beta + \delta x\beta) + nx\beta\big(x\beta\delta A - (\mu+n+\rho)(m\mu + m\delta) + (\mu^2 + \mu\delta)\big)}{(\mu x\beta + \delta x\beta)(\mu+n+\rho)(\mu x\beta)}$$

$$C^{**} = \frac{\rho x\beta\delta A - y(\mu+n+\rho)\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)}{(\mu^2 x\beta + \mu\delta x\beta)(\mu+n+\rho)}$$

thus obtained

$$E_1 = \begin{bmatrix} \frac{A}{(\delta+m)}, \frac{\delta A(\mu+n+y)}{(x\beta\delta A)}, \frac{x\beta\delta A - (\mu+n+y)\left(\left(m\mu + m\delta + (\mu^2 + \mu\delta)\right)\right)}{(\mu+n+y)(\mu x\beta + \delta x\beta)}, \\ \frac{m(\mu+n+y)^2(\mu x\beta + \delta x\beta) + x\beta\delta\left(x\beta\delta A - (\mu+n+y)\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)\right)}{(\mu x\beta + \delta x\beta)(\mu+n+y)(\mu x\beta)}, \\ \frac{yx\beta\delta A - y(\mu+n+y)\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)}{(\mu^2 x\beta + \mu\delta x\beta)(\mu+n+y)} \end{bmatrix} \quad (3)$$

Basic Reproduction Number R_0

Now, we turn into calculating the basic reproduction number R_0. R_0 is an important parameter in the dynamical analysis of the infectious diseases as it denotes the number of secondary infections in susceptible subpopulation from a single original

infection. Employing the *Next Generation Matrix Method* [14], a basic reproduction number (R_0) can be calculated, and this yields

$$R_0 = \frac{x\beta\delta A}{(\mu + n + y)(\mu^2 + \delta m + \delta\mu + \mu m)} \qquad (*)$$

The term $\frac{x\beta\delta A}{\mu^2+\delta m+\delta\mu+\mu m}$ represents the average number of populations that are newly infected whereas $\frac{1}{(\mu+n+y)}$ represents the average number of infected populations that have passed through the infection period and moved into the *cancer* (C) population. Therefore, the term $\frac{x\beta\delta A}{(\mu+n+y)(\mu^2+\delta m+\delta\mu+m)}$ indicates the average newly infected number of the population when the infected subpopulation is now in the *cancer* group.

Stability Analysis at the Equilibrium Point

To analyze the stability of the equilibrium points, first we need to linearize equation (1). The Linearization of equation (1), we obtain

$$\frac{\partial f_1}{\partial S_1} = -\delta, \frac{\partial f_1}{\partial S_2} = -\mu, \frac{\partial f_1}{\partial I} = 0, \frac{\partial f_1}{\partial R} = 0, \frac{\partial f_1}{\partial C} = 0$$
$$\frac{\partial f_2}{\partial S_1} = \delta, \frac{\partial f_2}{\partial S_2} = (-m) - (1-m)\beta I - \mu, \frac{\partial f_2}{\partial I} = (1-m)\beta S_2, \frac{\partial f_2}{\partial R} = 0, \frac{\partial f_2}{\partial C} = 0$$
$$\frac{\partial f_3}{\partial S_1} = 0, \frac{\partial f_3}{\partial S_2} = (1-m)\beta I, \frac{\partial f_3}{\partial I} = (1-m)\beta S_2 - (\mu + n + y), \frac{\partial f_3}{\partial R} = 0, \frac{\partial f_3}{\partial C} = 0$$
$$\frac{\partial f_4}{\partial S_1} = 0, \frac{\partial f_4}{\partial S_2} = m, \frac{\partial f_4}{\partial I} = n, \frac{\partial f_4}{\partial R} = -\mu, \frac{\partial f_4}{\partial C} = 0$$
$$\frac{\partial f_5}{\partial S_1} = 0, \frac{\partial f_5}{\partial S_2} = 0, \frac{\partial f_5}{\partial I} = \quad y, \frac{\partial f_5}{\partial R} = 0, \frac{\partial f_5}{\partial C} = -\mu$$

In the Jacobian matrix

$$J = \begin{bmatrix} -\delta & -\mu & 0 & 0 & 0 \\ \delta & -m - x\beta I - \mu & -x\beta S_2 & 0 & 0 \\ 0 & x\beta I & x\beta S_2 - (\mu + n + y) & 0 & 0 \\ 0 & m & n & -\mu & 0 \\ 0 & 0 & y & 0 & -\mu \end{bmatrix}$$

Stability Analysis at Disease-Free Equilibrium Point

Applying all the values in equation (2), the Jacobian matrix on the disease-free equilibrium point is as follows:

$$J(E_0) = \begin{bmatrix} -\delta & -\mu & 0 & 0 & 0 \\ \delta & -m - \mu & \frac{-x\beta\delta A}{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)} & 0 & 0 \\ 0 & 0 & \frac{x\beta\delta A}{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)} - (\mu + n + y) & 0 & 0 \\ 0 & m & n & -\mu & 0 \\ 0 & 0 & y & 0 & -\mu \end{bmatrix}$$

Hasnawati [7] stated that if the diagonal of a matrix $[-A] > 0$ and $[-A] > 0$ then the eigenvalue of the matrixis negative. If the eigenvalue of the matrix A is negative then the Jacobian matrix is asymptotically stable[15].

Theorem 1:

$R_0 < 1$ if and only if the disease-free equilibrium point is asymptotically stable.

Proof :

a. Proof to the right ($\Rightarrow$)

Consider $R_0 < 1$and the main diagonal of matrix $(-JE_0) > 0$ then the disease-free equilibrium point is asymptotically stable locally.

$$Diag(-JE_0) = \begin{bmatrix} \delta \\ m+\mu \\ \dfrac{x\beta\delta A}{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)} + (\mu + n + y) \\ \mu \\ \mu \end{bmatrix} > 0$$

Where $Diag(-JE_0)$ represents the diagonal of the matrix

And since $R_0 < 1$then$|-JE_0| > 0$is

$$|-JE_0| = \delta m\mu^2(\mu + n + y)\left[\frac{x\beta\delta A}{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)(\mu + n + y)} + 1\right] > 0$$

Therefore

$$\delta\mu^2 m(\mu + n + y)[-R_0] > 0$$

$$(1 - R_0) > 0$$

$$\therefore R_0 < 1$$

As$R_0 < 1$ and$(-JE_0 > 0)$thenJE_0has a negative eigenvalue with its negative real part. As a consequence,E_0 is locally asymptotically stable.

b. Proof to the right ($\Longrightarrow$)

$E_0$is locally asymptotically stable. We need to show that $R_0 < 1$. Since $E_0$is asymptotically stable locally then JE_0has a negative eigenvalue or negative real part. JE_0 has negative real eigenvalue if the diagonal of $(-JE_0) > 0$ and $|-JE_0| > 0$;

$$Diag(-JE_0) = \begin{bmatrix} \delta \\ m+\mu \\ \dfrac{x\beta\delta A}{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)} + (\mu + n + y) \\ \mu \\ \mu \end{bmatrix} > 0$$

Where $Diag(-JE_0)$ represents the diagonal of the matrix.

$|-JE_0| > 0$, means that

$\delta\mu^2 m(\mu + n + y) > 0$ if $R_0 < 1$. Therefore $R_0 > 0$ if and only if$E_0$is locally asymptotically stable. Therefore $E_0$is locally asymptotically stable[16][17]. This shows a strong relation between the disease-free equilibrium point and the value of R_0.

Stability Analysis at The Endemic Equilibrium Point

The Jacobian matrix on the endemic equilibrium Point is

$J(E_1)$

$$= \begin{bmatrix} -\delta & -\mu & 0 & 0 & 0 \\ \delta & -m - x\beta\dfrac{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)}{(\mu x\beta + \delta x\beta)}[R_0 - 1] - \mu & \dfrac{-x\beta\delta A(\mu + n + y)}{x\beta\delta A} & 0 & 0 \\ 0 & x\beta\dfrac{\left((m\mu + m\delta) + (\mu^2 + \mu\delta)\right)}{(\mu x\beta + \delta x\beta)}[R_0 - 1] & \dfrac{x\beta\delta A(\mu + n + y)}{x\beta\delta A} & 0 & 0 \\ 0 & m & n & -\mu & 0 \\ 0 & 0 & y & 0 & -\mu \end{bmatrix}$$

Theorem 2

$R_0 > 1$ if and only if the disease endemic equilibrium point exists and is locally asymptotically stable.

Proof:

a. Proof to the left($\Leftarrow$)

Consider An endemic equilibrium pointthat exists and is locally asymptotically stable. We will show that $R_0 > 1$

$$Diag(-JE_0) = \begin{bmatrix} \delta \\ m + x\beta\dfrac{\left((m\mu + m\delta) + (\ \mu^2 + \mu\delta)\right)}{(\mu x\beta + \delta x\beta)}[R_0 - 1] \\ -\dfrac{x\beta\delta A(\mu + n + y)}{x\beta\delta A} + (\mu + n + y) \\ \mu \\ \mu \end{bmatrix} > 0 \qquad (4)$$

Where $Diag(-JE_0)$ represents the diagonal of the matrix.

The determinant of matrix (4) is

$$|JE_1| = x\beta\delta\mu^2(\mu + n + y)\frac{\left((m\mu + m\delta) + (\mu^2 + \delta)\right)}{\mu x\beta + \delta x\beta}[R_0 - 1] > 0$$

Then

$[R_0 - 1] > 0$

$\therefore R_0 > 1$

Since $R_0 > 1$ then the endemic disease equilibrium point exists and is locally asymptotically stable.

b. Proof to the right ($\Rightarrow$)

Consider

R_0 then the endemic equilibrium point exists and is asymptotically stable. We need to calculate the eigenvalue of the matrix $J(E_1)$

$$|J(E_1) - \lambda I| = 0$$

$$\left\|\begin{bmatrix} -\delta & \mu & 0 & 0 & 0 \\ \delta & -m-\frac{C}{D}-\mu & -\frac{x\beta\delta Az}{x\beta\delta Az} & 0 & 0 \\ 0 & \frac{C}{D} & \frac{x\beta\delta Az}{x\beta\delta A} & 0 & 0 \\ 0 & m & n & -\mu & 0 \\ 0 & 0 & y & 0 & -\mu \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 & 0 & 0 \\ 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}\right\| = 0$$

Where $C = \big(x\beta\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)[R_0 - 1]\big), D = (\mu x\beta + \delta x\beta)$, and $z = (\mu + n + y)$

Then $det(JE_1 - \lambda I) = 0$
Define

$$C = \big(x\beta\big((m\mu + m\delta) + (\mu^2 + \mu\delta)\big)[R_0 - 1]\big)$$

$$D = (\mu x\beta + \delta x\beta)$$

$$z = (\mu + n + y)$$

Then the characteristic polynomial is

$$\lambda^5 + \left[\frac{C + (m + 3\mu + \delta)D}{D}\right]\lambda^4 + \left[\frac{(-z + \delta + 2\mu)C + (m\delta + 4\mu\delta + 2\mu m + 3\mu^2)D}{D}\right]\lambda^3$$

$$+\left[\frac{(-z2\mu - z\delta + 2\mu\delta + \mu^2)C + (m\mu^2 + 2m\mu\delta + 5\mu^2\delta + \mu^3)D}{D}\right]\lambda^2$$

$$+\left[\frac{(-z2\mu\delta - z\mu^2 + \mu^2\delta)C + (m\mu^2\delta + 2\mu^3\delta)D}{D}\right]\lambda + \left[\frac{(-z\mu^2\delta)C}{D}\right] = 0$$

$$\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_2\lambda + a_5 = 0 \qquad (5)$$

with: $a_0 = 1$

$$a_1 = \left[\frac{C + (m + 3\mu + \delta)D}{D}\right]$$

$$a_2 = \left[\frac{(-z + \delta + 2\mu)C + (m\delta + 4\mu\delta + 2\mu m + 3\mu^2)D}{D}\right]$$

$$a_3 = \left[\frac{(-z2\mu - z\delta + 2\mu\delta + \mu^2)C + (m\mu^2 + 2m\mu\delta + 5\mu^2\delta + \mu^3)D}{D}\right]$$

$$a_4 = \left[\frac{\left(-z2\mu\delta - z\mu^2 + \mu^2\delta\right)C + \left(m\mu^2\delta + 2\mu^3\delta\right)D}{D} \right]$$

$$a_5 = \left[\frac{\left(-z\mu^2\delta\right)C}{D} \right]$$

To identify the negative real part of the eigenvalue in equation (5), Routh-Hurwitz criteria are applied

$$H_1 = \left[a_1\right], H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix}$$

with :

$$H_1 = |a_1| > 0,\ H_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} > 0,\ H_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix} > 0$$

since $R_0 = \dfrac{x\beta\delta A}{(\mu + n + y)(\mu^2 + \delta m + \delta\mu + \mu m)}$

we will verify that $H_1 = |a_1| > 0$

$$H_1 = \left| \frac{C + \left(m + 3\mu + \delta\right)D}{D} \right|$$

Since $C, m, \mu, \delta, D > 0$ then it has been clear that $|a_1| > 0$

We will show that $H_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} > 0$

$$\Leftrightarrow \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} = a_1 \cdot a_2 - a_3$$

$$\Leftrightarrow a_1 \cdot a_2 - a_3$$

$$\Leftrightarrow \left| \frac{\begin{array}{l} C^2\left(-z + \delta + 2\mu\right) + CD(m\delta + 4\mu\delta + 2\mu m + 3\mu^2 - mz + m\delta + 2\mu m - 3\mu z + 3\mu\delta + 6\mu^2 \\ -z\delta + \delta^2 + 2\mu\delta + z2\mu + z\delta - 2\mu\delta - \mu^2) + D^2(m^2\delta + 7m\mu\delta + 8m\mu^2 + 2\mu m^2 + 10\mu^2\delta + 3\mu^2 \\ +5\mu^3 + m\delta^2 + 4\mu\delta^2 \end{array}}{D^2} \right|$$

Since

$C^2\left(-z + \delta + 2\mu\right) > 0$

$$CD(m\delta + 4\mu\delta + 2\mu m + 3\mu^2 - mz + m\delta + 2\mu m - 3\mu z + 3\mu\delta + 6\mu^2$$
$$-z\delta + \delta^2 + 2\mu\delta + z2\mu + z\delta - 2\mu\delta - \mu^2) > 0$$
$$D^2(m^2\delta + 7m\mu\delta + 8m\mu^2 + 2\mu m^2 + 10\mu^2\delta + 3\mu^2 + 5\mu^3 + m\delta^2 + 4\mu\delta^2 > 0$$

Then $a_1 \cdot a_2 - a_3 > 0$

Show that $H_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix} > 0$

$$\Leftrightarrow \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix} = a_1 \begin{bmatrix} a_2 & a_1 \\ a_4 & a_3 \end{bmatrix} - 1 \begin{bmatrix} a_3 & a_1 \\ a_5 & a_3 \end{bmatrix} + 0$$

$$\Leftrightarrow a_1\left[a_2.a_3 - a_1.a_4\right] - 1\left[a_3.a_3 - a_1.a_5\right] > 0$$
$$\Leftrightarrow \frac{IC^3 + JCD^2 + KC^2D + LD^3}{D^3} \qquad (6)$$

with:

$$I = \left(2z^2\mu + z^2\delta + 2\delta^2\mu + 4\delta\mu^2 + 2\mu^3 - 5\delta\mu z - 4\mu^2 z - z\delta^2\right)$$
$$J = (12m^2\mu^2\delta + 48m\delta\mu^3 + 36m\delta^2\mu^2 + 50\delta^2\mu^3 + 66\mu^4\delta + 6m^2\mu^3 + 17\mu^4 m + 3\mu^3 m + 18\mu^5 m + 6zm^2\mu^2$$
$$+ 4m^2\delta^2\mu - 4zm^2\delta\mu - 6zm\delta\mu^2 - 7mz\mu^3 + 3zm\mu^2 + 2zm\delta^2\mu - 11z\delta\mu^3 - 12z\mu^3 + 6z\delta^2\mu^2 + 4m\delta^3\mu$$
$$+ 12\delta^3\mu^2 + 3z\delta\mu^2 - 2\mu^5 + 2z\delta^3\mu)$$
$$K = (12m\delta\mu^2 + 6m\delta^2\mu + 18\delta^2\mu^2 + 19\delta\mu^3 + 13\mu^4 + 6\mu^3 m + 6z\mu^2 m - 9z\mu\delta m + 33z\delta\mu^2 + 4\mu^3 z + 3z\mu^2$$
$$- 4z\mu\delta^2 + 2mz^2\mu + z^2 m\delta - 4zm\mu^3 - zm\delta^2 - 2z^2\mu^2 + z^2\mu\delta - 12\mu^4 z + 2\mu\delta^3 - 4z\mu^3\delta - z\delta^3$$
$$+ 2z\mu\delta - 7\mu^3\delta)$$
$$L = (4m^3\delta\mu^2 + 24m^2\mu^3\delta - 14m\delta\mu^4 - 4m^2\delta^2\mu^2 + 50\mu^3 m\delta^2 + 2\mu^3 m^3 + 5\mu^4 m^2 + 5m^2\mu^3 - 7\mu^5$$
$$+ 42\mu^5\delta + 42\mu^4\delta^2 + 33\mu^3 m\delta + 4\mu^5 m + 9\mu^4 m + 8\mu^6 + 12\mu^2 m\delta^3 + 18\mu^3\delta^3)$$

since :

$IC^3 > 0$, $JCD^2 > 0$, $KC^2D > 0$, $LD^3 > 0$

then it is obvious that $a_1\left[a_2.a_3 - a_1.a_4\right] - 1\left[a_3.a_3 - a_1.a_5\right] > 0$

The determinant of the Routh-Hurwitz matrixH_1, H_2 and H_3 is obtained with a positive value. It can be concluded that all polynomial $\left(P(\lambda)\right)$ roots have negative real parts which means that all eigenvalues are negative. Therefore the endemic equilibrium point is asymptotically stable.

Numerical Simulation

The numerical simulation is conducted to assess which parameters affect HPV transmission. The parameter values are taken from sources as displayed in Table 1.

Table 1. Parameter Values for Numerical Simulation

NO	Parameter	Description	Values	Source
1	$(1-m)$	The proportion of the susceptible population that is unvaccinated	0.05	[18]
2	β	HPV-infected population growth	0.65	[19]
3	μ	The natural death rate	0.014	[20]
4	δ	Population growth	0.1	[18]
5	n	Recovered population growth from a treatment	0.001	[18]
6	$(1-n)$	Cancer-infected population from the infected group because of no treatment	0.00035	[2]
7	m	The proportion of the susceptible population that is vaccinated	0.95	[18]

Numerical Simulation Results on Disease-free Equilibrium Point for $R_0 < 1$

With values of parameters $(1-m) = 0.02,\ m = 0.98,\ \beta = 0.52,\ n = 0.003$ and initial values $S_1(0) = 50,\ S_2(0) = 50,\ I = 50,\ C = 50, R = 50$ we obtain the value of $R_0 = 0.5411015443$. The diagram of the point is displayed in Figure 2.

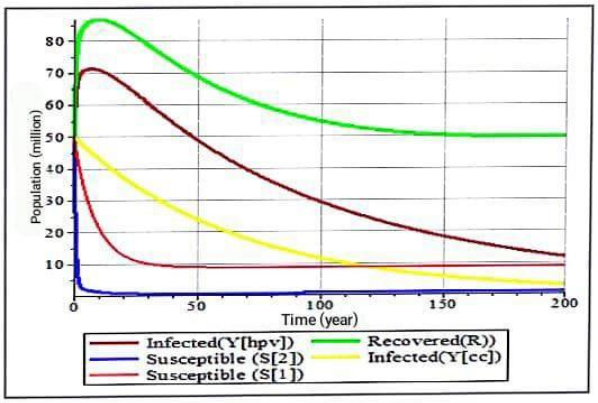

Figure 2. Diagram for R_0<1

From the diagram in Figure 2 it can be clearly seen that with the initial values considered, all subpopulations experienced a decrease trend in the long run. For both *infected HPV* (I) and Cancer (C) subpopulations, the trends go to zero after a slight increase from 50 million 70 million people in the first few years for infected group. Similar trend also experienced by the recovered subpopulation where it rises from 50 million to about 85 million people in the first few years before it declined to reach about 50 million after 125 years. For the susceptible population aged 1-10 years (S_1) of 50 million people experienced a decline to 10 million people after 25 years and remains stable onwards. The susceptible population aged 10 years and over (S_2) also decreased from 50 million people to about 5 million after 3 to 4 years, and then reach zero after 5 years onwards. This is due to the successful use of vaccine treatment as well as the number of individuals recovering naturally. If the *susceptible* subpopulation is infected by the virus they will move to the infected population.

Sensitivity Analysis

The analysis was undertaken to examine which parameters affected the value of R_0 significantly. Table 1 shows the sensitivity index expressions and their values.

Table 2. Sensitivity Index Expressions

PARAMETER	SENSITIVITY INDEX	Initial Values	Result	$R_0 = 1,886114072$ $P + 10\%$	$P - 10\%$
β	1	0,65	1,000	2,0747	1,6975
δ	$\frac{(\mu^2 + \delta m)}{(\mu^2 + \delta m + \delta\mu + \mu m)}$	0,1	0,121	1,9074	1,8607
x	1	0,05	1,000	2,0747	1,8607
y	$-\frac{y}{\mu + n + y}$	0,00035	−0,023	1,8818	1,8904
m	$-\frac{m(\delta + \mu)}{(\mu^2 + \delta m + \delta\mu + \mu m)}$	0,95	0,987	1,7169	2,0923
n	$\frac{-n}{\mu + n + y}$	0,001	−0,065	1,8739	1,8985
μ	$-\frac{\mu\left[\begin{matrix}(\mu^2 + \delta m + \delta\mu + \mu m) + (\mu + n + y) \\ (2\mu + \delta + m)\end{matrix}\right]}{(\mu + n + y)(\mu^2 + \delta m + \delta\mu + \mu m)}$	0,014	−0,376	1,7050	2,1043

Based on Table 2, the parameters that influence the basic reproduction number R_0 are the natural death rate μ, the HPV-infected population growth rate β, and the proportion unvaccinated susceptible population x. Parameters β and x are positively related to R_0. This implies that if the values of x and β are added, the value of R_0 increases. Conversely, if x and β are reduced the value of R_0 decreases. Meanwhile, the parameter μ has a negative relationship with R_0, which means that if the μ value increases, the R_0 value decreases. Apart from that, when increasing or decreasing the values of the parameters β and x by 10%, the value of R_0 will increase by 10%. In addition, if the 10% increase in the parameter μ then the value of R_0 reduces by 10%, and vice versa 10% reduction to the μ parameter can increase the R_0 value by 10%.

Numerical simulation on the endemic equilibrium point $R_0 > 1$

With the choices of parameter values in Table 1 and initial values $S_1(0) = 50$, $S_2(0) = 50, I = 50, C = 50$, $R = 50$ the value of $R_0 = 1.886114072$. The diagram is displayed in Figure 3.

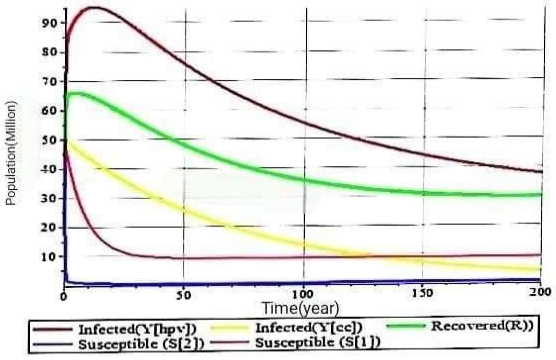

Figure 3. Diagram for $R_0>1$

From Figure 3, we can also see similar trend with Figure 2 but with different margin of changes. For the group I, the number of people roses to 50 million people to 95 million after about 10 years and then decreases continuously to reach about 40 million people in after 200 years. For the cancer group (C), in experience 10 million people after 150

years onwards. This is because people who are infected by HPV not automatically develop cancer [2]. However, the number of people who suffer of cancer will always exist if there is no vaccine treatment. For the Susceptible population aged 1-10 years (S_1) of 50 million people experienced a decline of down to 10 million people after 25 years onwards. The susceptible population aged 10 years and over (S_2) also decreased from 50 million people to 0 after 1 to 2 years and remains stable. The recovered population (R) follows similar pattern (with Figure 2) where it rises from 50 million people to 65 million in about 10 years and then decreases to reach 30 million people after about 110 years and remains stable onwards.

CONCLUSIONS

Based on the results obtained, it can be concluded that by applying the Routh-Hurwitz criteria to the model formed, it is found that for $R_0 < 1$, the disease-free equilibrium point will be locally asymptotically stable, while the disease-endemic equilibrium point will be locally asymptotically stable if $R_0 > 1$. Numerical simulation using Mathlab shows that in both conditions where $R_0 < 1$ or $R_0 > 1$ vaccine treatment affects HPV transmission. This can be seen from the decrease in population in both conditions, although the decrease in $R_0 > 1$ is not as large as in $R_0 < 1$. Vaccine treatment have an effect that can reduce the number of infected populations by up to 90%.

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