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Dynamical Analysis Of Cervical Cancer Disease Model With Treatment

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ABSTRACT

This study proposes a model of cervical cancer due to infection with the Human Papilloma Virus (HPV). Various new assumptions are considered to get the model as ideal as possible. Among them, the transmission process depends on interactions with individuals infected with HPV, and the chance of cure is quite high with treatment. In this case, treatment can be in the form of radiotherapy, chemoradiation, chemotherapy, and palliative care. Five subpopulations were constructed, namely the subpopulation of susceptible individuals (S), the subpopulation of vaccinated individuals (V), the subpopulation of individuals infected with HPV (H), the subpopulation of individuals with cervical cancer (K), and the subpopulation of cured individuals (R). The model is formed into a five-dimensional nonlinear differential equation system. Dynamic analysis is carried out by determining the model's equilibrium point and the conditions for the existence and local stability of the equilibrium point. The results of the analysis show that the system has two equilibrium points, namely the disease-free equilibrium point and the endemic equilibrium point. The disease-free equilibrium point exists unconditionally and is shown to be stable under certain conditions. The endemic equilibrium point exists fR_0>1 and is unstable because it has positive eigenvalues. Thus, based on the model that has been formed, the spread of cervical cancer can be controlled with treatment and the number of individuals being vaccinated is increasing.
Keywords : Dynamical Analysis, Mathematical Model, Human Papilloma Viruses, Cervical Cancer

ABSTRAK

Pada penelitian ini diusulkan model penyebaran penyakit kanker serviks akibat infeksi Human Papiloma Virus (HPV). Berbagai asumsi baru dipertimbangkan untuk mendapatkan model seideal munngkin. Diantaranya, proses penularan yang bergantung pada interaksi dengan individu terinveksi HPV, dan peluang kesembuhan yang cukup tinggi dengan pengobatan. Dalam hal ini, pengobatan dapat berupa radioterapi, kemoradiasi, kemoterapi, dan perawatan paliatif. Dikontruksi lima subpopulasi yakni subpopulasi individu rentan (S), subpopulasi individu tervaksin (V), subpopulasi individu terinfeksi HPV(H), subpopulasi individu penderita kanker serviks(K), dan subpopulasi individu sembuh (R). Model terbentuk menjadi suatu sitem persamaan diferensial nonlinear lima dimensi. Metode kualitatif yang dilakukan pada analisis dinamik adalah dengan menentukan titik kesetimbangan model serta menentukan syarat eksistensi dan kestabilan lokal titik kesetimbangan tersebut. Hasil analisis menunjukkan sistem memiliki dua titik kesetimbangan yakni titik kesetimbangan bebas penyakit dan titik kesetimbangan endemik. Titik kesetimbangan bebas penyakit eksis tanpa syarat dan terbukti stabil dengan syarat tertentu. Titik kesetimbangan endimik eksis untuk R_0>1 dan tidak stabil karena memiliki nilai eigen positif. Dengan demikian berdasarkan model yang telah terbentuk penyebaran penyakit kanker serviks dapat terkendali dengan adanya pengobatan dan jumlah individu tervaksin yang semakin banyak.
Kata kunci: Analisis Dinamik, Model Matematika, Human Papiloma Viruses, Kanker Serviks.

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PRELIMINARY

Cervical cancer is a type of cancer in women that 99% is caused by human papillomaviruses (HPV). A person infected with HPV can indeed be partially cured, however, persistent infection by this virus causes cervical cancer. In 2018, it is estimated that 570,000 women in the world have been diagnosed with cervical cancer, 311,000 of whom have died. Control of cervical cancer is carried out in various ways including HPV vaccination, early detection, and treatment of precancerous lesions. When detected early, cervical cancer can generally be treated with radiotherapy, at an advanced stage cervical cancer can be controlled with appropriate treatment and palliative care (Torgovnik, 2020).

Research on mathematical models of cervical cancer has been carried out previously such as Humulongo (2017), Sharomi (2017), Wildana (2018) Saldana (2019), Gurmu (2020), and Hidayatika (2021). Hasnawati, 2017 divided the subpopulation into five parts: the vulnerable population, the vaccinated population, the population infected with HPV, and the population with cervical cancer. In this model, one endemic critical point has been proven for its existence and stability. Thus the interpretation is obtained that cervical cancer will persist in this population.

Kristanti (2020) builds a mathematical model of the spread of cervical cancer which includes vaccination and early detection. This model describes the process of infection that occurs due to direct contact through sexual intercourse between susceptible women and infected men and vulnerable men with infected women. The model has a disease-free equilibrium point and an endemic equilibrium point that exists and is stable under certain conditions. It can be concluded, based on this model, that a cervical cancer-free state may occur if the conditions given are met.

In this study, a model with five populations will be built as researched by Hasnawati (2017), but consider the factors of infection that occur and the chance of recovery in individuals with cervical cancer.

METHODS

Dynamic analysis is a qualitative method in mathematics to find out and predict the condition of the model in the future (Darajat, 2019). The steps taken in the dynamic analysis process are depicted in Figure 1. As follows.

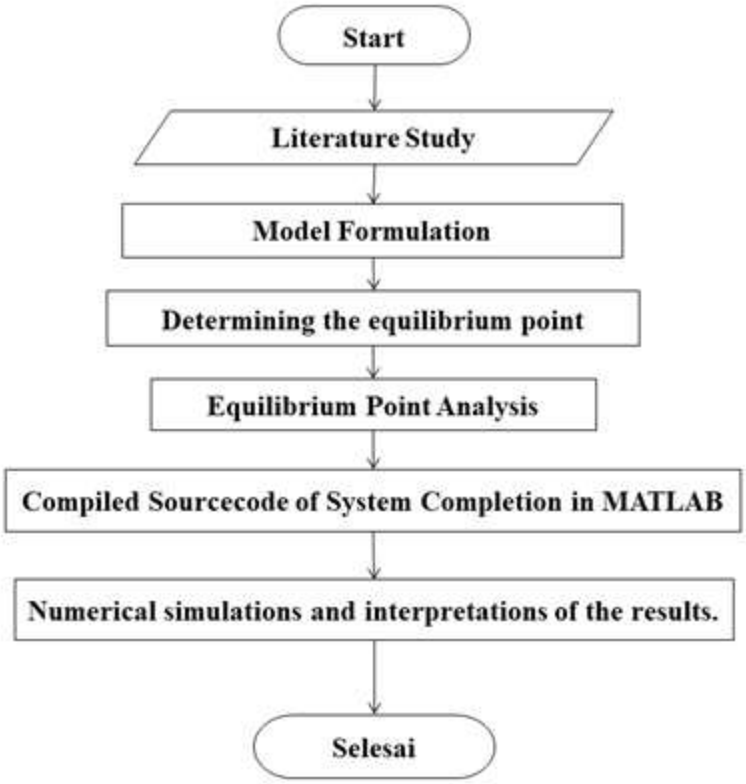

Figure 1. Flowchart of Dynamic Analysis Process Research Methods

The first step in this study was to construct a model for the spread of cervical cancer with treatment. The model to be built is in the form of a five-dimensional system of differential equations. The model is a modification of the mathematical model of the spread of disease that is commonly used, namely the SIR model with assumptions from the model built by Hasnawati (2017) and Kristanti (2020).

$$\frac{dS}{dt} = f_1(S,V,H,R,K)$$
$$\frac{dV}{dt} = f_2(S,V,H,R,K)$$
$$\frac{dH}{dt} = f_3(S,V,H,R,K)$$
$$\frac{dR}{dt} = f_4(S,V,H,R,K)$$
$$\frac{dK}{dt} = f_5(S,V,H,R,K) \qquad (1)$$

Next, the dynamic analysis will be carried out on the model with the following procedure,

a. Determination of the model equilibrium point. The equilibrium point of system (1) is $E = (S^*, V^*, H^*, R^*, K^*)$ which is the solution of system (1) which satisfies $\frac{dS}{dt} = \frac{dV}{dt} = \frac{dH}{dt} = \frac{dR}{dt} = \frac{dK}{dt} = 0$

b. Analysis of the existence of the model equilibrium point. The analysis of the existence of the equilibrium point is a condition given to the equilibrium point to fulfill the interpretation of the model. In this case, because the model describes the total population, the equilibrium point is said to exist if the values of S^*, V^*, H^*, R^* and , , K^* are not negative.

c. Equilibrium point analysis. The behavior of the solution system (1) will be analyzed through the local stability of the equilibrium point. Local stability analysis is carried out by linearizing the system (1) around the equilibrium point based on the following equation,

$$\frac{d}{dt}\vec{w} = J\vec{w} \tag{2}$$

Which $\vec{w} = (S, V, H, R, K) - (S^*, V^*, H^*, R^*, K^*)$ and J is a jacobian matrix at $E = (S^*, V^*, H^*, R^*, K^*)$ as follows,

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial V} & \frac{\partial f_1}{\partial H} & \frac{\partial f_1}{\partial R} & \frac{\partial f_1}{\partial K} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial V} & \frac{\partial f_2}{\partial H} & \frac{\partial f_2}{\partial R} & \frac{\partial f_2}{\partial K} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial V} & \frac{\partial f_3}{\partial H} & \frac{\partial f_3}{\partial R} & \frac{\partial f_3}{\partial K} \\ \frac{\partial f_4}{\partial S} & \frac{\partial f_4}{\partial V} & \frac{\partial f_4}{\partial H} & \frac{\partial f_4}{\partial R} & \frac{\partial f_4}{\partial K} \\ \frac{\partial f_5}{\partial S} & \frac{\partial f_5}{\partial V} & \frac{\partial f_5}{\partial H} & \frac{\partial f_5}{\partial R} & \frac{\partial f_5}{\partial K} \end{pmatrix} \tag{3}$$

The stability of the equilibrium point E is determined by the real part of the eigenvalues of the matrix J. The equilibrium point E is said to be asymptotically stable when all the eigenvalues have negative real parts. The equilibrium point E is said to be stable if all the eigenvalues have a non-positive real part. The equilibrium point E is called unstable if one of the eigenvalues has a positive real part (Alligood, 2000).

After the series of dynamic analyzes were completed, a numerical simulation was performed using the fourth order Runge-Kutta method with MATLAB software.

Analytical results are illustrated using several scenarios presented by selecting parameter values.

RESULTS AND DISCUSSION

The research stages that have been described in the next research method will be presented below

3.1 Construction of Cervical Cancer Model With Treatment

Five subpopulations were built, S is a subpopulation of vulnerable individuals. V represents a subpopulation of vaccinated individuals. H is a subpopulation of individuals infected with the HPV virus, R is a subpopulation of cured individuals, and K is a subpopulation of individuals with cervical cancer. The relationship between subpopulations is illustrated in the following compartment diagram.

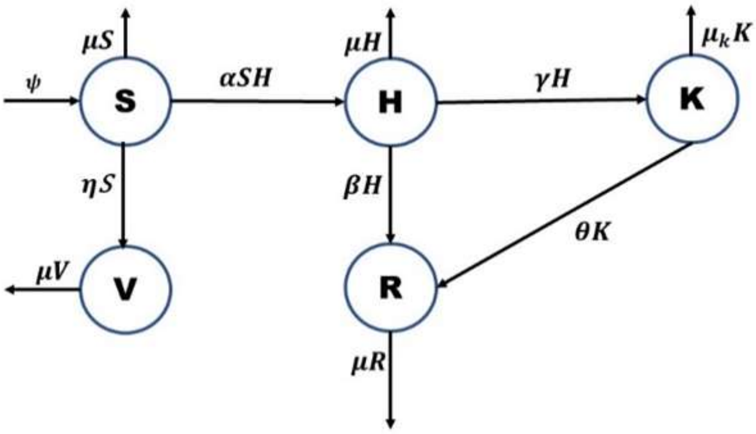

Figure 2. Compartment Diagram of Cervical Cancer Disease Model with Treatment

The birth rate in the population is symbolized by ψ. Newborns are included in the subpopulation of susceptible individuals and reduced by vaccination by η, transmission by infected individuals symbolized by α , and natural death by μ. The probability of an individual being infected with HPV and becoming cervical cancer is symbolized by γ. Individuals infected with HPV will recover with probability β. The subpopulation of cervical cancer patients will recover with treatment, the probability of recovery is θ. The probability of death from cervical cancer is μ_k.

$$\frac{dS}{dt} = \psi - \eta S - \alpha SH - \mu S$$
$$\frac{dV}{dt} = \eta S - \mu V$$
$$\frac{dH}{dt} = \alpha SH - \beta H - \gamma H - \mu H$$
$$\frac{dR}{dt} = \beta H + \theta K - \mu R$$
$$\frac{dK}{dt} = \gamma H - \theta K - \mu_k K \quad (4)$$

3.2 Equilibrium Point

The equilibrium point of the system (4) is obtained when the system is in a steady state condition, that is, $\frac{dS}{dt} = \frac{dV}{dt} = \frac{dH}{dt} = \frac{dR}{dt} = \frac{dK}{dt} = 0$. Two equilibrium points are obtained, that is disease-free equilibrium point E_1 and the endemic equilibrium point E_2.

$$E_1 = \left(\frac{\psi}{\eta + \mu}, \frac{\eta\psi}{(\eta + \mu)\mu}, 0,0,0\right). \quad (5)$$

Equilibrium point $E_2 = (S^*, V^*, R^*, H^*, K^*)$ i.e,

$$S^* = \frac{A}{\alpha} \quad (5a)$$

$$V^* = \frac{\eta A}{\alpha\mu} \quad (5b)$$

$$H^* = \frac{\alpha\psi - \mu A - \eta A}{\alpha A} \quad (5c)$$

$$R^* = \frac{\gamma(\alpha\psi - \mu A - \eta A)(\mu_k\beta + \beta\theta + \gamma\theta)}{\alpha\mu(A\mu_k + A\theta)} \quad (5d)$$

$$K^* = \frac{\gamma(\alpha\psi - \mu A - \eta A)}{\alpha\mu(A\mu_k + A\theta)} \quad (5e)$$

Where A satisfies the following equation,

$$A = \beta + \gamma + \mu \quad (6)$$

The equilibrium point E_1 exists because it has a non-negative value. Meanwhile, the equilibrium point E_2 exists with the following conditions,

$$\alpha\psi > (\mu + \eta)A \quad (7)$$

3.2 Stability Analysis of Equilibrium Point

The Jacobian matrix for system (4) is,

$$J = \begin{pmatrix} -\alpha H - \eta - \mu & 0 & -\alpha S & 0 & 0 \\ \eta & -\mu & 0 & 0 & 0 \\ \alpha H & 0 & \alpha S - \beta - \gamma - \mu & 0 & 0 \\ 0 & 0 & \beta & -\mu & \theta \\ 0 & 0 & \gamma & 0 & -\mu_k - \theta \end{pmatrix}. \quad (8)$$

The Jacobian matrix for equilibrium point E_1 satisfy the following equation,

$$J(E_1) = \begin{pmatrix} -\alpha H - \eta - \mu & 0 & -\alpha S & 0 & 0 \\ \eta & -\mu & 0 & 0 & 0 \\ \alpha H & 0 & \alpha S - \beta - \gamma - \mu & 0 & 0 \\ 0 & 0 & \beta & -\mu & \theta \\ 0 & 0 & \gamma & 0 & -\mu_k - \theta \end{pmatrix}. \quad (9)$$

based on the jacobian matrix (9) the eigenvalues are obtained as follows,

$$\lambda_1^1 = -(\eta + \mu). \quad (10a)$$

$$\lambda_2^1 = \lambda_3^1 = -\mu \quad (10b)$$

$$\lambda_4^1 = \frac{\alpha\psi - \mu A - \eta A}{\alpha A} \quad (10c)$$

$$\lambda_5^1 = -(\mu_k + \theta) \quad (10d)$$

The equilibrium point E_1 will be locally asymptotically stable when all eigenvalues are negative. Based on (10) value of λ_1^1, λ_2^1, $\lambda_3^1, \lambda_4^1 < 0$, but a condition is required for λ_4^1 to be negative. Therefore, the condition for locally asymptotically stable E_1 is $\alpha\psi < (\mu + \eta)A$.

Due to the condition for the existence of the equilibrium point E_2 in equation (7), it can be concluded that the equilibrium point E_2 does not exist when the equilibrium point E_1 is locally asymptotically stable. It can also be determined that the basic reproduction number for this model is, $\frac{\alpha\psi}{(\mu+\eta)A} > 1$.

The Jacobian matrix for the equilibrium point $E_2 = (S^*, V^*, R^*, H^*, K^*)$ is,

$$J(E_1) = \begin{pmatrix} -\frac{\alpha\psi}{A} & 0 & -A & 0 & 0 \\ \eta & -\mu & 0 & 0 & 0 \\ \frac{\alpha\psi - \eta A - \mu A}{A} & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta & -\mu & \theta \\ 0 & 0 & \gamma & 0 & -\mu_k - \theta \end{pmatrix}. \quad (11)$$

based on the jacobian matrix (11) the eigenvalues are obtained as follows,

$$\lambda_1^2 = -(\mu_k + \theta). \quad (11a)$$

$$\lambda_2^2 = \lambda_3^3 = -\mu. \quad (11b)$$

Meanwhile, the eigenvalues λ_3^2 and λ_4^2 satisfy the following equation,

$$A\lambda^2 + B\lambda + C = 0 \quad (11c)$$

Where B, and C are defined as follows,

$$B = \alpha\psi \quad (12)$$

$$C = A^2\left(\mu + \eta - \frac{\alpha\psi}{A}\right) \quad (13)$$

According to the condition of existence of E_2 in (7) then C is negative while B is positive. Thus λ_3^2 and λ_4^2 are positive and negative. It can be concluded that the equilibrium point E_2 is unstable. Equilibrium points, conditions for existence, and conditions for stability are presented in the following table,

Tabel 1. Equilibrium Point Properties

Equilibrium Point	Terms of Existence	Equilibrium Point Properties	Equilibrium Point Stability Conditions
E_1 **(disease free)**	-	Locally Asymptotically Stable	$\alpha\psi < (\mu + \eta)A$
E_2 **(Endemic)**	$\alpha\psi > (\mu + \eta)A$	unstable	-

NUMERICAL ANALYSIS

Numerical simulations are performed to illustratesasasatisfiessults of the system analysis. The initial value is selected $S(0) = 20, V(0) = 5, H(0) = 10, R(0) = 3$ and $K(0) = 8$. The parameters refer to Kristanti (2020) and Hasnawati (2017) so the stability criteria E_1 satisfy $\frac{\alpha\psi}{(\mu+\eta)A} < 1$.

Tabel 2. Parameter Values

ψ	α	η	μ	μ_k	β	γ	θ
0.2	0.01	0.05	0.012	0.01	0.001	0.1	0.003

The simulation results using MATLAB show the total population at the end is $(S, V, H, R, K) = (3, 13, 0, 4, 1)$. The simulation results are presented in the following figure,

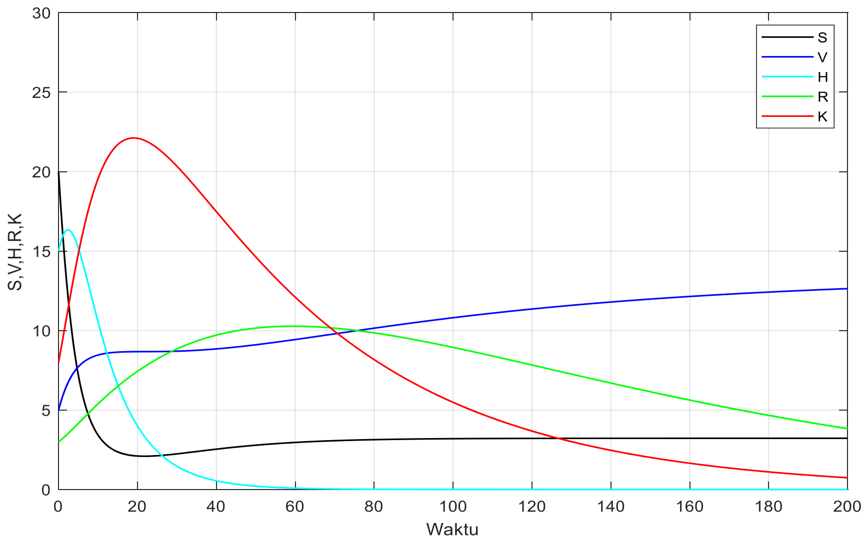

Figure 3. Numerical simulation result for $R_0 < 1$.

It can be interpreted that at one time a disease-free state will be achieved $(H = 0, K = 1)$. Susceptible individuals will decrease as vaccinations are carried out (shown by black and dark blue lines). Cervical cancer sufferers will increase due to a large number of susceptible individuals and individuals infected with HPV (indicated by the red line which initially increased). The effect of treatment seen on the number of cured individuals will increase as the number of cancer patients increases and decrease when the number of cancer sufferers also decreases (shown by the green line). When the number of vaccinated individuals increases, the number of individuals with cervical cancer decreases towards the disease-free point $(K = 1)$. In the end, the largest number of subpopulations was the vaccinated individual subpopulation $(V = 13)$.

CONCLUSION

The cervical cancer model is built by taking into account the individual's chances of recovering if they receive treatment. Dynamic analysis shows the model has a disease-free equilibrium point that is locally asymptotically stable under certain conditions. Based on the simulation results, it is shown that $(S, V, H, R, K) = (3, 13, 0, 4, 1)$ which means in the future the number of individual subpopulations infected with HPV 0, while cervical cancer sufferers will decrease. up to point 1. This is in line with the increasing subpopulation of vaccinated individuals who have the largest number of 13. Therefore, from this study, it can be concluded that the spread of cervical cancer can be controlled with treatment and the number of individuals vaccinated is increasing.

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