



Modeling the Epidemiology of Human Papilloma Virus Infection and Vaccination and Its Impact on Cervical Cancer in Ghana

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

This paper is purported to assess the impact of the modeling of bivalent Human Papillomavirus (HPV) vaccine and Pap test on prevalence of carcinogenic HPV 16/18 types in Ghanaian females. For this purpose, a non-linear dynamic *SIR* model of homogeneous transmission for HPV 16/18 type's infection is developed, which accounts for immunity due to vaccination in particular. The recovery class *R* was partitioned into two compartments, temporary recovery R_T and permanent recovery R_p . We propose ODE equations to study HPV infection in the general female population. The vaccinated reproduction number R_0 for general female population was derived using the approach described by Diekmann (2010) called the Next Generation Operator approach. The proposed models were analyzed using quantitative method, with regard to steady-state stability and sensitivity analysis. Precisely, the stability of the models is investigated depending on the value for R_0 for the disease free steady-state and Routh-Hurwitz criterion employed to study the stability of the endemic steady-state. Prevalence data are used to fit a numerical HPV model, so as to assess infection rates. We also support our theoretical analysis with numerical simulations. This provides a framework for future

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research and public-health policy to determine the dependence of HPV vaccination programs on age, as well as how the vaccine and Pap test can reduce the number of infections and deaths due to cervical cancer. We estimated the basic reproductive number for the general female population based on current vaccination statistics using the systems of ODE's to be $R_0 > 1$, which indicates that the pathogen is able to invade the general female population and cervical cancer cases will increase in the future. The derivation and analysis of the modified *SIR* mathematical model $SIR_T R_T$ enabled a better understanding of the dynamics of the spread of Human Papilloma Virus infection and reduction of cervical cancer cases in Ghana.

Keywords: Differential equations; susceptible; infected; temporary recovery and permanent recovery; simulation; transmission dynamics; Human papillomavirus; cervical cancer.

1. INTRODUCTION

Viruses are very small organisms – most cannot even be seen with a regular microscope. They cannot reproduce on their own. They must enter a living cell, which becomes the host cell, and “hijack” the cell's machinery to make more viruses. Viruses can enter the body through the mucous membranes, such as the nose, mouth, the lining of the eyes, or the genitals. They can also enter through the skin and any breaks in the skin. Once inside, they find their specific type of host cell to infect. For example, cold and flu viruses find and invade cells that line the respiratory tract (nose, sinuses, breathing tubes, and lungs) [1].

HPVs are called papilloma viruses because some of the HPV types cause warts or papilloma's, which are non-cancerous tumors. The papilloma viruses are attracted to and are able to live only in squamous epithelial cells in the body [2]. Of the more than 150 known strains, about 3 out of 4 (75%) HPV types cause warts on skin, such as that of the arms, chest, hands, and feet. These are the common warts. The other 25% of the HPV types are mucosal types of HPV. “Mucosal” refers to the body's mucous membranes, or the moist surface layers that line organs and cavities of the body that open to the outside [3]. For example, the vagina and anus have this moist mucosal layer. The mucosal HPV types are also called the genital (or anogenital) type HPVs because they often affect the anal and genital area. The mucosal HPVs prefer the moist squamous cells found in this area [1,4].

Genital Human papillomavirus (HPV) is one of the most common sexually transmitted infections and has been shown in epidemiological and molecular studies to be a necessary etiologic agent for cervical cancer [5-7]. Most people who become infected with HPV do not even know that they have it. Human papilloma viruses (HPVs) are a group of more than 150 related viruses. Each HPV virus in the group is given a number, which is called an HPV type. The HPV types 16-18 are the most common high-risk type, accounting for more than half (56%) of all cervical cancers [8,9]. Persistent infection with high-risk types of HPV is the most important risk factor for cervical cancer [10]. Other risk factors for HPV and Cervical cancer include having sexual partners, having a weakened immune system and not getting a regular Pap test [11]. The long premalignant course of HPV infection means that screening programs can detect and treat early disease and prevent progression to cervical cancer. At the advanced stage of HPV infection normal cells in the body turns abnormal and leads to cancer. Infections with carcinogenic HPV at the cervix cause cervical cancer in females [12]. Women who have many sexual partners or who have sex with men who have had many other partners have a greater risk [13].

Primary prevention of HPV infection begins with HPV vaccination of girls aged 9-25 years, before they become sexually active [14]. After many years of testing, two HPV vaccines have been approved by the USA Food and Drugs Administration (FDA) [15]. They are Gardasil and Cervarix which reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93% [16]. HPV vaccines are typically given to female age 9 to 25 as the vaccine is greatly effective if given before infection occurs. The vaccines have been shown to be effective for at least 4 to 20 years, and it is believed they will be effective for longer; however, the duration of effectiveness and whether a booster will be needed is unknown. The vaccine is a course of three injections at 0, 2 and 6 months so there is a question about uptake. If an individual does not complete the course, they will need to start the course from the beginning again to be protected [17]. The bivalent HPV vaccine Cervarix has been licensed for use in Ghana [18].

Although there is currently no medical treatment for Human papilloma virus infections, the cellular changes that come from an HPV infection can be treated. For example, genital warts can be treated. Pre-cancerous cell changes caused by HPV can be detected by Pap tests and treated. Cervical, anal, and genital cancers can also be treated. Getting the HPV vaccine before being exposed to HPV will prevent High risk HPV 16-18 types that cause HPV infections.

Mathematical modeling of a disease is a rapidly growing field reflecting interdisciplinary cooperation of mathematics and biology in solving complex real life problems. Mathematical models have become a viable approach to analyzing biological phenomenon and evaluating the impact of public health intervention strategies to suggest the optimal course of action in the ongoing fight against persistent and emerging infectious diseases [19].

The early stages of HPV infection may be completely asymptomatic until it is quite advanced and hard to treat [20]. Vaginal bleeding, contact bleeding, or rarely a vagina mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of HPV infection. Primary prevention of HPV infection begins with HPV vaccination of girls aged 9-25 years, before they become sexually active [5].

High-risk HPV persistent infections will progress to cancer and when cervical cancer is diagnosed in the early stages, it can be easily treated; however treating advanced cervical cancer is very challenging. Treatment of precancerous and cancerous changes caused by the virus, reduce the viral load and consequently transmission.

2. MATERIALS AND METHODS

We modify a *SIR* compartmental model developed by Kernack–McKendrick (1927) to describe the epidemiology of HPV infection and its impact on cervical cancer in Ghana. Our new *SIR* models will be used in epidemiology to calculate the amount of susceptible, infected, temporary recovered and permanently recovered under the two equilibrium states: the disease-free equilibrium state and endemic equilibrium states in Ghana. The model equations will be solved using quantitative method and MatLab software. Sensitivity analysis shall be performed on the model equations to determine the effect of the parameter values on the spread of the HPV infection.

In view of the above, the main gap in knowledge to be filled by the paper was to propose a new model to study the mode of transmission of Human papillomavirus in females in Ghana

by using the SIR model where the R compartment is partitioned into temporary and permanent recovery based on data obtained to analyse it to see whether the infection will be endemic or not when there is an outbreak in the country.

2.1 The Models

Revealing the literatures across the globe has modeled the Human papillomavirus (HPV) using SIR model or its variants. The models for HPV and its vaccination do not reflect the realities on the ground since a person recovers fully from the HPV after receiving all the three dose of HPV vaccine.

As at now, the Recovery, R compartment has not been partitioned into two as a susceptible can move to recovery compartment either temporarily or permanently based on the number of doses of HPV vaccine received. Anyone who has either received one or two but not all three doses of the vaccine has recovered temporarily since the person is at a risk of contracting the HPV virus. Anyone who has received all three dose of HPV vaccine recovers permanently.

We present a vaccinated SIR model where the individuals in the population are divided into four compartments (Fig. 1). The susceptible (S) which refers to the healthy individuals that has not yet attracted the HPV virus. The infective (I) are those who have become infected with HPV and are able to transmit the disease and the temporarily recovered (R_T) are those who have received one or two dose but not full of HPV vaccine, permanent recovered (R_P) are those who have received all three dose of HPV vaccine.

The proportions of the individuals in the compartment of the population, i.e. S, I, R_T and R_P at time t is denoted as $S(t), I(t), R_T(t)$ and $R_P(t)$ respectively. These have also been described in Tables 1 and 2.

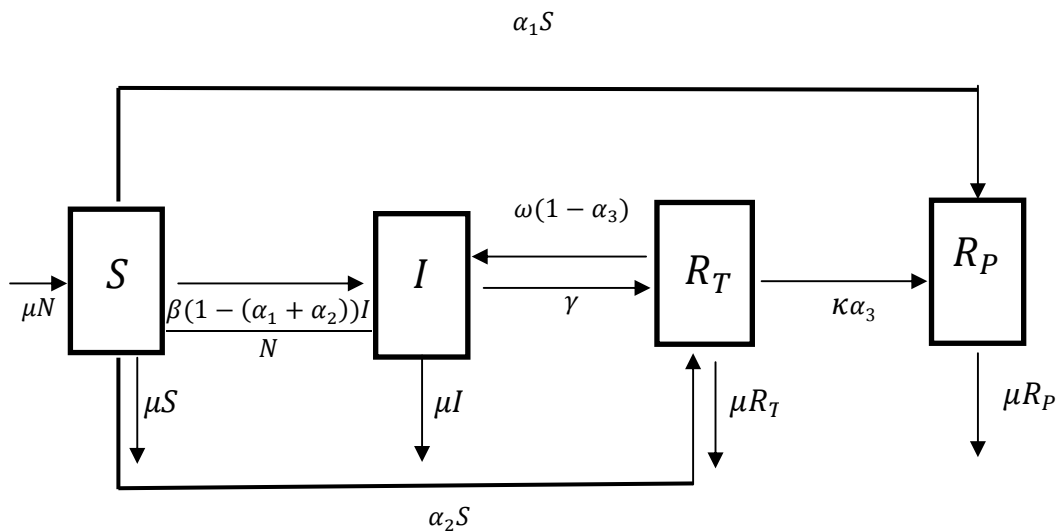


Fig. 1. Flow chart for HPV infection

2.2 Model Assumption

1. Recovery is in two compartments, temporary and permanent.
2. Population size is constant.
3. The individuals in the population mix homogeneously.
4. The rate at which people acquire the virus is proportional to the product of susceptible and infective present.

2.3 Model Equations

From the diagram above, we obtain the following systems of ordinary differential equation

$$\begin{aligned}
 \frac{dS}{dt} &= \mu N - \frac{\beta(1 - (\alpha_1 + \alpha_2))SI}{N} - ((\alpha_1 + \alpha_2) + \mu)S \\
 \frac{dI}{dt} &= \frac{\beta(1 - (\alpha_1 + \alpha_2))SI}{N} - (\mu + \gamma)I + \omega(1 - \alpha_1)R_T \\
 \frac{dR_T}{dt} &= \alpha_2 S + \gamma I - (\omega(1 - \alpha_3) + \alpha_3 \kappa + \mu)R_T \\
 \frac{dR_P}{dt} &= \alpha_3 \kappa + \alpha_1 S - \mu R_P
 \end{aligned} \tag{1}$$

with initial conditions given as follows

$$S(0) = S_0 > 0, I(0) = I_0 > 0, R_T(0) = R_T > 0, R_P(0) = R_P > 0$$

We non-dimensionalize the variables in the system of equations (1) by using the following equations

$$\begin{aligned}
 s &= \frac{S}{N}, \quad i = \frac{I}{N}, \quad r_p = \frac{R_P}{N}, \quad r_T = \frac{R_T}{N}, \quad \tau = \kappa t, \\
 \psi &= \mu/\kappa, \quad \phi = \omega/\kappa, \quad \xi = \beta/\kappa, \quad \varphi = \gamma/\kappa, \quad \eta = \alpha_1/\kappa, \\
 \rho &= \alpha_2/\kappa, \quad \vartheta = \alpha_3/\kappa. \\
 s + i + r_T + r_p &= 1, \quad \alpha_1, \alpha_2, \alpha_3 \in [0,1]
 \end{aligned} \tag{2}$$

A new system of differential equations is obtained from (1) by using the system of equations (2) as

$$\begin{aligned}
 \frac{ds}{d\tau} &= \psi - \xi(1 - (\eta + \rho))si - ((\eta + \rho) + \psi)s \\
 \frac{di}{d\tau} &= \xi(1 - (\eta + \rho))si - (\psi + \varphi)i + \phi(1 - \vartheta)r_T \\
 \frac{dr_T}{d\tau} &= \rho s + \varphi i - (\phi(1 - \vartheta) + \vartheta + \psi)r_T \\
 \frac{dr_P}{d\tau} &= \vartheta r_T + \eta s - \psi r_P
 \end{aligned} \tag{3}$$

$$s(0) = s_0 > 0, i(0) = i_0 > 0, r_T(0) = r_T > 0, r_P(0) = r_P > 0$$

Then $s(\tau) + i(\tau) + r_T(\tau) + r_P(\tau) = 1$

Table 1. Variables and definitions

Variable	Definition
$S(t)$	The number of Susceptible individuals in the population at time, t
$I(t)$	The number of Infected individuals in the population at time, t
$R_T(t)$	The number of Temporarily recovered individuals in the population at time, t
$R_P(t)$	The number of Permanent recovered individuals in the population at time, t
N	Total population

Table 2. Parameters and their definitions

Parameter	Definition
β	The rate of contact. It is defined as the average number of effective contacts with other individuals (susceptible) per infective unit time.
γ	The rate at which the infectious individuals recovers temporarily per unit time.
ω	The rate at which temporarily recovered individuals get re-infected.
κ	The rate at which the infectious individuals recovers permanently per unit time.
μ	The birth and death rate
α_1	Proportion of susceptible that have received all three dose of HPV vaccine
α_2	Proportion of susceptible that have received only one or two dose of HPV vaccine
α_3	Proportion of temporarily recovered individuals that have received all three dose of HPV vaccine.

2.4 Analysis of the Model

In this section, we present the results of stability analysis of the equilibrium points:

2.4.1 Equilibrium of the model

The system of equations of the model (Equations 3) has three non-negative equilibrium points, one disease-free equilibrium, where $i = 0$ and two endemic equilibrium, where $i \neq 0$. The equilibrium point for the disease – free equilibrium is given as:

$$(s^*, i^*, r_T^*, r_P^*) = (1, 0, 0, 0) \tag{4}$$

and the endemic equilibrium states as

$$\begin{aligned}
 (s_1^*, i_1^*, r_{T1}^*, r_{P1}^*) = & \left(\frac{\psi}{\xi(1-(\eta+\rho))i_1^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-(\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-(\eta+\rho)+\psi](\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}{2[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]} \right. \\
 & + \frac{\sqrt{[\xi(1-(\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-(\eta+\rho)+\psi](\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]\phi(1-\vartheta)\rho\psi}}{2[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}, \\
 & \left. \frac{\rho s_1^* + \varphi i_1^*}{(\phi(1-\vartheta) + \vartheta + \psi)}, \frac{\rho r_{T1}^* + \eta s_1^*}{\psi} \right) \tag{5}
 \end{aligned}$$

and

$$\begin{aligned}
 (s_2^*, i_2^*, r_{T2}^*, r_{P2}^*) = & \left(\frac{\psi}{\xi(1-(\eta+\rho))i_2^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-(\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-(\eta+\rho)+\psi](\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}{2[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]} \right. \\
 & - \frac{\sqrt{[\xi(1-(\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-(\eta+\rho)+\psi](\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]\phi(1-\vartheta)\rho\psi}}{2[\xi(1-(\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-(\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}, \\
 & \left. \frac{\rho s_2^* + \varphi i_2^*}{(\phi(1-\vartheta) + \vartheta + \psi)}, \frac{\rho r_{T2}^* + \eta s_2^*}{\psi} \right) \tag{6}
 \end{aligned}$$

2.4.2 Stability of the equilibria

To determine the stability of the system, we will consider linearizing the systems of equation (3) about the equilibrium points by taking the Jacobian of the equation.

$$J(s, i, r_T, r_P)$$

$$= \begin{bmatrix} -\xi(1-(\eta+\rho))i - ((\eta+\rho) + \psi) & -\xi(1-(\eta+\rho))s & 0 & 0 \\ \xi(1-(\eta+\rho))i & \xi(1-(\eta+\rho))s - (\psi + \varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta) + \vartheta + \psi) & 0 \\ \eta & 0 & \vartheta & -\psi \end{bmatrix} \tag{7}$$

For the disease-free equilibrium, we evaluate the Jacobian matrix at the equilibrium points $(s^*, i^*, r_T^*, r_P^*) = (1,0,0,0)$ and hence we get

$$J(s^*, i^*, r_T^*, r_P^*) = \begin{bmatrix} -\psi & -\xi & 0 & 0 \\ 0 & \xi - (\psi + \varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta) + \vartheta + \psi) & 0 \\ 0 & 0 & \vartheta & -\psi \end{bmatrix} \tag{8}$$

For the purpose of our model, we use the approach by [10] to determine the basic reproductive number for this paper and is given by

$$R_0 = \frac{\xi}{\psi+\varphi} \tag{9}$$

This shows that the basic reproductive number of our model is directly proportional to contact rate in which a human infects another human with HPV and inversely proportional to the recovery rate plus the mortality rate.

If $R_0 < 1$ on the average each infected individual infect less than one other individual and the infection dies out. If $R_0 > 1$, on the average each infected individual infect more than one individual so we would expect the infection to spread.

We evaluate the Jacobian matrix at the first endemic equilibrium state, equation (5) to obtain

$$J(s_1^*, i_1^*, r_{T1}^*, r_{P1}^*) = \begin{bmatrix} -\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi) & -\xi(1 - (\eta + \rho))s_1^* & 0 & 0 \\ \xi(1 - (\eta + \rho))i_1^* & \xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi) & \phi(1 - \vartheta) & 0 \\ \rho & \varphi & -(\phi(1 - \vartheta) + \vartheta + \psi) & 0 \\ \eta & 0 & \vartheta & -\psi \end{bmatrix} \quad (10)$$

Solving for the roots of the polynomial in the Jacobian matrix leads to the characteristic equation

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0 \quad (11)$$

Where

$$A_1 = (\phi(1 - \vartheta) + \vartheta + \psi) - (\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi)) - (\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi) - \psi)$$

$$A_2 = ((\phi(1 - \vartheta) + \vartheta + \psi)\psi) + (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))(\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi)) - (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))((\phi(1 - \vartheta) + \vartheta + \psi)) + \xi(1 - (\eta + \rho))s_1^*(\xi(1 - (\eta + \rho))i_1^*) - (\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi))((\phi(1 - \vartheta) + \vartheta + \psi)) - ((\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi) - \psi))(\psi)$$

$$A_3 = (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))(\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi))((\phi(1 - \vartheta) + \vartheta + \psi)) + (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))(\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi))(\psi) - (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))((\phi(1 - \vartheta) + \vartheta + \psi)\psi) - (\xi(1 - (\eta + \rho))s_1^*)((\phi(1 - \vartheta) + \vartheta + \psi))(\psi) + (\xi(1 - (\eta + \rho))s_1^*)(\xi(1 - (\eta + \rho))i_1^*)((\phi(1 - \vartheta) + \vartheta + \psi)) + \xi(1 - (\eta + \rho))s_1^*(\xi(1 - (\eta + \rho))i_1^*)(\psi)$$

$$A_4 = (-\xi(1 - (\eta + \rho))i_1^* - ((\eta + \rho) + \psi))(\xi(1 - (\eta + \rho))s_1^* - (\psi + \varphi))((\phi(1 - \vartheta) + \vartheta + \psi)) + (\xi(1 - (\eta + \rho))s_1^*)(\xi(1 - (\eta + \rho))i_1^*)((\phi(1 - \vartheta) + \vartheta + \psi))(\psi)$$

Using Routh-Hurwitz criterion, the equilibrium for equation (11) is locally stable if the following conditions are satisfied:

$$A_1 > 0, A_3 > 0, A_4 > 0, A_1 A_2 A_3 > A_3^2 + A_1^2 A_4$$

Otherwise the endemic equilibrium state is unstable.

We evaluate the Jacobian matrix at the second endemic equilibrium state, equation (6) to obtain

$$J(s_2^*, i_2^*, r_{T2}^*, r_{P2}^*) = \begin{bmatrix} -\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) & -\xi(1 - (\eta + \rho))s_2^* & 0 & 0 \\ \xi(1 - (\eta + \rho))i_2^* & \xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) & \phi(1 - \vartheta) & 0 \\ \rho & \varphi & -(\phi(1 - \vartheta) + \vartheta + \psi) & 0 \\ \eta & 0 & \vartheta & -\psi \end{bmatrix} \quad (12)$$

Solving for the roots of the polynomial in the Jacobian matrix leads to the characteristic equation

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0 \quad (13)$$

Where

$$B_1 = (\phi(1 - \vartheta) + \vartheta + \psi) - \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) - \left(\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) - \psi \right)$$

$$B_2 = ((\phi(1 - \vartheta) + \vartheta + \psi)\psi) + \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) - \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) + \xi(1 - (\eta + \rho))s_2^* \left(\xi(1 - (\eta + \rho))i_2^* \right) - \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) - \left(\left(\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) - \psi \right) \right) (\psi)$$

$$B_3 = \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) + \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) (\psi) - \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left((\phi(1 - \vartheta) + \vartheta + \psi)\psi \right) - \left(\xi(1 - (\eta + \rho))s_2^* \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) (\psi) + \left(\xi(1 - (\eta + \rho))s_2^* \right) \left(\xi(1 - (\eta + \rho))i_2^* \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) + \xi(1 - (\eta + \rho))s_2^* \left(\xi(1 - (\eta + \rho))i_2^* \right) (\psi)$$

$$B_4 = \left(-\xi(1 - (\eta + \rho))i_2^* - ((\eta + \rho) + \psi) \right) \left(\xi(1 - (\eta + \rho))s_2^* - (\psi + \varphi) \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) + \left(\xi(1 - (\eta + \rho))s_2^* \right) \left(\xi(1 - (\eta + \rho))i_2^* \right) \left((\phi(1 - \vartheta) + \vartheta + \psi) \right) (\psi)$$

Using Routh-Hurwitz criterion, the equilibrium for equation (13) is locally stable if the following conditions are satisfied:

$$B_1 > 0, B_3 > 0, B_4 > 0, B_1 B_2 B_3 > B_3^2 + B_1^2 B_4$$

Otherwise the endemic equilibrium state is unstable.

3. NUMERICAL ANALYSIS AND RESULTS

The table below shows the estimates of the parameters used in the model.

Table 3. Parameters and their descriptions for general female population

Parameters	Parameter description	Typical value (units)
ψ	Birth and death rate	0.186
ξ	Rate at which female get infected	0.968
φ	Temporal recovery rate in female	0.395
κ	Permanently recovery rate	0.7
η	Proportion of female who have 3 doses.	0.094
ρ	Proportion of female with 1 and 3 doses.	0.281
ϑ	Proportion of female receiving full dose after 1 and 2 dose	0.025
ϕ	Rate of re-infection in general female after partial doses	0.003

Source: Ghana statistical service report (2007)

3.1 Estimation of the Equilibrium Points

From equation (4), the equilibrium point of the disease – free steady state was determined to be $(s^*, i^*, r_T^*, r_P^*) = (1, 0, 0, 0)$

Using the typical values for the parameters in Table 3, the estimates of the two endemic steady state were determined from equation (5) and (6) and is given by

$$(s_1^*, i_1^*, r_{T1}^*, r_{P1}^*) = (0.34, -0.05, 0.34, 0.69) \text{ and } (s_2^*, i_2^*, r_{T2}^*, r_{P2}^*) = (0.258, 0.392, 0.991, 1.628)$$

3.2 Stability Analysis of the Equilibrium Points

By substituting the parameter values in Table 4 for general female population in into equation (9) we estimated the basic reproductive number R_0 to be;

$$R_0 = \frac{\xi}{\psi + \varphi} = \frac{0.964}{0.186 + 0.395} = 1.66 \approx 2 > 1$$

Since $R_0 > 1$, the disease free equilibrium is unstable and an endemic will occur when an infected person is introduced into the general female population. The infected person on an average is capable of infecting more than one susceptible. This is because the transmission rate is greater than the temporarily recovery rate.

Table 4. Sensitivity indices of R_0 evaluated at the general female parameter values

Parameter	Sensitivity index
ξ	+0.5
φ	+0.49

The first endemic equilibrium state is left from the analysis since it is not biologically meaningful. Therefore we analyse the stability of only the second endemic equilibrium state. Using the characteristics equation (13) which was evaluated at this endemic equilibrium state and the parameter values;

We obtain;

$$\lambda^4 + 0.674\lambda^3 + 0.697\lambda^2 + 0.256\lambda + 0.088 = 0 \tag{14}$$

$$B_1, B_3, B_4 > 0, B_1B_2B_3 = 0.120, B_3^2 + B_1^2B_4 = 0.106$$

Using the Routh-Hurwitz criterion on equation (14) the endemic equilibrium state is locally asymptotically stable since all criteria are satisfied.

3.3 Sensitivity Analysis

Sensitivity analysis deals with the study of how the uncertainty in the output of a mathematical model or system (numerical or otherwise) can be apportioned to different sources of uncertainty in its inputs [9].

The effect on the reproduction number, R_0 and the stability of the endemic equilibrium states were analyzed. This will be done when the value of the parameters $\xi, \varphi, \eta, \rho, \vartheta, \phi$ changes while ψ remain unchanged.

We increase all parameter values for the general female population except the death rate as $\xi = 0.68, \varphi = 0.53, \eta = 0.12, \rho = 0.46, \vartheta = 0.051, \phi = 0.06, \psi = 0.186$. and decrease all parameter values as $\xi = 0.48, \varphi = 0.13, \eta = 0.05, \rho = 0.14, \vartheta = 0.011, \phi = 0.01$.

Using the characteristics equation (13) and the increased parameter values.

We obtain;

$$\lambda^4 + 1.796\lambda^3 + 1.239\lambda^2 + 0.470\lambda + 0.164 = 0 \tag{15}$$

$$B_1, B_3, B_4 > 0, B_1B_2B_3 = 0.660, B_3^2 + B_1^2B_4 = 0.750$$

Using the Routh-Hurwitz criterion on equation (15) the endemic equilibrium state is unstable since all the conditions do not hold.

Using the characteristics equation (13) and the decreased parameter values.

We obtain;

$$\lambda^4 + 1.263\lambda^3 + 1.034\lambda^2 + 0.532\lambda + 0.097 = 0 \tag{16}$$

$$B_1, B_3, B_4 > 0, B_1B_2B_3 = 0.694, B_3^2 + B_1^2B_4 = 0.438$$

Using the Routh-Hurwitz criterion on equation (16) the endemic equilibrium state is stable since all the conditions holds.

We estimate the sensitivity index of R_0 based on the main parameters that affect it as;

3.4 Sensitivity Analysis by Simulation

Numerical simulations on our model for HPV infection using the data were done. MatlabR2010a was used with the value of the parameters found in Table 3. The Matlab codes are found in the appendix. The effects and the changes that will occur in the model when the values of each of the compartments of the model were altered .i.e. Susceptible(S), Infected (I), Temporarily Removed (R_T) and Permanent Recovered (R_R)were looked at. Time was measured in years for a period of 25 years. The simulation gave the graph as shown in Fig. 2.

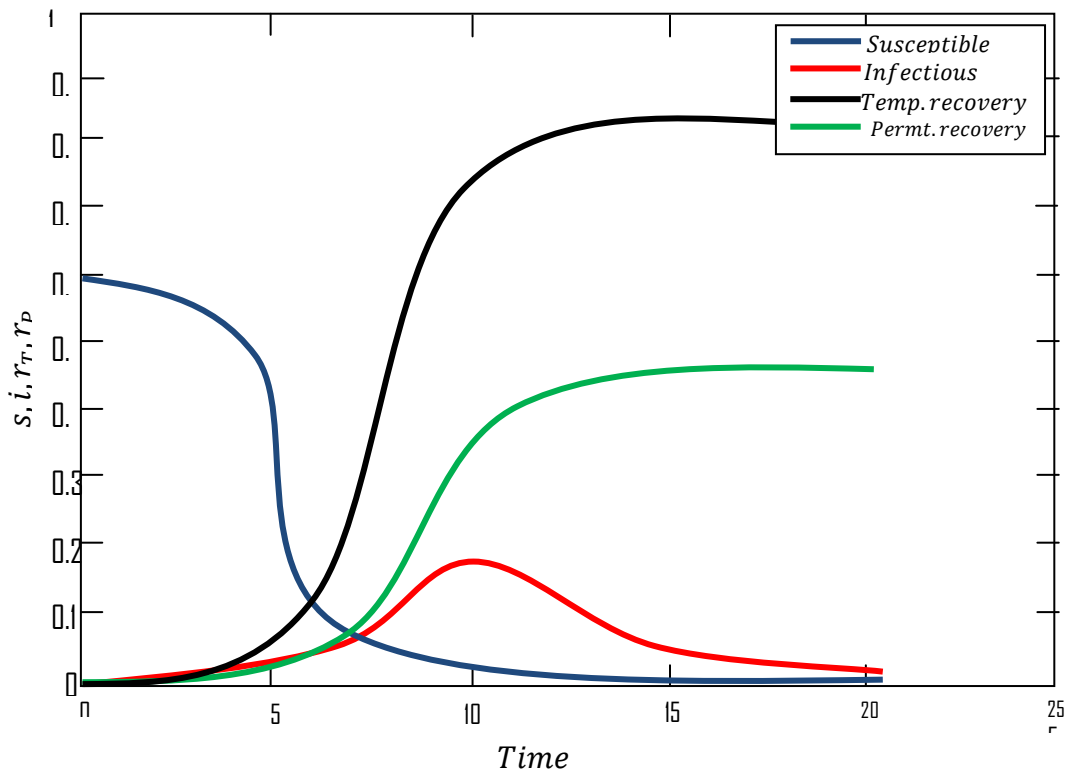


Fig. 2. State variables of the ODE system with initial conditions and parameters

In Fig. 2 we observe that the susceptible reduce with time and approaches zero but do not disappear. The infective grows but reduces with time. The temporarily and permanent recovery increases exponentially with time.

4. DISCUSSION OF RESULTS

In this paper, we used standard ordinary differential equation obtained from our proposed SIR model to predict the spread of HPV infection in general female population in the

presence of HPV vaccine in Ghana. We discussed the existence and stability of the disease free and endemic equilibrium state for the ordinary differential equations of our model and performed sensitivity analysis on the parameters.

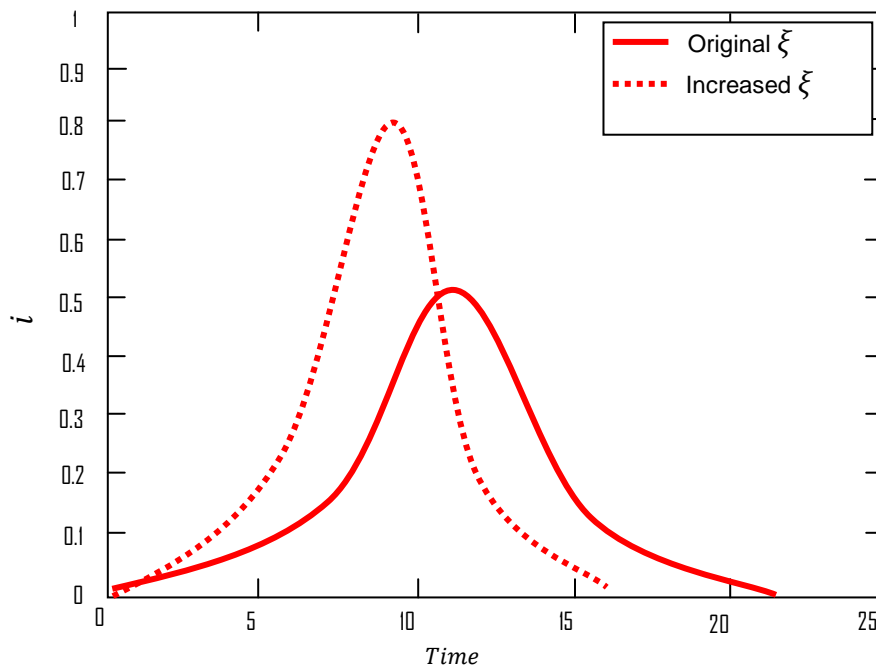
We estimated the basic reproductive number for the general female population in the presence of vaccination using the systems of ODE's to be $R_0 > 1$, which indicates that the pathogen is able to invade the general female population and cervical cancer cases will increase in the future.

Two endemic equilibrium states were found and was observed that the first endemic equilibrium states was not biologically meaningful so only the second endemic equilibrium states were used for the analysis.

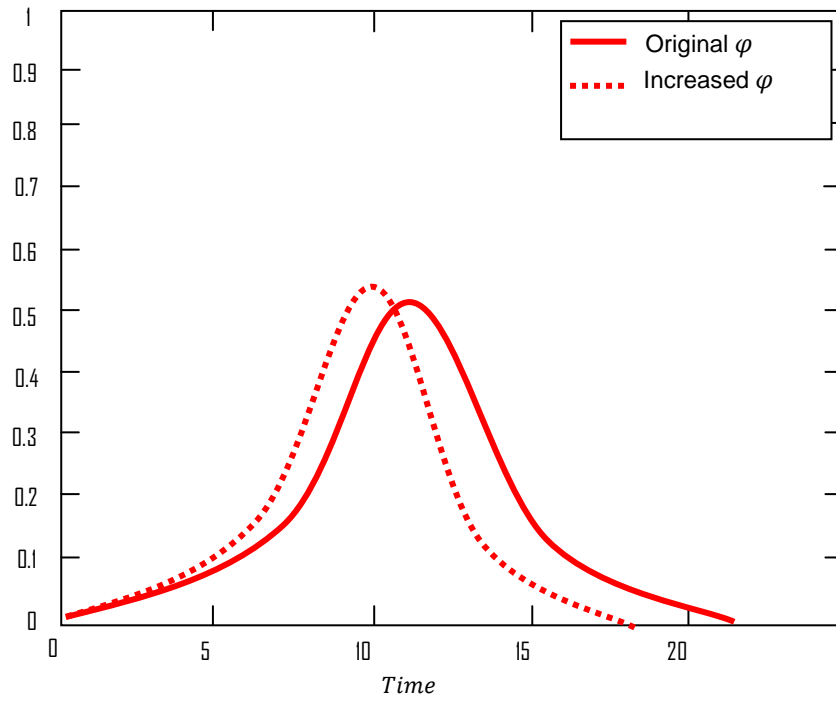
In the general female population the endemic equilibrium was locally asymptotically stable. We performed sensitivity analysis on our models to see how our model parameters influence our models. We observed from our analysis that the transmission rate (ξ) and the temporarily recovery rate (φ) are the main parameters to consider in controlling HPV infection in Ghana if death rate is assumed constant.

From the sensitivity index analysis for example $\Gamma_{\xi}^{R_0} = +0.5$, means that increasing (or decreasing) ξ by 30% increases(or decreases) always R_0 by 15% in the general female population.

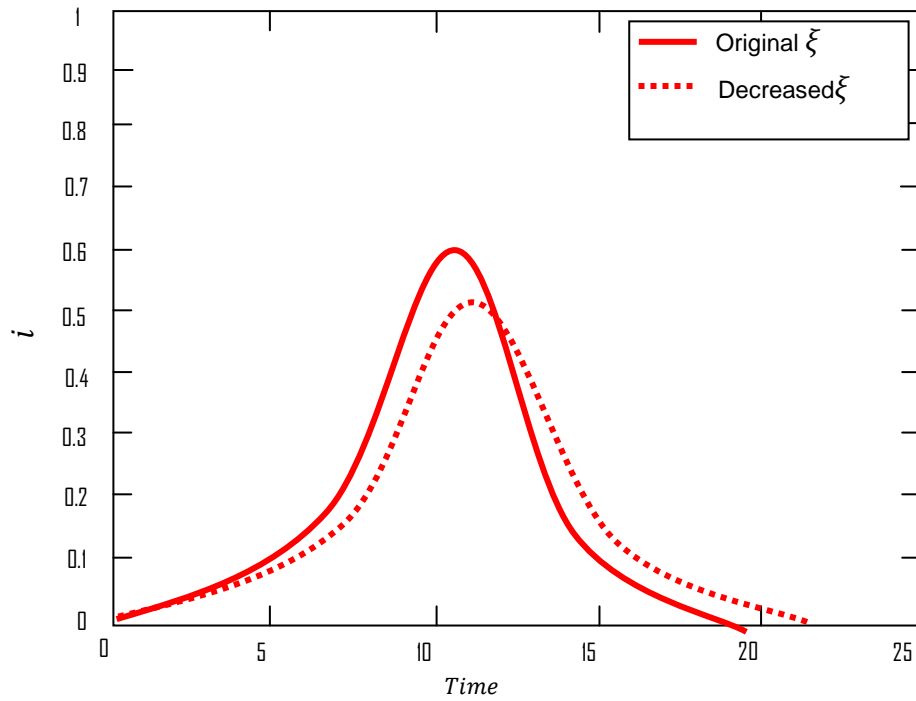
In this situation the infected humans also increases (or decreases) accordingly, as can be seen in Figs. 3(i-iv) below.



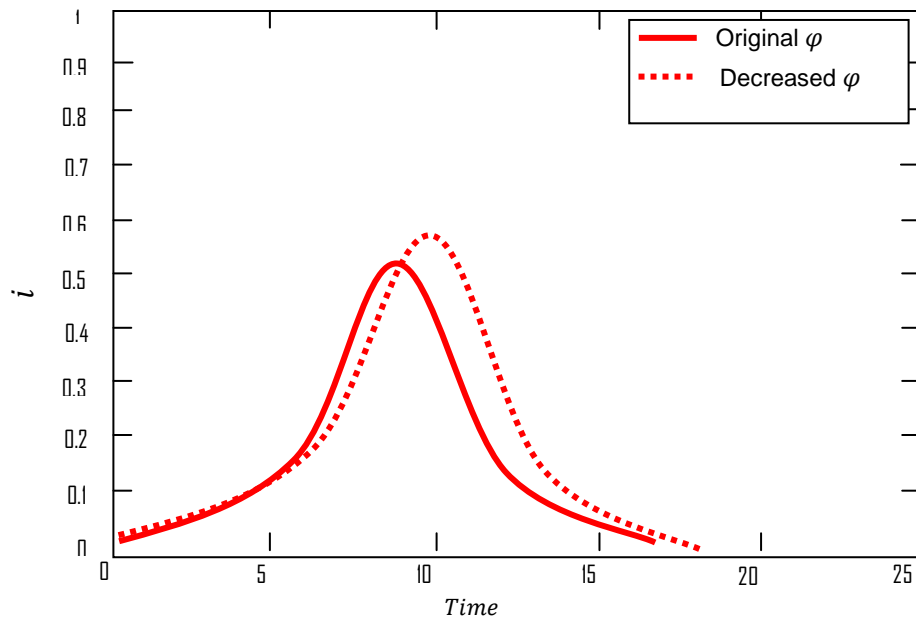
(i) Effect on i of the variation of ξ



(ii) Effect on i of the variation of φ



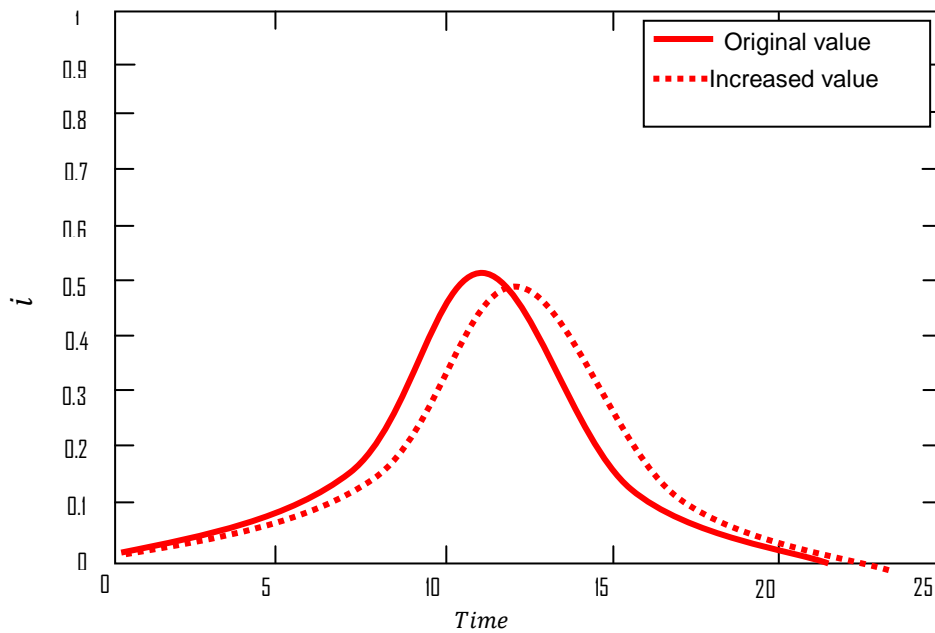
(iii) Effect on i of the variation of ξ



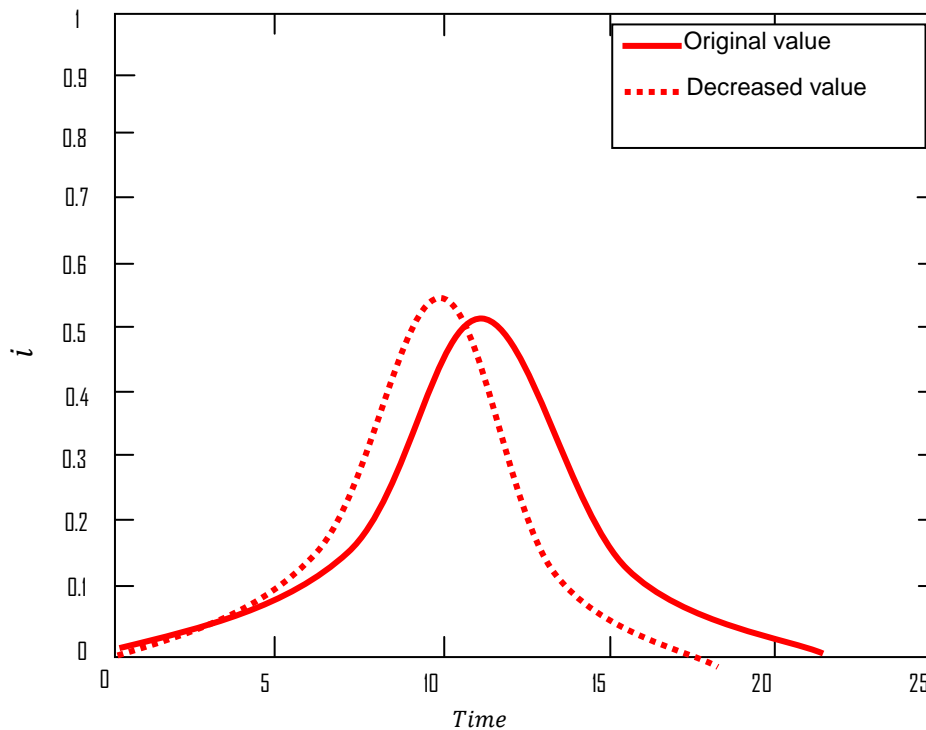
(iv) Effect on i of the variation of φ

Figs. 3(v-vi) presents the comparison of the infected humans when the original parameters are considered and all the parameters are increased (or decrease) by 30%.

From the simulations, it was found out that, a decrease in all parameters by 30% will reduce infection in the population hence cervical cancer cases will reduce in the future.



(v) Effect on i when all parameters increase 30%



(vi) Effect on i when all parameters decrease 30%

Fig. 3. State variables of the infective class with increased and decreased parameters

5. CONCLUSION

The derivation and analysis of the modified SIR mathematical model SIR_{TRT} enabled a better understanding of the dynamics of the spread of Human Papilloma Virus infection and reduction of cervical cancer cases in Ghana.

The reproductive ratio is greater than one for the general female population which indicates that epidemic can occur based on current infectivity and vaccination statistics in Ghana. However, the disease will die out if the reproductive ratio is less than one.

Numerical simulations analysis was extensively helpful in the determination of the effect of the various parameters especially the transmission rate and recovery rate on the spread of the infection and disease.

We conclude that vaccination coverage should be increased to cover a greater proportion of the female population especially the adolescent population. Again Pap test screening should be intensified in the country to detect precancerous cells in the cervix earlier for treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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