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Mathematical Model Analysis of Cervical Cancer Disease with Immunotheraphy

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Abstract

Cervical cancer is one type of disease that has the highest risk of death in the female population in Indonesia. Almost 95% of cervical cancer in women is caused by Human Papillomavirus (HPV) infection, which is common in women of reproductive age. In this study, a mathematical model is discussed for the case of the spread of the HPV virus to become pre-cancerous with immunotheraphy treatment. This research was conducted by building a mathematical model, analyzing the equilibrium point, and interpreting the mathematical model with numerical simulations using Maple software. This study divides the population into 5 sub-populations including susceptible (S), infected (I), precancer (P), and treatment (T) sub-populations. From the model formed, the disease-free equilibrium point and endemic equilibrium point are obtained as well as the basic reproduction number R_0. The disease-free equilibrium point is locally asymptotically stable when $R_0 < 1$ and the endemic equilibrium point is locally asymptotically stable when $R_0 > 1$. Based on the results of numerical simulation analysis, it is obtained that the immunotheraphy treatment (ω) is greatly affects on individual recovery.

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1. Introduction

Cervical cancer is one type of disease that has the second highest risk of death after breast cancer in the female population in Indonesia (Dzulhidayat, 2022). Breast cancer patients are 42.1% per 100000 population while cervical cancer is 23.4% incidence per 100000 population, of which 75% have had sexual intercourse. This cancer has affected more than 1.4 million women worldwide (Suhaid *et al.,* 2022). Almost 95% of cervical cancers in women are caused by the HPV virus. Human Papillomavirus (HPV) infection is common in women of reproductive age. There are two classes of HPV, namely high-risk HPV called oncogenic HPV, namely types 16, 18, and 31, 33, 45, 52, 58, while low-risk HPV or called non-oncogenic HPV such as types 6, 11, 32 (Ministry of Health, 2016).

In general, HPV infection is thought to be transmitted only through sexual intercourse, but HPV can also infect the anogenital region (the area around the anus and genitals). Keep in mind that HPV can be transmitted through skin to skin contact, through fingers, during masturbation and masturbation or through sex toys (Rahayu, 2018). There are about 130 HPV types that have been identified and more than 40 HPV types can infect the male and female genital area, mouth, and throat. In Indonesia, only 5% are screened for cervical cancer, resulting in 76.6% of patients being detected at an advanced stage (Field & Gilson, 2018).

The current cancer treatments when someone has cancer are surgery, radiation therapy, chemotherapy and immunotherapy. Each of these treatments has advantages and disadvantages. For example, chemotherapy has side effects, which in addition to killing tumor cells also kills normal cells and causes several side effects such as nausea, vomiting, abdominal pain, frequent fatigue, reduced hemoglobin, platelets, and white blood cells, easy bleeding, easy infection, hair loss, mouth sores, pain in the body, and decreased fertility (Yanti *et al.,* 2021). For some cancers, the best treatment is done with a combination of surgery, radiation therapy and chemotherapy. Immunotherapy is the latest treatment method for treating cancer that relies on the natural ability of the immune system to recognize and kill tumor cells directly (Ocktariyania, 2024). Immunotherapy has been researched and approved by the United States to treat cancer, after years of testing this method has proven more effective results (Barus & Sanjaya, 2020).

Previously, there have been many studies related to cervical cancer and HPV disease models. Obeng-Denteh *et al.* (2014) previously examined the epidemiological modeling of HPV infection and vaccination and its impact on cervical cancer in Ghana which divides individual compartments into four groups namely Susceptible (S), Infected (I), Temporarily Recovered (R_t), and Permanent Recovered (R_p). Where individuals with three doses of vaccine can become permanently recovered individuals, while giving one or two doses of vaccine still allows them to return to being susceptible or infected individuals (temporarily recovered). Humulogo & Paudi's research (2019) discusses the SIUC model in Cervical Cancer cases by considering vaccination. The analysis carried out is analytically and numerically. Analytical analysis includes determining the disease-free equilibrium point and endemic equilibrium point along with its stability properties. Furthermore, numerical simulations are carried out to test the analytical results. From the numerical simulation results, a graph is obtained which shows that the solution of the system is stable, and it can be shown that vaccination against cervical cancer has a good impact. Aminah & Subhan (2022) studied the mathematical model of cervical cancer with chemotherapy treatment or to determine the effect of chemotherapy on cell growth in cervical cancer. Where the stability analysis is carried out on the fixed point of the model where there are two fixed points. The result of this study is that cervical cancer treatment with chemotherapy is effective enough to kill abnormal cells, although there is a side effect, namely the killing of normal cells.

Previous research conducted by Dadi Gurmu & Rao Koya (2019) was to analyze the impact of chemotherapy and HPV modeling with the SITR method. In the study, a mathematical model of Human Papilloma Virus (HPV) with chemotherapy as treatment was formulated. In particular, the stability analysis of the model was investigated using the basic reproduction number and the Routh Hurwitz criterion. Also, the solution of the model equations was numerically completed and the sensitivity analysis of the model was analyzed. Manaqib *et al.* (2022) studied the $SVICTR$ model to model the transmission of Human Papillomavirus (HPV) in cervical cancer. The analysis was carried out analytically and numerically. The analysis includes determining the disease-free equilibrium point and the endemic equilibrium point as well as its stability properties. Numerical simulation is carried out to provide a geometric picture with results that are in line with the analysis of the model.

Based on previous studies, the author developed a mathematical model of cervical cancer with immunotheraphy treatment. The model built in this study refers to the model used by Gurmu & Koya (2019) by adding cervical pre-cancer variables to the population. Providing treatment to a population of individuals suffering from pre-cancer is used to see its effect on individual recovery.

2. Method

The stages carried out so that the research objectives can be achieved are as follows:

1) Literature study. At this stage several references regarding similar previous research will be reviewed.
2) Make assumptions that support the formation of compartmental diagrams of mathematical models of the spread of HPV infection and cervical pre-cancer and form differential equations of the model.
3) Find the disease equilibrium point and determine the basic reproduction number (R_0) by finding the largest positive eigenvalue of the next generation matrix.

Given a system of equations:

$$\frac{dx}{dt} = F(x,y,z), \frac{dy}{dt} = G(x,y,z), \frac{dz}{dt} = H(x,y,z)$$

then the jacobian matrix J can be written as follows:

$$J = J[F,G,H](x,y,z) = \begin{pmatrix} \frac{\partial F}{\partial x} & \frac{\partial F}{\partial y} & \frac{\partial F}{\partial z} \\ \frac{\partial G}{\partial x} & \frac{\partial G}{\partial y} & \frac{\partial g}{\partial z} \\ \frac{\partial H}{\partial x} & \frac{\partial H}{\partial y} & \frac{\partial H}{\partial z} \end{pmatrix} = \begin{pmatrix} F_x & F_y & F_z \\ G_x & G_y & G_z \\ H_x & H_y & H_z \end{pmatrix}$$

4) Analysis of the stability of the equilibrium point is done by looking at the real value of the eigenvalue of the jacobian matrix that has been formed from the differential equation. If the roots of the characteristic equation are not easily determined, a criterion is needed that ensures that the roots of the characteristic equation are negative or there is a positive characteristic equation. As an alternative to determine the eigenvalues, the Routh-Hurwitz criterion is used. Suppose there is a characteristic equation as follows

$$p(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda^1 + a_n$$

with $n = 1,2,\ldots,i$ which are real numbers. Define n Hurwitz matrices using the a_i coefficients of the characteristic polynomial:

$$H_1 = (a_1), H_2 = \begin{pmatrix} a_1 & a_0 \\ a_3 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \ldots,$$

$$H_n = \begin{pmatrix} a_1 & a_0 & 0 & 0 & \ldots & 0 \\ a_3 & a_2 & a_1 & a_0 & \ldots & 0 \\ a_5 & a_4 & a_3 & a_2 & \ldots & 0 \\ a_7 & a_6 & a_5 & a_4 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{2n-1} & a_{2n-2} & a_{2n-3} & a_{2n-4} & \ldots & a_n \end{pmatrix}$$

If the determinants of $H_1, H_2, \ldots, H_n$ obtained are positive, then it is certain that all the roots of the characteristic equation $P(\lambda)$ have negative real values.

5) Numerical simulation is carried out using the Maple program which aims to compare the suitability between the results of the model equilibrium point analysis and its numerical simulation.
6) Drawing conclusions from the results and discussion on the problem solving steps that have been carried out previously in accordance with the objectives to be achieved.

3. Results and Discussions

3.1. Model Formulation

In the formation of this model is limited by several assumptions. The assumptions used in the model of the spread of HPV infection and cervical cancer with immunotheraphy treatment are as follows:

1) Population is assumed to be constant.
2) Cervical cancer is a dangerous disease that if infected can cause death, so precencer class deaths occur due to natural death and due to suffering from cervical cancer.
3) Each individual is assumed to be a vulnerable individual.
4) individuals who come into contact with infected individuals will enter the infection class.
5) HPV infected individuals will become individuals with precancerous lesions.
6) Every precancerous Individual will be treated with immunotheraphy.
7) Individuals who have received treatment are assumed to be in the recovery class.
8) Recovered individuals are assumed to relapse, so recovered individuals return to the susceptible class after losing immunity.
9) All individuals are subject to natural death.

The mathematical model that is formed divides the population into 5 sub-populations, namely susceptible (S), infected sub-population (I), precencered sub-population (P), treatment sub-population (T) with immunoteraphy, and recovered sub-population (R). Explanation of Variables and Parameters that will be used in the Human Papillomavirus (HPV) transmission model in cervical cancer disease will be presented in Table 1 and Table 2 below.

Table 1 Variable notation and description

Variable Symbols	Description	Condition
$S(t)$	Number of susceptible individuals at time t	$S(t) \geq 0$
$I(t)$	Number of individuals infected with Human Papilloma Virus (HPV) at time t	$I(t) \geq 0$
$P(t)$	Number of individuals with cervical pre-cancer at time t	$P(t) \geq 0$

$T(t)$	Number of individuals treated with immunotheraphy at time t	$T(t) \geq 0$
$R(t)$	Number of individuals who have recovered after receiving treatment	$R(t) \geq 0$
$N(t)$	Population size of the individual at time t	$N(t) \geq 0$

Table 2 List of model parameters

Parameter Symbols	Description	Condition
π	Natural birth rate	$\pi > 0$
β	Infection transmission rate	$\beta \geq 0$
α	The rate at which infected individuals develop into precancerous ones	$\alpha \geq 0$
ω	Rate of individuals receiving treatment	$\omega \geq 0$
δ	Recovery rate	$\delta \geq 0$
φ	Rate of individuals who become vulnerable again after recovery	$\varphi \geq 0$
μ	Natural mortality rate	$\mu \geq 0$
γ	Cervical cancer death rate	$\gamma \geq 0$

The diagram of the mathematical model of HPV transmission that develops into cervical pre-cancer with immunotheraphy treatment can be can be depicted in Figure 1.

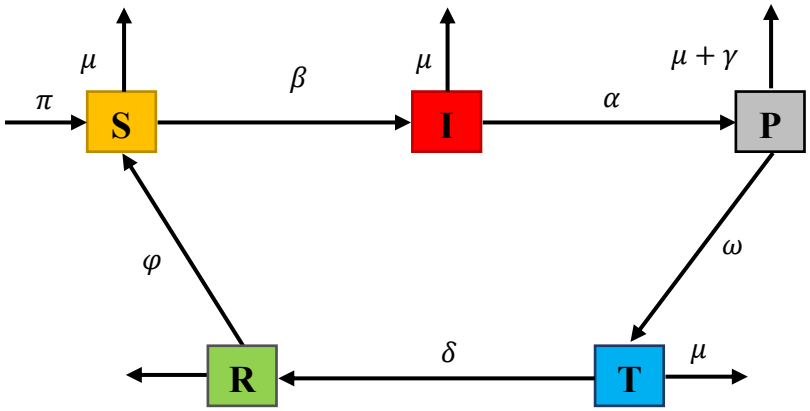


Figure 1 Transmission diagram of mathematical model

Based on the diagram in Figure 1, a mathematical model is obtained which is formulated in the following System of Equations (1):

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \mu S - \left(\frac{\beta IS}{N}\right) + \varphi R \\
\frac{dI}{dt} &= \left(\frac{\beta IS}{N}\right) - (\alpha + \mu +)I \\
\frac{dP}{dt} &= \alpha I - (\mu + \gamma + \omega)P \\
\frac{dT}{dt} &= \omega P - (\delta + \mu)T \\
\frac{dR}{dt} &= \delta T - (\varphi + \mu)R
\end{aligned} \tag{1}$$

values $S \geq 0, I \geq 0, P \geq 0, T \geq 0$, and $R \geq 0$. The total population (N) can be written as follows $N = S + I + P + T + R$, and it is known that

$$\frac{dN}{dt} = (\pi - \mu)N - \gamma P$$

Furthermore, in this study, a simplification of the model was carried out by setting the assumption that the natural birth rate (π) is equal to the natural death rate (μ) so that $\pi = \mu = 0$, and the death rate due to cervical cancer is also assumed to be $\gamma = 0$, so that the following is obtained

$$\frac{dN}{dt} = 0$$

Thus it is known that $N(t) = a$, for a is a positive integer because $N(t)$ is constant.
The system of Equation (1) can then be simplified by expressing each sub-population by calculating the proportion for each sub-population, where the proportion is expressed as follows:

$$\frac{S}{N} = s, \frac{I}{N} = i, \frac{P}{N} = p, \frac{T}{N} = z, \frac{R}{N} = r$$

And obtained

$$s + i + p + z + r = \frac{S}{N} + \frac{I}{N} + \frac{P}{N} + \frac{T}{N} + \frac{R}{N} = \frac{N}{N} = 1$$

So that the System of Equations (1) becomes

$$\begin{aligned}
\frac{ds}{dt} &= \pi - \mu s - \beta i s + \varphi r \\
\frac{di}{dt} &= \beta i s - (\alpha + \mu) i \\
\frac{dp}{dt} &= \alpha i - (\mu + \gamma + \omega) p \\
\frac{dz}{dt} &= \omega p - (\delta + \mu) z \\
\frac{dr}{dt} &= \delta z - (\varphi + \mu) r
\end{aligned} \qquad (2)$$

3.2. Model Equilibrium Points

The equilibrium point of the model is obtained when the system is in an equilibrium state. The condition when the change in the number of individuals in each population over time is zero is called the equilibrium state. Therefore, the equilibrium point of the model is obtained when the system $\frac{ds}{dt} = \frac{di}{dt} = \frac{dp}{dt} = \frac{dz}{dt} = \frac{dr}{dt} = 0$. Furthermore, the disease-free equilibrium point is obtained by solving equation (2) with $i = 0$ so that it is obtained:

$E_0 = (s_0, i_0, p_0, z_0, r_0)$, dengan $E_0 = \left(\frac{\pi}{\mu}, 0,0,0,0\right)$

Then next look for the endemic equilibrium point (E^*) with $i \neq i$ and $s = \frac{\alpha+\beta}{\mu}$, then the following results are obtained $E\hat{}* = (s^*, i^*, p^*, z^*, r^*)$ with,

$$\begin{aligned}
s^* &= \frac{\alpha + \mu}{\beta} \\
i^* &= \frac{\big(\beta\pi - \mu(\alpha + \mu)\big)(\mu + \gamma + \omega)(\delta + \mu)(\varphi + \mu)}{\beta((\alpha + \mu)(\mu + \gamma + \omega)(\delta + \mu)(\varphi + \mu) - \varphi\delta\omega\alpha)} \\
p^* &= \frac{\alpha i}{(\mu + \gamma + \omega)} \\
z^* &= \frac{\alpha i \omega}{(\mu + \gamma + \omega)(\delta + \mu)} \\
r^* &= \frac{\delta\omega\alpha i}{(\mu + \gamma + \omega)(\delta + \mu)(\varphi + \mu)}
\end{aligned}$$

3.3. Basic Reproduction Number

The calculation of the basic reproduction number is obtained by finding the largest positive eigenvalue of the next generation matrix involving the equation of the infected individual subpopulation, the precancerous individual subpopulation and the treatment individual subpopulation. The first thing to do is to linearize the disease-free equilibrium point with the Jacobi matrix.

$$J = \begin{pmatrix}
\frac{\partial\left(\frac{di}{dt}\right)}{\partial i} & \frac{\partial\left(\frac{di}{dt}\right)}{\partial p} & \frac{\partial\left(\frac{di}{dt}\right)}{\partial z} \\
\frac{\partial\left(\frac{dp}{dt}\right)}{\partial i} & \frac{\partial\left(\frac{dp}{dt}\right)}{\partial p} & \frac{\partial\left(\frac{dp}{dt}\right)}{\partial z} \\
\frac{\partial\left(\frac{dz}{dt}\right)}{\partial i} & \frac{\partial\left(\frac{dz}{dt}\right)}{\partial p} & \frac{\partial\left(\frac{dz}{dt}\right)}{\partial z}
\end{pmatrix}$$

$$J(E_0) = \begin{pmatrix} \beta s_0 - (\alpha+\mu) & 0 & 0 \\ \alpha & -(\mu+\gamma+\omega) & 0 \\ 0 & \omega & -(\delta+\mu) \end{pmatrix}$$

Furthermore, by performing decomposition, the following transmission matrix F and transmission matrix V are obtained,

$$F = \begin{pmatrix} \beta s_0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (\alpha+\mu) & 0 & 0 \\ -\alpha & (\mu+\gamma+\omega) & 0 \\ 0 & -\omega & (\delta+\mu) \end{pmatrix}$$

Then the eigenvalue of FV^{-1} is calculated by using the equation $\det(\lambda I - FV^{-1}) = 0$. The eigenvalues of FV^{-1} matrix are $\lambda_{1,2} = 0$ and $\lambda_3 = \frac{\beta s_0}{(\alpha+\mu)}$. Since the value of the basic reproduction number is obtained from the largest eigenvalue of FV^{-1}, the value of the basic reproduction number (R_0) is obtained:

$$R_0 = \frac{\beta s_0}{(\alpha+\mu)}$$

Theorem 3.1

We have $R_0 = \frac{\beta s_0}{(\alpha+\mu)}$

Based on the System of Equations (2), two equilibrium points are obtained, namely:

(1) Disease-free equilibrium point $E_0 = (s_0, i_0, p_o, z_0, r_0)$ with $E_0 = \left(\frac{R_0(\alpha+\mu)}{\beta}, 0,0,0,0\right)$

The point E_0 exists in the state $R_0 < 1$ or $R_0 > 1$.

(2) Endemic equilibrium point $E^* = (s^*, i^*, p^*, z^*, r^*)$, with:

$$s^* = \frac{\alpha+\mu}{\beta}$$

$$i^* = \frac{(R_0-1)(\mu+\gamma+\omega)(\delta+\mu)(\varphi+\mu)\pi}{R_0\left((\alpha+\mu)(\mu+\gamma+\omega)(\delta+\mu)(\varphi+\mu)-\varphi\delta\omega\alpha\right)}$$

$$p^* = \frac{\alpha(R_0-1)(\delta+\mu)(\varphi+\mu)\pi}{R_0((\alpha+\mu)(\mu+\gamma+\omega)(\delta+\mu)(\varphi+\mu)-\varphi\delta\omega\alpha)}$$

$$z^* = \frac{\omega\alpha\pi(R_0-1)(\varphi+\mu)}{R_0((\alpha+\mu)(\mu+\gamma+\omega)(\delta+\mu)(\varphi+\mu)-\varphi\delta\omega\alpha)}$$

$$r^* = \frac{\delta\omega\alpha\pi(R_0-1)}{R_0((\alpha+\mu)(\mu+\gamma+\omega)(\delta+\mu)(\varphi+\mu)-\varphi\delta\omega\alpha)}$$

The point E^* exists in the state $R_0 > 1$.

3.4. Equilibrium Points Stability

3.4.1. Stability of Disease-Free Equilibrium Point

To see the stability of the equilibrium point, the nonlinear equation is linearized. The linearization process around $E_{0=\left(\frac{R_0(\alpha+\mu)}{\beta},0,0,0,0\right)}$ produces the following Jacobi matrix

$$J(E_0) = \begin{pmatrix} -\mu & \beta s_0 & 0 & 0 & \varphi \\ 0 & \beta s_0 - (\alpha+\mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu+\gamma+\omega) & 0 & 0 \\ 0 & 0 & \omega & -(\delta+\mu) & 0 \\ 0 & 0 & 0 & \delta & -(\varphi+\mu) \end{pmatrix}$$

Next, we will find the eigenvalues of matrix $J(E_0)$ by using the characteristic equation $0 = \det(\lambda I - J(E_0))$, so the following characteristic equation is obtained

$$(\lambda+\mu)(\lambda-\beta s_0+(\alpha+\mu))(\lambda+(\mu+\gamma+\omega))(\lambda+(\delta+\mu))(\lambda+(\varphi+\mu)) = 0$$

The eigenvalues obtained are

$$\lambda_1 = -\mu, \lambda_2 = \beta s_0 + (\alpha+\mu), \lambda_3 = -(\mu+\gamma+\omega), \lambda_4 = -(\delta+\mu), \text{ dan } \lambda_5 = -(\varphi+\mu)$$

The equilibrium point E_0 is locally asymptotically stable if all eigenvalues are negative. It is obvious that λ_1, λ_3, λ_4, and $\lambda_5$are negative since all parameters are positive. With $R_0 = \frac{\beta s_0}{(\alpha+\mu)}$, the value λ_2 can be changed to $\lambda_2 = (R_0-1)(\alpha+\mu)$ so that λ_2 is also negative when $R_0 < 1$. It can be concluded that all the real parts of the eigenvalues are negative when $R_0 < 1$, so the disease-free equilibrium point is locally asymptotically stable when$R_0 < 1$.

3.4.2. Stability of the Endemic Equilibrium Point

The linearization result around E^* produces the following Jacobi matrix.

$$J(E^*) = \begin{pmatrix} -\mu - \beta i^* & \beta s^* & 0 & 0 & \varphi \\ \beta i^* & \beta s^* - (\alpha + \mu) & 0 & 0 & 0 \\ 0 & 0 & -(\mu + \gamma + \omega) & 0 & 0 \\ 0 & 0 & \omega & -(\delta + \mu) & 0 \\ 0 & 0 & 0 & \delta & -(\varphi + \mu) \end{pmatrix}$$

The characteristic equation $(\lambda + \varphi + \mu)(\lambda + \delta + \mu)[(\lambda + \mu + \gamma + \omega)\big((\lambda + \mu + \beta i^*)(\lambda) - \beta i^*(\alpha + \mu)\big] = 0$. Thus, the eigenvalues $\lambda_1 = -(\varphi + \mu)$ dan $\lambda_2 = -(\delta + \mu)$ are obtained. It is clear that λ_1 and λ_2 are negative because all parameters are positive. The other eigenvalues can be determined by the following third degree equation $a_0\lambda^3 + a_1\lambda^2 + a_2\lambda^1 + a_3\lambda^0 = 0$.

Based on the Routh-Hurwitz criterion, it is shown that$a_0 > 0$, $a_1 > 0$, $a_2 > 0, a_3 > 0,$ and $a_1a_2 - a_3 > 0$ jika $R_0 > 1$. So it can be concluded that all real parts of the eigenvalues are negative and the endemic equilibrium point is locally asymptotically stable.

3.5. Equilibrium Points Stability

Simulation of the mathematical model of cervical cancer disease with immunotheraphy was carried out using Maple software. Simulations were conducted on the disease-free equilibrium point (E_0) and the endemic equilibrium point (E^*). To determine the effect of immunotheraphy on the population of individuals with precancer is done by making variations of the value of ω, with the fastest time of treatment after diagnosis is one week so that the limit of $\omega = \frac{1}{7\ days} = 0142$. Therefore, the variation of $\omega = 0.142, 0.0714, 0.047, 0.035$. This study will be analyzed with the parameter values shown in Table 3 and the initial values shown in Table 4.

Table 3 Parameter values in numerical simulation

Parameters	Description	Value	Source
π	Natural birth rate	0.0167	(Badan Pusat Statistik, 2024)
μ	Natural mortality rate	0.0167	Assumption
β	Infection rate	0.3	(Dadi Gurmu & Rao Koya, 2019)
α	Rate of individuals with pre-cancerous lesions	0.473	(Shaban & Mofi, 2014)
γ	Cervical pre-cancer death rate	0	Assumption
ω	Rate of individuals receiving care	$0 \leq \omega \leq 1$	Assumption
δ	The rate of individuals who have recovered	0.0238	(Cancer Research UK, 2023)
φ	The rate at which susceptible individuals return	0.0013	(Cancer *Treatment* Centers, 2022)

Table 4 Initial value of variables in the model

Variables	Value	Source
$s(t)$	0.7	(Manaqib et al., 2022)
$i(t)$	0.13	(Manaqib et al., 2022)
$p(t)$	0.08	Assumption
$z(t)$	0.05	Assumption
$r(t)$	0.04	Assumption

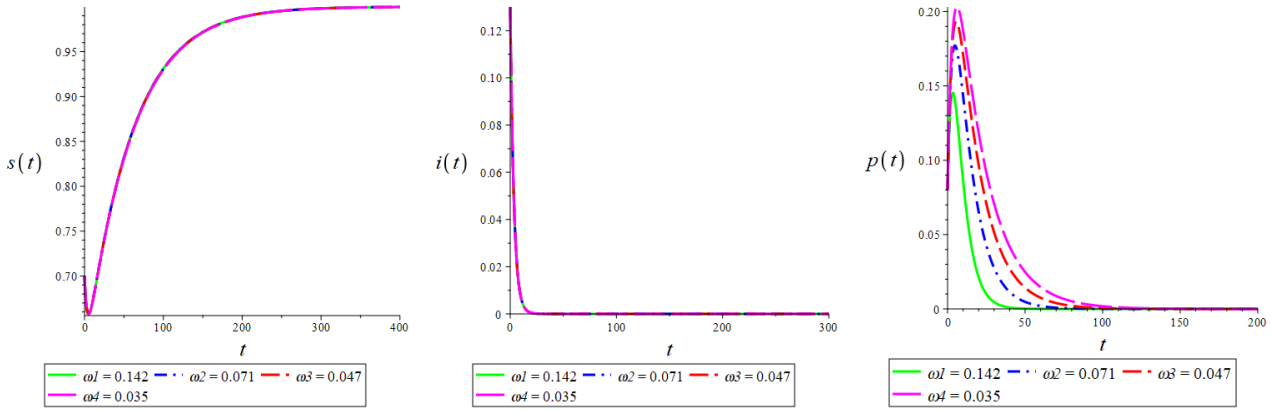
3.5.1. Simulation at Disease-Free Equilibrium Point

Numerical simulation with the above parameter values results in a basic reproduction number of $R_0 = 0.6126$. Since $R_0 < 1$, the disease will disappear from the population in a certain period of time. To determine the effect of immunotheraphy treatment, the variation of ω value can be seen in Table 5.

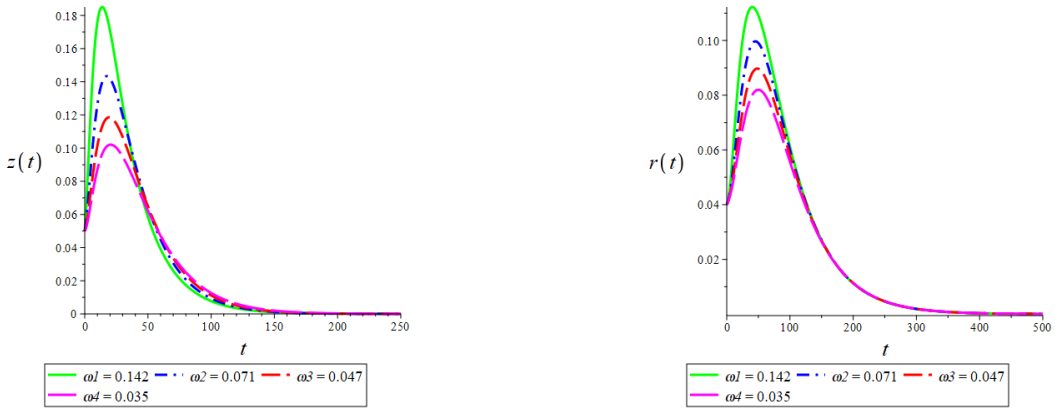
Table 4 Value of $R_0 < 1$ and variation of $\omega \leq 0.142$

ω	R_0	Equilibrium Point $(s^*, i^*, p^*, z^*, r^*)$
0.142	0.6126	(1,0,0,0,0)
0.071	0.6126	(1,0,0,0,0)
0.047	0.6126	(1,0,0,0,0)
0.035	0.6126	(1,0,0,0,0)

The following are the results of the analysis of changes in the ω value shown in Figure 2.



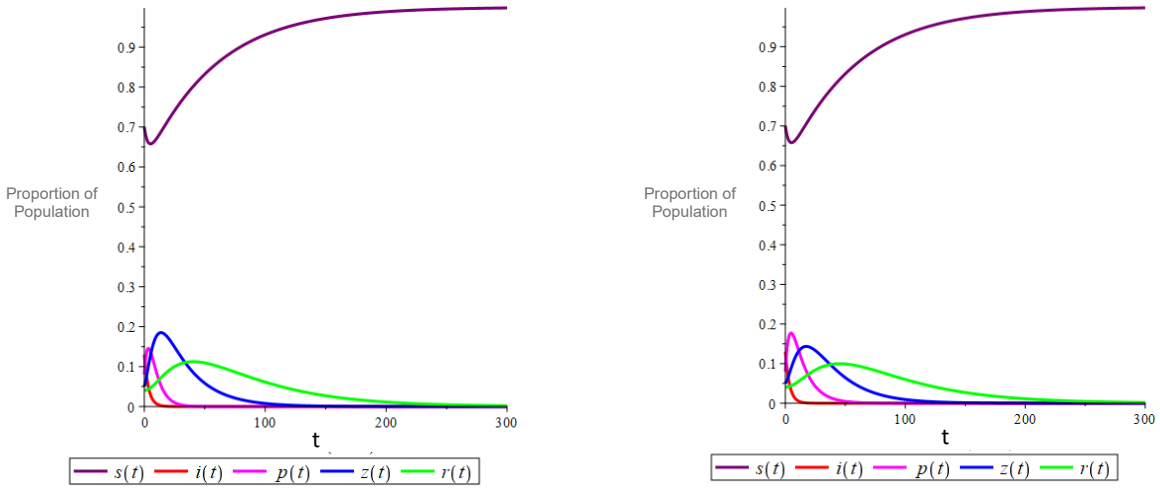
a. Graph of s class against t b. Graph of i class against t c. Graph of p class against t



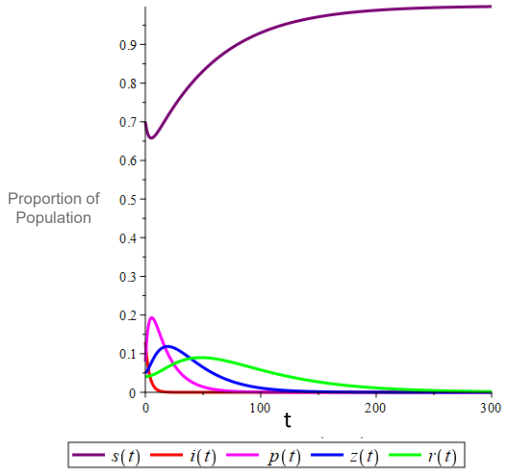
d. Graph of z class against t e. Graph of r class against t

Figure 2 Graph of population size dynamics (a) s(t), (b) i(t), (c) p(t), (d) z(t) (e) r(t) against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$

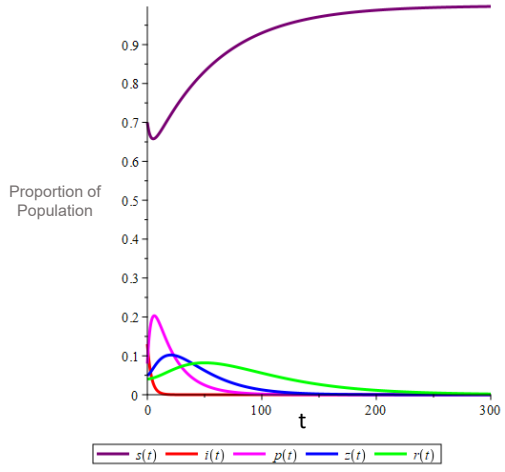
To find out the difference in population size of classes $s(t), i(t), p(t), z(t), r(t)$ against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$ can be seen in Figure 3.



a. Graph of s, i, p, z, r classes with $\omega = 0.142$ b. Graph of s, i, p, z, r classes with $\omega = 0.071$



c. Graph of s, i, p, z, r classes with $\omega = 0.047$



d. Graph of s, i, p, z, r classes with $\omega = 0.035$

Figure 3 Graph of population proportion s, i, p, z, r against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$

Figure 2 and Figure 3 show that all populations stabilize at the point $(1,0,0,0,0)$ at time t. Then with the immunotheraphy treatment on individuals who have precancer (ω) has an influence on the recovery of individuals. Initially, susceptible individuals (s) decreased due to natural death and no transfer to the infection class so that the population of HPV-infected individuals (i) immediately decreased from the initial condition due to the natural death of individuals and the transfer of the population of infected individuals (i) to the precancer class (p), which resulted in the population in the precancer class (p) increasing. Furthermore, the population of individuals with precancer (p) decreased due to the natural death of individuals, death due to disease, and the movement of individuals undergoing immunotheraphy treatment (z), this resulted in the population of individuals in the treatment class (z) increasing. The decrease in the treatment population (z) is due to the natural death of individuals and individuals who undergo immunotheraphy treatment have recovered so that the population of individuals who have recovered (r) has increased. The population of individuals in the recovery class (r) decreases due to the natural death of individuals and individuals who have recovered lose immunity so that individuals become susceptible again (s). Variations in the value of ω have an influence on the population size of precancer (p), immunotheraphy treatment (z), and recovery (r). A higher value of ω causes the precancer population (p) to decrease quickly after the peak because more individuals move to the treatment stage, so that the population of individuals in the treatment class (z) increases in the initial time condition and decreases after the peak which results in the population of individuals in the recovery class (r) also increasing. Whereas a smaller value of ω causes the population of precancerous individuals (p) to last longer and the increase in individuals is higher because fewer individuals move to the treatment class (z), so the increase in the population of individuals undergoing immunotheraphy treatment (z) becomes longer and not too high. Since there are not many individuals undergoing treatment, the population of recovered individuals (r) also lasts longer and only increases slightly.

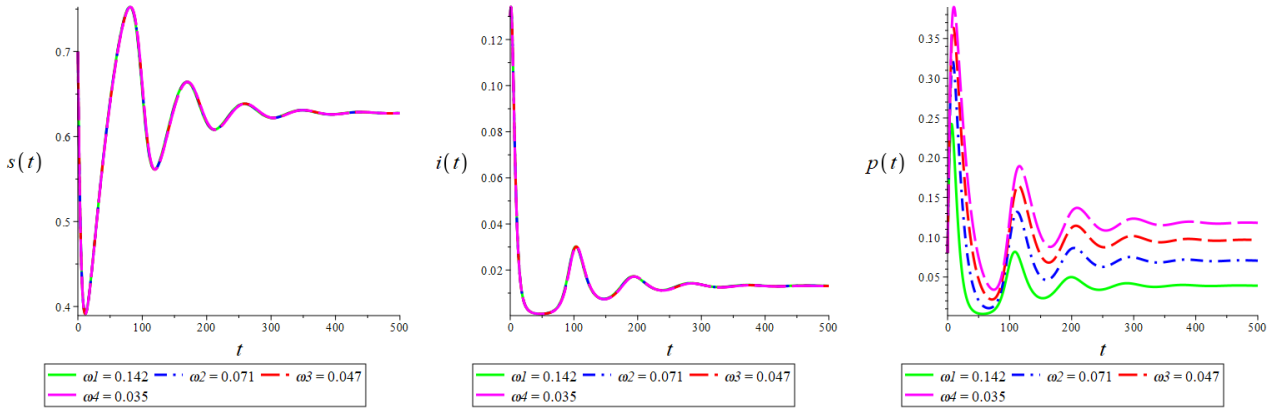
3.5.2. Simulation at the Endemic Equilibrium Point

Simulations at the endemic equilibrium point were carried out by making the value of the parameter β enlarged 2.66 times from the initial value to $\beta = 0.78$ (Manaqib *et al*., 2022). And make variations in the parameter ω to determine the effect of immunotheraphy treatment on individuals with precancer. The variation of ω parameter value can be seen in Table 6 below.

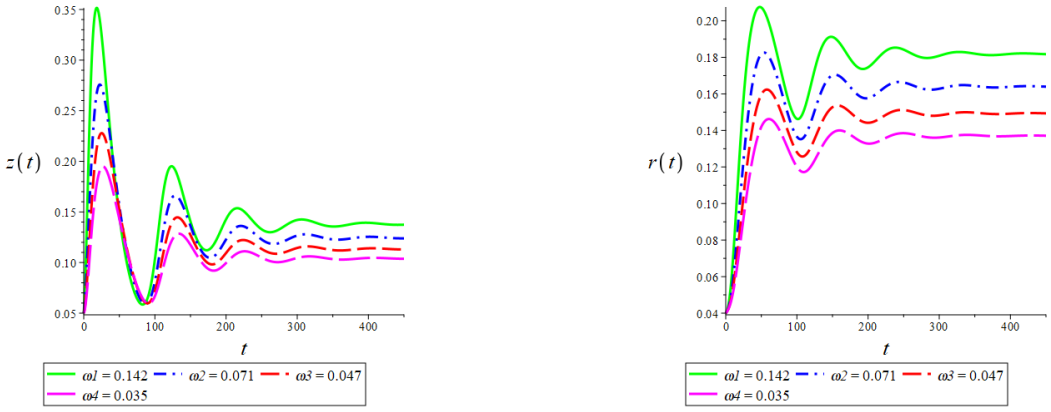
Table 6 $R_0 > 1$ and variation $\omega \leq 0.142$ with $\beta = 0.78$

$\boldsymbol{\omega}$	$\boldsymbol{R_0}$	**Equilibrium Point** $(\boldsymbol{s^*, i^*, p^*, z^*, r^*})$
0.142	1.592	$(0.627, 0.013, 0.039, 0.138, 0.181)$
0.071	1.592	$(0.627, 0.013, 0.070, 0.124, 0.163)$
0.047	1.592	$(0.627, 0.013, 0.096, 0.113, 0.149)$
0.035	1.592	$(0{,}627, 0.013, 0.117, 0.104, 0.137)$

Here are the simulation results with the variation of ω value for $R_0 > 1$ as shown in Figure 4.



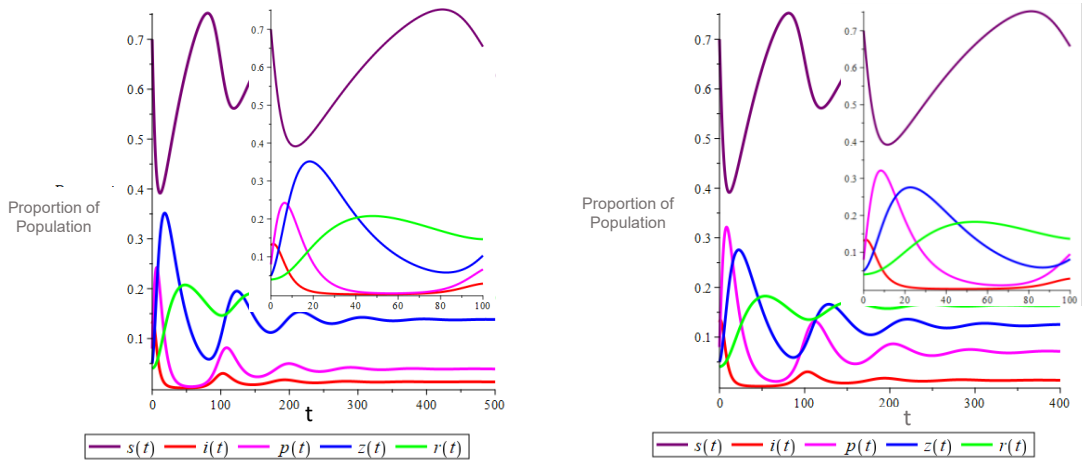
a. Graph of s class against t b. Graph of i class against t c. Graph of p class against t



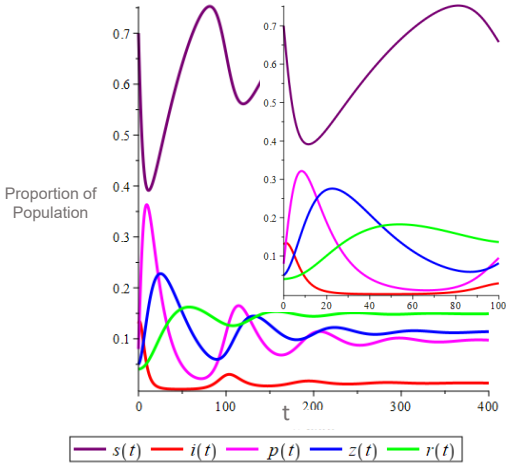
d. Graph of z class against t e. Graph of r class against t

Figure 4 Graph of population size dynamics$(a)\ s(t), (b)\ i(t), (c)\ p(t), (d)\ z(t)\ (e)\ r(t)$ against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$

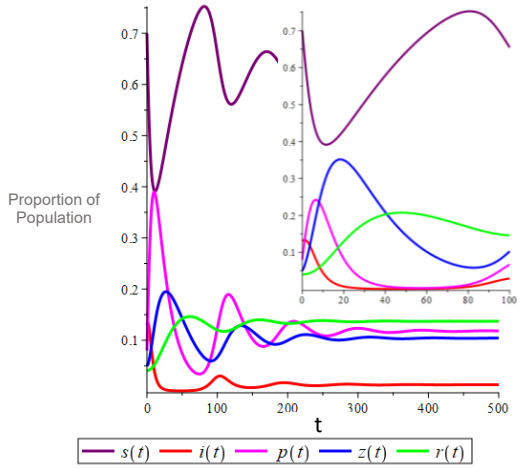
To find out the difference in the number of populations of $(t), i(t), p(t), z(t), r(t)$ classes against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$ can be seen in Figure 5.



a. Graph of s, i, p, z, r class with $\omega = 0.142$ b. Graph of s, i, p, z, r class with $\omega = 0.071$



c. Graph of s, i, p, z, r class with $\omega = 0.047$



d. Graph of s, i, p, z, r class with $\omega = 0.035$

Figure 5 Graph of population proportion ofs, i, p, z, r against time t with $\omega = 0.142, 0.0714, 0.047, 0.035$

Figure 5 shows that all populations experience fluctuations in initial conditions and become stable at a certain time t. Then with the immunotheraphy treatment for individuals with precancer (ω), it has an influence on the recovery of individuals. Then with the immunotheraphy treatment on individuals with precancer (ω) has an influence on the recovery of individuals. Initially, susceptible individuals (s) decreased due to natural deaths and movement to the infected class (i), this resulted in an increase in the population of infected individuals (i). The increase in the population of susceptible individuals (s) occurs due to the birth of new individuals into the population. HPV-infected individuals (i) decreased due to the natural death of individuals and the movement of the population of infected individuals (i) to the precancer class (p), which resulted in the population in the precancer class (p) increasing. Furthermore, the population of individuals with precancer (p) decreases due to the natural death of individuals, death due to disease, and the movement of individuals undergoing immunotheraphy treatment (z), this results in the population of individuals in the treatment class (z) increasing.The decrease in the treatment population (z) is due to the natural death of individuals and individuals who undergo immunotheraphy treatment have recovered so that the population of individuals who have recovered (r) has increased. The population of individuals in the recovery class (r) decreases due to the natural death of individuals and individuals who have recovered lose immunity so that individuals become susceptible again (s) but this is so unlikely that it is not visible in the graph. Variations in the value of ω have a significant impact on the population size of precancer (p), treatment immunotheraphy (z), and recovery (r). Higher values of ω such as $\omega 1$ cause the precancer population (p) to rapidly decrease after the peak as more individuals move to the treatment stage, so the population of individuals in the treatment class (z) increases significantly in the initial time conditions and decreases after the peak which results in the population of individuals in the recovery class (r) also increasing. Whereas a smaller value of ω such as ω4 causes the population of precancerous individuals (p) to last longer and the increase in individuals is higher because fewer individuals move to the treatment class (z), so the increase in the population of individuals who undergo immunotheraphy treatment becomes longer and not too high. Since there are not many individuals undergoing treatment, the population of recovered individuals (r) is also longer and has only a slight increase

4. Conclusion

The simulation analysis of the mathematical model of cervical cancer with immunotheraphy treatment shows the same results as the analysis. Based on the analysis, the basic reproduction number $R_0 = \frac{\beta\pi}{\mu(\alpha+\mu)}$ is obtained. The disease-free equilibrium point will be asymptotically stable if $R_0 < 1$ while the endemic equilibrium point will be asymptotically stable if $R_0 > 1$. The model simulation results show that the spread of HPV virus and cervical cancer will disappear from the population if $R_0 < 1$ and the disease will persist and increase when $R_0 > 1$. Then the rate of individuals undergoing immunotheraphy treatment (ω) affects the recovery of individuals where the higher the value of ω, the disease will decrease quickly and towards the stability point so that many individuals recover. Conversely, a smaller value of ω causes the disease to last longer and the increase in individuals infected and suffering from cervical cancer is higher because fewer individuals undergo treatment so that individuals who recover will also be longer.

References

Aminah, S., & Subhan, M. (2022). Model Matematika Penyebaran Penyakit Kanker Serviks dengan Pengobatan Kemoterapi. *Journal of Mathematics UNP*, *7*(3), 110. https://doi.org/10.24036/unpjomath.v7i3.12725

Badan Pusat Statistik. (2024). *Jumlah Penduduk Pertengahan Tahun (Ribu Jiwa), 2022-2024*.

Barus, O. P., & Sanjaya, T. (2020). *Prediksi Tingkat Keberhasilan Pengobatan Kanker Menggunakan Imunoterapi Dengan Metode Naive Bayes*. *5*(1), 1–6.

Cancer Research UK. (2023). *After your treatment for abnormal cervical cells*.

Cancer Treatment Centers. (2022). *Cervical Cancer Stage*.

Dadi Gurmu, E., & Rao Koya, P. (2019). Sensitivity Analysis and Modeling the Impact of Screening on the Transmission Dynamics of Human Papilloma Virus (HPV). *American Journal of Applied Mathematics*, *7*(3), 70. https://doi.org/10.11648/j.ajam.20190703.11

Dzulhidayat. (2022). Edukasi kesehatan tentang deteksi dini kanker serviks di desa cibadung, gunung sindur, bogor dora. *Jurnal Kreativitas Pengabdian Kepada Masyarakat (Pkm)*, *5*(8.5.2017), 2243–2258.

Field, N., & Gilson, R. (2018). Human Papillomavirus (HPV). Case Studies in Infection Control, 101–111. https://doi.org/10.1201/9780203733318-9

Kemenkes. (2016). *Kenali Gejala Kanker Serviks Sejak Dini*.

Manaqib, M., Fauziah, I., & Asih, W. T. (2022). Model Matematika Transmisi Human Papillomavirus (Hpv) Pada Penyakit Kanker Serviks. *Jurnal Matematika UNAND*, *11*(4), 230. https://doi.org/10.25077/jmua.11.4.230-245.2022

Obeng-Denteh, W., Afrifa, R., Barnes, B., & Addo, K. (2014). Modeling the Epidemiology of Human Papilloma Virus Infection and Vaccination and Its Impact on Cervical Cancer in Ghana. *Journal of Scientific Research and Reports*, *3*(19), 2501–2518. https://doi.org/10.9734/jsrr/2014/11019

Ocktariyana, O., Haq, N. A., Mahdalena, V., Fertilita, S., Amanda, A. I. E., Purnamasari, S., & Yusuf, K. (2024). Potensi Imunoterapi untuk Pengobatan Kanker Serviks: sebuah ulasan nasrasi: The Potential of Immunotherapy for the Treatment of Cervical Cancer: A Narrative review. *JURNAL CENDIKIA SAINS MEDIKA*, *1*(1), 18-25.

Rahayu, A. S. (2018). Inveksi Human Papilloma Virus (HPV) dan Pencegahannya pada Remaja dan Dewasa Muda. *Jurnal Biologi Papua*, *2*(2), 81–87. https://doi.org/10.31957/jbp.564

Shaban, N., & Mofi, H. (2014). Modelling the impact of vaccination and screening on the dynamics of human papillomavirus infection. *International Journal of Mathematical Analysis*, *8*(9–12), 441–454. https://doi.org/10.12988/ijma.2014.312302

Suhaid, D. N., Wardani, D. W. K. K., Aningsih, B. S. D., Manungkalit, E. M., & Kusmiyanti, M. (2022). Deteksi Dini Kanker Serviks Dan Payudara Dengan Pemeriksaan IVA Serta Sadanis di Perumahan Kartika Sejahtera Kelurahan Sasak Panjang Kecamatan Tajur Halang Kabupaten Bogor Jawa Barat. *Jurnal Kreativitas Pengabdian Kepada Masyarakat (Pkm)*, *5*(2), 406–413. https://doi.org/10.33024/jkpm.v5i2.4630

Yanti, E., Harmawati, H., Irman, V., & Dewi, R. I. S. (2021). Peningkatan Kesiapan Pasien Kanker Menjalani Kemoterapi. *Jurnal Abdimas Saintika*, *3*(1), 85-88.