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Epidemiology of Cervical Cancer with Human Papilloma Virus in Ethiopia: A Mathematical Model Analysis

Tesfaye Tefera Mamo[1]
[1]Departement of Mathematics, college of natural and computational science, Debre Berhan University, Debre Berhan, Ethiopia

Abstract : Cervical cancer is one of the leading causes of cancer death among females worldwide and its behavior epidemiologically likes a venereal disease of low infectiousness. Early age at first intercourse and multiple sexual partners have been shown to exert strong effects on risk. Genital Human papilloma virus is the central risk factor for developing cervical cancer. Ethiopia has a population of 36.9 million women ages 15 years and older who are at risk of developing cervical cancer. Its incidence is 31.0 per 100,000 women with 7,445 annual number of new cases and 5,338 deaths every year. In order to investigate the epidemiology of cervical cancer associated with the human papillomavirus in Ethiopia, I construct mathematical model for progression of human papilloma virus with vaccination intervention; and I took into consideration nonlinear ordinary differential equations. I used a nonlinear stability analysis method for proving the local and global stability of the existing equilibrium point. I proved that the disease free equilibrium point is locally asymptotically stable and also globally asymptotically stable. Using second generation matrix, I obtained the effective and basic reproduction number for the dynamical system.Using standard parameter estimation I found that the numerical value of effective reproduction number is $R_{eff} = 1.9$ and the basic reproduction number is$R_0 = 21.5$. From this numerical value it is possible to conclude that vaccination intervention strategy is effective to control the spread of human papilloma virus diseases. The most sensitive parameter is q; the proportion rate of vaccinated Individuals. I also conduct numerical simulations which support the finding in the sensitivity analysis.

Key words: Human papilloma virus, cervical cancer, Vaccination, Stability, Simulation

1. Introduction

Genital Human papilloma virus is one of the most common sexually transmitted infections (STI) [1] and has been shown in epidemiological and molecular studies to be a necessary etiologic agent for cervical cancer [1-3].The human papilloma virus is a big group of highly ubiquitous, small, non-enveloped double-stranded circular DNA viruses that infect cutaneous and mucosal surfaces and induce squamous epithelial tumors (warts and papilloma) in many different anatomical sites [30].Genital Human papilloma virus is spread mainly by direct genital contact during vaginal, oral and/or anal sex. It is not spread through blood or body fluids. Infection is very common soon after a woman becomes sexually active.Transmission from mother to newborn during delivery is rare. When it occurs, it can cause warts in the infant's throat called respiratory papillomatosis[12].

More than 100 different types of viruses fall under the umbrella term "Human Papilloma Virus" (HPV), and more than 40 of these viruses are the most prevalent and sexually transmitted in the globe. HPV can infect the genital areas of men and women, including the skin of the penis, vulva (area outside the vagina), anus and the linings of the vagina, cervix, and rectum. Most people who become infected with HPV do not even know that they have it. Genital warts may appear within weeks or months after contact with a partner who has HPV. About 85% of cervical cancers are caused by the "high-risk" HPV strains 16, 18, 31, and 45 [4]. The HPV type 16 is the most common high-risk type, accounting for more than half (56%) of all cervical cancers [5].

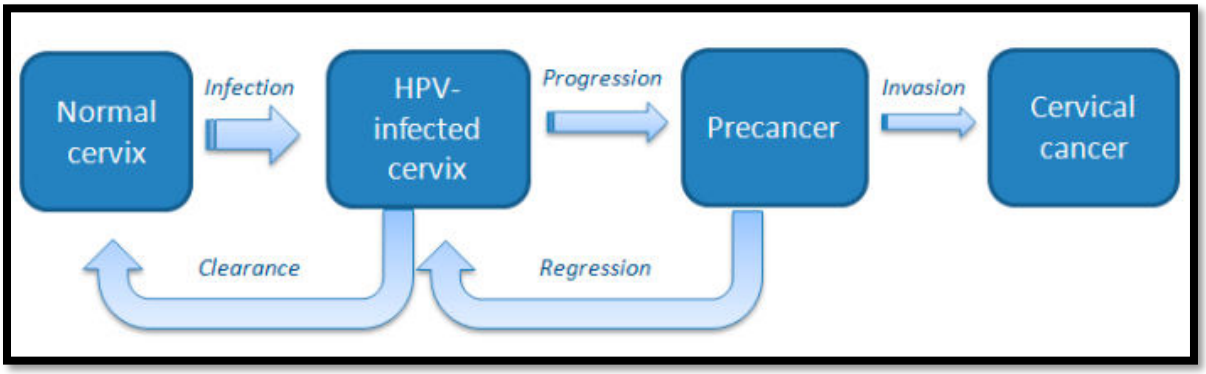

Figure 1: HPV progression to cause cervical cancer

The majority of HPV infections is asymptomatic and might eventually go away on their own after a few years.For instance, 90% of HPV infections were eradicated after two years and roughly 70% after a year. However, in some people, infection can persist for many years and can cause warts or low risk genotype of HPV, while other types lead to different kinds of cancers or high risk genotype of HPV including cervical cancer and pre-

cancerous cervical lesions. [6,7]. Statistics show that there are 18.1 million new cases, 9.6 million cancer related deaths, and 43.8 million people living with cancer in 2018 globally. The number of new cases is expected to rise from 18 million to 22 million by 2030 and the number of global cancer deaths is projected to increase by 45% in 2030 [8].

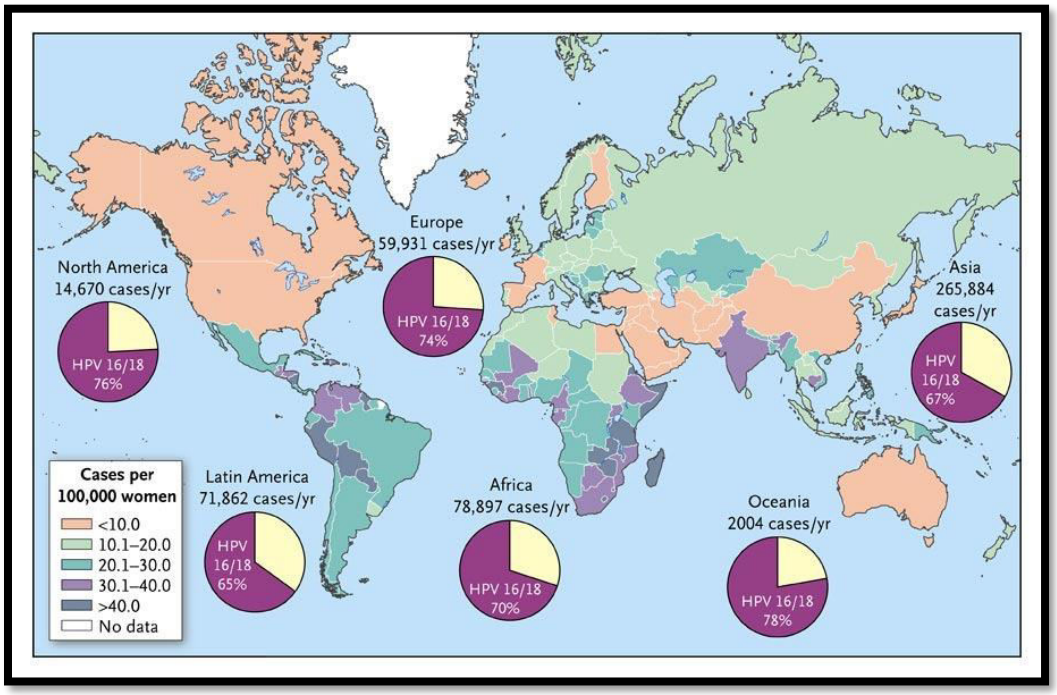

Figure 2: Prevalence of new cases of cervical cancer in the world

There is a vaccine available to prevent HPV, but to maximize its effectiveness, immunizations should be given before infection; the vaccine is not meant to treat infections that have already occurred[17, 18]. However, some vaccines have already undergone review, while others are still in the process. Modeling studies suggest that if HPV vaccinations are administered during adolescence and prior to a woman engaging in sexual activity, it may be useful in avoiding cervical cancer [17, 19]. There is need to sensitize these young women on the importance of the HPV vaccine and research needs to be done in areas of coverage and modalities of delivery to these adolescents.

High effectiveness, immunogenicity, and safety have been proven for primary immunization against HPV infections[20]. Pre-exposure vaccination can be given to both young boys and girls as HPV is sexually transmitted. However, vaccination of boys has been found to be less cost-effective in low resource setting. For the vaccine to be effective there must be high coverage of vaccination among pre-adolescent girls and lowering of vaccine costs.Furthermore, vaccinations would not benefit women who are already HPV-positive[21]. There is no single vaccine which can provide immunity against all typeof

strains of HPV. Even among the few women receiving vaccine against HPV, around 15% do not complete the vaccination doses , while acceptability of the vaccine vary among different groups of women [21,22].

Cervical cancer is the most common cancer which affects women next to breast cancer in the world. Most cervical cancers are related to HPV infection.Over the past 30 years, the increasing proportion of young women affected by cervical cancer has ranged from 10% to 40% [12]. Cervical cancer is estimated to account for 15% of all female cancers and cause approximately 46,000 deaths each year in women aged 15–49 in developing countries [13, 14]. The symptoms of cervical cancer are pain during sexual intercourse, unusual vaginal bleeding, increased amount of discharge and foul-smelling discharge from vagina. Cervical cancer is an abnormal kind of cancer that develops in woman's cervix; it is the entrance to the womb from vagina [9, 10, and 11].The known risk factors of developing cervical cancer are HPV, low socio-economic status, smoking, marrying before age 18 years, sexually active at younger age, multiple sexual partners, multiple sexual partners of spouse, and multiple childbirths [27].

Figure 3: Risk factors of cervical cancer

Numerous approaches have been proposed and/or put into practice to address the proble m of cervical cancer in both developed and developing nations.These include use of vaccination, Cervical Cancer screening, health education, radiation, chemotherapy treatment and a chemotherapy/radiation combined therapy among others [23,24]. The stage of infection determines the course of treatment for cervical cancer. Treatment methods include cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), cone biopsy and Laser ablation [25]. As long as the cervical cancer has not progressed beyond the local area, these techniques are successful. Treatment intervention of Cervical Cancer has been estimated to reduce mortality rate by 76 % [26].

The incidence and mortality in sub-Saharan Africa are among the highest in the world and accounts for over 70% of the global cervical cancer burden with 70,000 new cases annually [32,33].Ethiopia has a population of 36.9 million women ages 15 years and older who are at risk of developing cervical cancer [31]. In Ethiopia, cervical cancer is a series reproductive health problem and is a major cause of mortality and morbidity in women than any other cancers. Its incidence is 31.0 per 100,000 women with 7,445 annual number of new cases and 5,338 deaths every year [31].Thus, cervical cancer ranks as the second most frequent cancer among women in Ethiopia. Despite this fact, very few women receive screening services [34].

Using a system of sequential differential equations that captures the dynamics of HPV and cervical cancer, I built a mathematical modeling based on the biology of both diseases. The system was then analyzed using the method of the next generation matrix, with a basic reproduction number. Parameters were defined and estimated (Table 1) and the model was developed considering all possible scenarios which individuals might take in regard to HPV and cervical cancer mitigations. This is shown as a flow diagram in which the boxes represent the different compartments and the arrows show the transitions between compartments.

2. The mathematical model

2.1 Assumptions of the model

The total individual population at time t is divided into 7 mutually exclusive subpopulations. Let the total population is$N(t)$, susceptible female population is$S(t)$, human papilloma virus is $H(t)$, vaccinated population is$V(t)$, exposed individuals is$E(t)$, infectious and pre-cancer with lesions individuals is $I(t)$, individuals contract cervical cancer is$C(t)$, treated individuals is$T(t)$ and recovered individuals is$R(t)$.Susceptible population are all girls and women after 15 years.Genital Human

papilloma virus is spread mainly by direct genital contact during vaginal, oral and/or anal sex. Vaccination of HPV is given only to females before infection.

2.2 Flow chart of the model

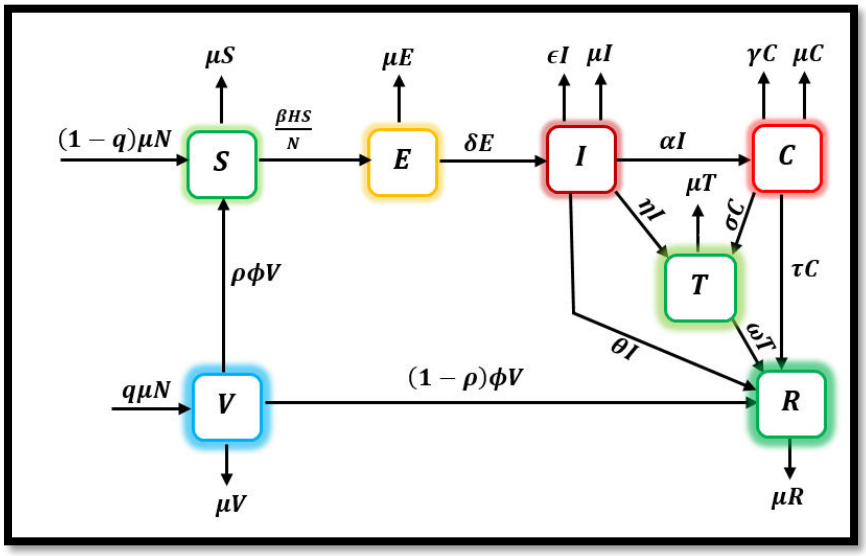

Figure 4: Flow chart

Table 1: Parameters

Parameters	Meaning of parameters
β	Contact rate HPV with susceptible female
q	Proportion rate of vaccinated individuals
ϕ	The vaccine efficacy rate
ρ	Proportions of the vaccine efficacy waning rate
δ	Rate of moving from exposed to infectious and pre-cancer with lesions compartment
α	Rate of moving from infectious and pre-cancer with lesions compartment to cervical cancer compartment
η	The rate by which infectious individuals move to treatment group
σ	The rate by which individuals move from cervical cancer compartment to treatment group
θ	Recovery rate of infectious individuals
τ	Recovery rate of individuals from cervical cancer compartment
ω	Recovery rate of treated individuals
ϵ	Disease induced rate of infectious individuals

γ	Disease induced rate of individuals by cervical cancer
μ	Natural death rate

2.3 Dynamics of the model

$$\frac{dS}{dt} = (1-q)\mu N + \rho\phi V - \frac{\beta HS}{N} - \mu S \quad (1)$$

$$\frac{dV}{dt} = q\mu N - (\phi + \mu)V \quad (2)$$

$$\frac{dE}{dt} = \frac{\beta HS}{N} - (\delta + \mu)E \quad (3)$$

$$\frac{dI}{dt} = \delta E - (\alpha + \eta + \theta + \epsilon + \mu)I \quad (4)$$

$$\frac{dC}{dt} = \alpha I - (\sigma + \gamma + \tau + \mu)C \quad (5)$$

$$\frac{dT}{dt} = \eta I + \sigma C - (\omega + \mu)T \quad (6)$$

$$\frac{dR}{dt} = (1-\rho)\phi V + \theta I + \omega T + \tau C - \mu R \quad (7)$$

The total population $N(t)$ is classified in to seven non-intersecting compartments. That is,

$$N(t) = S(t) + V(t) + E(t) + I(t) + T(t) + C(t) + R(t)$$

$$\Rightarrow \frac{dN}{dt} = \frac{dS}{dt} + \frac{dv}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt}$$

$\Rightarrow \frac{dN}{dt} = -(\epsilon I + \gamma C)$. Thus, the total population is not constant.

2.4 Positivity and bounded ness of solution

For the human population of model (1)-(7) to be epidemiologically meaningful, all solution of the model with positive initial value must remain positive for all time $t > 0$.The feasibility of invariant region is a region where the solution of the given dynamical system is bounded as time is goes on.

THEOREM 1: (Positivity of solution)

Let the initial data for the model be $S(0) > 0, V(0) > 0, E(0) > 0, I(0) > 0, T(0) > 0,$ $C(0) > 0$ *and* $R(0) > 0$. Then, the solutions $S(t), V(t), E(t), I(t), T(t), C(t)$ *and* $R(t)$ of the model will be remain positive for all time $t > 0$.

Proof: Assume that all parameters are positive, $S(0) > 0, V(0) > 0, E(0) > 0, I(0) > 0,$

$T(0) > 0, C(0) > 0, R(0) > 0$and the total population N(t) is positive. Also, let the force of infection $\lambda = \frac{\beta H}{N}$ is positive.

I) From equation (2), we have:

$$\frac{dV}{dt} = q\mu N - (\phi + \mu)V$$

$\Longrightarrow \int_0^t d(Ve^{(\phi+\mu)t}) = q\mu N \int_0^t e^{(\phi+\mu)t}dt$, with integrating factor $e^{(\phi+\mu)t}$

$\Longrightarrow V(t) = V(0) + q\mu N \int_0^t e^{(\phi+\mu)t}dt > 0$, Since $V(0) > 0$,

$q\mu N \int_0^t e^{(\phi+\mu)t}dt > 0 \; for \; all t > 0$. Hence $V(t)$ positive.

II) From equation (1), we get:

$\frac{dS}{dt} = (1-q)\mu N + \rho\phi v - (\lambda + \mu)S$

$$\Longrightarrow \int_0^t d(Se^{(\lambda+\mu)t}) = \int_0^t [(1-q)\mu N + \rho\phi V]e^{(\lambda+\mu)t}dt$$

$\Longrightarrow S(t) = S(0) + \int_0^t [(1-q)\mu N + \rho\phi V]e^{(\lambda+\mu)t}dt > 0$. Thus, $S(t)$ is positive

III) From equation (3), we have:

$\frac{dE}{dt} = \lambda S - (\delta + \mu)E$

$$\Longrightarrow \int_0^t d(Ee^{(\delta+\mu)t}) = \int_0^t \lambda S e^{(\delta+\mu)t}dt$$

$\Longrightarrow E(t) = E(0) + \int_0^t \lambda S e^{(\phi+\mu)t}dt > 0$. Hence, $E(t)$ is positive.

IV) From (4), we get:

$$\frac{dI}{dt} = \delta E - (\alpha + \eta + \theta + \epsilon + \mu)I$$

$$\Longrightarrow \int_0^t d(Ie^{(\alpha+\eta+\theta+\epsilon+\mu)t}) = \int_0^t \delta E e^{(\alpha+\eta+\theta+\epsilon+\mu)t}dt$$

$\Longrightarrow I(t) = I(0) + \int_0^t \delta E e^{(\alpha+\eta+\theta+\epsilon+\mu)t}dt > 0$. So, $I(t)$ is positive.

V) From equation (5), we have:

$\frac{dC}{dt} = \alpha I - (\sigma + \gamma + \tau + \mu)C$

$$\Longrightarrow \int_0^t d(Ce^{(\sigma+\gamma+\tau+\mu)t}) = \int_0^t \alpha I e^{(\sigma+\gamma+\tau+\mu)t}dt$$

$\Longrightarrow C(t) = C(0) + \int_0^t \alpha I e^{(\sigma+\gamma+\tau+\mu)t}dt > 0$. Thus, $C(t)$ is positive.

VI) From equation (6), we get the following:

$$\frac{dT}{dt} = \eta I + \sigma C - (\omega + \mu)T$$

$$\Longrightarrow \int_0^t d(Te^{(\omega+\mu)t}) = \int_0^t (\eta I + \sigma C)e^{(\omega+\mu)t}dt$$

$\Longrightarrow T(t) = T(0) + \int_0^t (\eta I + \sigma C)e^{(\omega+\mu)t}dt > 0$. Therefore, $T(t)$ is positive.

VII) From equation (7), we get:

$$\frac{dR}{dt} = (1-\rho)\phi V + \theta I + \omega T + \tau C - \mu R$$

$$\Rightarrow \int_0^t d(Re^{\mu t}) = \int_0^t ((1-\rho)\phi V + \theta I + \omega T + \tau C)e^{(\omega+\mu)t}dt$$

$$\Rightarrow R(t) = R(0) + \int_0^t ((1-\rho)\phi V + \theta I + \omega T + \tau C)e^{(\omega+\mu)t}dt > 0.$$

So, $R(t)$ is positive.

THEREM 2: (Bounded ness of solution)

The feasible region Ω of the model (1) – (7) is defined as:

$\Omega = \{(S(t), V(t), E(t), I(t), T(t), C(t), R(t)) \epsilon \Re_+^7 \cup (0,0,0,0,0,0,0)$:

$$0 \le S(t) \le \frac{N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\lambda+\mu)(\phi+\mu)}, 0 \le V(t) \le \frac{qN}{\phi+\mu}, 0 \le E(t) \le \frac{\lambda N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\delta+\mu)(\lambda+\mu)(\phi+\mu)},$$

$$0 \le I(t) \le \frac{\lambda\delta N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}, 0 \le T(t) \le \frac{\lambda\delta N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}[\eta + \frac{\sigma\alpha}{\sigma+\gamma+\tau+\mu}],$$

$$0 \le C(t) \le \frac{\lambda\alpha\delta N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}, 0 \le R(t) \le \frac{1}{\mu(\phi+\mu)}\{(1-\rho)\phi qN + \frac{\lambda\delta N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)}[\theta + \eta\omega + \frac{\alpha(\tau+\omega)}{\sigma+\gamma+\tau+\mu}]\}$$

If$\big(S(0), V(0), B_A(0), B_C(0), I_1(0), I_2(0), R(0)\big) \in \Omega$, then the solution of $(S(t), V(t), E(t), I(t), T(t), C(t), R(t)) \in \Omega$, for all time $t > 0$.

Proof:

Assume that all state variables $S(t), V(t), E(t), I(t), T(t), C(t), R(t)$and parameters are positive. Also, let $S(0) \ge 0, V(0) \ge 0, E(0) \ge 0, I(0) \ge 0, T(0) \ge 0, C(0) \ge 0,\ R(0) \ge 0$ and the force of infection $\lambda = \frac{\beta H}{N} \epsilon (0,1)$

I) From equation (2), $\frac{dV}{dt} = q\mu N - (\phi+\mu)V$,we have:

$\frac{dV}{dt} + (\phi+\mu)V = q\mu N \le qN$ … Since $\mu\epsilon(0,1)$

$$\Rightarrow \int_0^t de^{(\phi+\mu)t}V(t) \le qN\int_0^t e^{(\phi+\mu)t}dt$$

$$\Rightarrow V(t) \le \frac{qN}{\phi+\mu} + \left[V(0) - \frac{qN}{\phi+\mu}\right]e^{-(\phi+\mu)t}$$

$$\Longrightarrow \lim_{t\to\infty}\sup V(t) \le \lim_{t\to\infty}\left\{\frac{\pi N}{\phi+\mu}+\left[V(0)-\frac{\pi N}{\phi+\mu}\right]e^{-(\phi+\mu)t}\right\} \le \frac{qN}{\phi+\mu}.$$

Thus, $0 \le V(t) \le \frac{qN}{\phi+\mu}$ and $V(t)$ is bounded.

II) From equation (1), we get:

$0 \le S(t) \le \frac{N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\lambda+\mu)(\phi+\mu)}$. Hence, $S(t)$ is bounded.

III) From equation (3), we have:

$$0 \le E(t) \le \frac{\lambda N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\delta+\mu)(\lambda+\mu)(\phi+\mu)}$$

IV) From equation (4), we get:

$$0 \le I(t) \le \frac{\lambda\delta N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}$$

V) From equation (5), we have:

$$0 \le C(t) \le \frac{\lambda\alpha\delta N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}$$

VI) From equation (6), we get:

$0 \le T(t) \le \frac{\lambda\delta N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)(\phi+\mu)}[\eta+\frac{\sigma\alpha}{\sigma+\gamma+\tau+\mu}]$

VII) From equation (7), we have:

$$0 \le R(t) \le \frac{1}{\mu(\phi+\mu)}\{(1-\rho)\phi qN+\frac{\lambda\delta N[(1-q)(\phi+\mu)\mu+\rho\phi q]}{(\alpha+\eta+\theta+\epsilon+\mu)(\delta+\mu)(\lambda+\mu)}[\theta+\eta\omega+\frac{\alpha(\tau+\omega)}{\sigma+\gamma+\tau+\mu}]\}$$

In general, all state variables are positive and bounded.

Nondimensionalization

We consider the equations for the normalized quantities because it is easier to analyze my model in terms of proportions of quantities than of actual populations. This can be done by scaling the population of each class by the total population. Here,

$N(t) = S(t)+V(t)+E(t)+I(t)+T(t)+C(t)+R(t)$ and $\frac{dN}{dt} = -(\epsilon I+\gamma C)$.

$\Longrightarrow 1 = \frac{S(t)}{N}+\frac{V(t)}{N}+\frac{E(t)}{N}+\frac{I(t)}{N}+\frac{T(t)}{N}+\frac{C(t)}{N}+\frac{R(t)}{N}$. Suppose

$$s(t)=\frac{S(t)}{N}, v(t)=\frac{V(t)}{N}, e(t)=\frac{E(t)}{N}, i(t)=\frac{I(t)}{N}, f(t)=\frac{T(t)}{N}, c(t)=\frac{C(t)}{N}, r(t)=\frac{R(t)}{N}$$

Thus, the transformed dynamical system is:

$$\frac{ds}{dt} = (1-q)\mu+\rho\phi v+(\epsilon i+\gamma c)s-(\lambda+\mu)s \quad (8)$$

$$\frac{dv}{dt} = q\mu+(\epsilon i+\gamma c)v-(\phi+\mu)v \quad (9)$$

$$\frac{de}{dt} = \lambda s + (\epsilon i + \gamma c)e - (\delta + \mu)e \quad (10)$$

$$\frac{di}{dt} = \delta e + (\epsilon i + \gamma c)i - (\alpha + \eta + \theta + \epsilon + \mu)i \quad (11)$$

$$\frac{dc}{dt} = \alpha i + (\epsilon i + \gamma c)c - (\sigma + \gamma + \tau + \mu)c \quad (12)$$

$$\frac{df}{dt} = \eta i + \gamma c + (\epsilon i + \gamma c)f - (\omega + \mu)f \quad (13)$$

$$\frac{dr}{dt} = (1 - \rho)\phi v + \theta i + \omega f + \tau c + (\epsilon i + \gamma c)r - \mu r \quad (14)$$

2.5 Disease Free Equilibrium (DFE) point

At disease free equilibrium point, there is no disease and so;$e = i = c = f = H = 0$, and thus, the disease free equilibrium point of the dynamical system (8)-(14) is:

$$(\boldsymbol{s, v, e, i, c, f, r}) = (\frac{\boldsymbol{\mu[(1-q)(\phi+\mu)+\rho\phi q]}}{\boldsymbol{(\lambda+\mu)(\phi+\mu)}}, \frac{\boldsymbol{q\mu}}{\boldsymbol{\phi+\mu}}, \boldsymbol{0, 0, 0, 0}, \frac{\boldsymbol{(1-\rho)\phi q}}{\boldsymbol{\phi+\mu}})$$

Basic and effective reproduction numbers

Reproduction number (basic or effective) is the number of new infections produced by a typical infective individual in a population at a disease free equilibrium point. We calculate the effective reproduction number $R_{eff}$and basic reproduction number$R_0$by using the next generation operator method on the system as described by Van den Driessche and Watmough [16].

Using next generation method, the effective reproduction number (reproduction number with vaccination intervention) of this model is:

$$\boldsymbol{R_{eff}} = \frac{\boldsymbol{\lambda\delta[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma][(1-q)(\phi+\mu)^2+\rho\phi q(\phi+\lambda+2\mu)]}}{\boldsymbol{(\phi+\mu)^2(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}}.$$

The basic reproduction number (reproduction number without vaccinationintervention), that is $q = \rho = 0$ is:

$$\boldsymbol{R_0} = \frac{\boldsymbol{\lambda\delta[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma]}}{\boldsymbol{(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}}.$$

THEOREM 3:

If the effective reproduction number$R_{eff} < 1$, then the disease free equilibrium point$(s, v, e, i, c, f, r) = (\frac{\mu[(1-q)(\phi+\mu)+\rho\phi q]}{\phi+\mu}, \frac{q\mu}{\phi+\mu}, 0, 0, 0, 0, \frac{(1-\rho)\phi q}{\phi+\mu})$is globally asymptotically stable (G.A.S).

Proof:-Suppose the effectivereproduction number $R_{eff} < 1$, and $E^0 = (s^0, v^0, e^0, i^0, c^0, f^0, r^0) = (\frac{\mu[(1-q)(\phi+\mu)+\rho\phi q]}{\phi+\mu}, \frac{q\mu}{\phi+\mu}, 0, 0, 0, 0, \frac{(1-\rho)\phi q}{\phi+\mu})$is the disease free equilibrium point. Let the Lyapunov function $W: R_+^7 \longrightarrow R_+$ is defined by:

$W(s, v, e, i, c, f, r) = A[s - s^0 - s^0 \ln\left(\frac{s}{s^0}\right)] + B[v - v^0 - v^0 \ln\left(\frac{v}{v^0}\right)] + De + Ei + Fc + Gf + J[r - r^0 - r^0 \ln(\frac{r}{r_0})]$, where A, B, D, E, F G and J are positive constants.

I) W is continuous function for all $(s, v, e, i, c, f, r) \in \Re_+^7 \cup (0,0,0,0,0,0,0)$ and has 1st order partial derivatives.

II) W has minimum at $(s^0, v^0, e^0, i^0, c^0, f^0, r^0) = (\frac{\mu[(1-q)(\phi+\mu)+\rho\phi q]}{\phi+\mu}, \frac{q\mu}{\phi+\mu}, 0, 0, 0, 0, \frac{(1-\rho)\phi q}{\phi+\mu})$, which is $W(\frac{(1-q)(\phi+\mu)+\rho\phi q}{\phi+\mu}, \frac{q\mu}{\phi+\mu}, 0, 0, 0, 0, \frac{(1-\rho)\phi q}{\phi+\mu}) = 0$

III) Now, $\frac{dW}{dt} = A\frac{\partial W}{\partial s}\frac{ds}{dt} + B\frac{\partial W}{\partial v}\frac{dv}{dt} + D\frac{\partial W}{\partial e}\frac{de}{dt} + E\frac{\partial W}{\partial i}\frac{di}{dt} + F\frac{\partial W}{\partial c}\frac{dc}{dt} + G\frac{\partial W}{\partial f}\frac{df}{dt} + J\frac{\partial W}{\partial r}\frac{dr}{dt}$

$$\Longrightarrow \frac{dW}{dt} = A\left[\left(1 - \frac{s^0}{s}\right)\left((1-q)\mu + \rho\phi v + (\epsilon i + \gamma c)s - (\lambda + \mu)s\right)\right] +$$

$$B\left[\left(1 - \frac{v^0}{v}\right)(q\mu + (\epsilon i + \gamma c)v - (\phi + \mu)v)\right] + D[\lambda s + (\epsilon i + \gamma c)e - (\delta + \mu)e] +$$

$$\boldsymbol{E}[\delta e + (\epsilon i + \gamma c)i - (\alpha + \eta + \theta + \epsilon + \mu)i] + \boldsymbol{F}[\alpha i + (\epsilon i + \gamma c)c - (\sigma + \gamma + \tau + \mu)c] +$$

$$\boldsymbol{G}[\eta i + \gamma c + (\epsilon i + \gamma c)f - (\omega + \mu)f] + J[(1 - \frac{r^0}{r})((1-\rho)\phi v + \theta i + \omega f + \tau c + (\epsilon i + \gamma c)r - \mu r)]$$

Now, at disease free equilibrium point

$E^0 = (s^0, v^0, e^0, i^0, c^0, f^0, r^0) = (\frac{\mu[(1-q)(\phi+\mu)+\rho\phi q]}{\phi+\mu}, \frac{q\mu}{\phi+\mu}, 0, 0, 0, 0, \frac{(1-\rho)\phi q}{\phi+\mu})$,we have:

$(1-q)\mu + \rho\phi v + (\epsilon i + \gamma c)s - (\lambda + \mu)s = 0$

$\Longrightarrow (1-q)\mu = -\rho\phi v^0 - (\lambda + \mu)s^0$...(a) From equation number [8]

Also, $q\mu + (\epsilon i + \gamma c)v - (\phi + \mu)v = 0$

$\Longrightarrow q\mu = -(\phi + \mu)v^0$ ... (b) From equation number [9]

Again, $(1-\rho)\phi v + \theta i + \omega f + \tau c + (\epsilon i + \gamma c)r - \mu r = 0$

$\Longrightarrow (1-\rho)\phi v = -\mu r^0$ … (d) From equation number [14]. With substitution of (a), (b), (d)in $\frac{dW}{dt}$, and choosing the constants D, E, F, G such that the coefficient of e, i, c, f are equal to zero, we get:

$$\frac{dW}{dt} = -\{\left[A(\lambda+\mu)\left(1-\frac{s^0}{s}\right)^2 - D\lambda\right]s + \left[B(\phi+\mu)\left(1-\frac{v^0}{v}\right)^2 - A\rho\phi\left(1-\frac{s^0}{s}\right)\left(1-\frac{v^0}{v}\right)\right]vJ\left(1-\frac{r^0}{r}\right)r\} < 0, \text{for} A(\lambda+\mu)\left(1-\frac{s^0}{s}\right)^2 > D\lambda \text{ and}$$

$B(\phi+\mu)\left(1-\frac{v^0}{v}\right)^2 > A\rho\phi\left(1-\frac{s^0}{s}\right)\left(1-\frac{v^0}{v}\right)$. Thus, if$R_{eff} < 1$, then the disease free equilibrium point is globally asymptotically stable (G.A.S).

2.6 Parametric estimation, sensitivity analysis and simulations

In this work, I used secondary data from the Federal Republic of Ethiopia's Ministry of Health to examine a non-linear mathematical model of HPV with sexual contact transmission. Ethiopia is the tenth largest country in Africa, covering 1,104,300 square kilometers and the major constituent of the land marks known as Horn of Africa. The current population of Ethiopia; estimated by projection and taken from Google is listed below:

Table 2: Ethiopian population in 2024[42]

Description	Notation	Values
Total number of Femalein Ethiopia	F	63.890,631
Total number of Male in Ethiopia	M	63,304,754
Total number of population in Ethiopia	T	127,195,383

In Ethiopia, a nationwide HPV vaccination program was launched in December 2018 with the goal of immunizing all eligible females in both public and private institutions. The program was given in schools. Girls who are not in school receive the vaccination in any health center countrywide.The best intervention for cervical cancer prevention can be HPV vaccination of girls aged 9–13 years [43].The available vaccine in the country is Gardasil-4, which targets HPV6, 11, 16, and 18 [45]. According to the information from WHO African region report, girls aged 9–14 years are taking vaccination in the country [46].Cervical cancer affects 29.43 million Ethiopian women who are 15 years of age or older [44].

It is estimated that the number of Ethiopian females age 9-14 is about 7,786,000. About 6.3 million females take at least the first dose of HPV vaccine and about 5,839,000 take the last dosesin Ethiopia [47].

Table 3. Parametric values

Parameters	Parameter descriptions	Value	Reference
β	Contact rate HPV with susceptible female	0.31	[29]
q	Proportion rate of vaccinated individuals	0.81	[37]
ϕ	The vaccine efficacy waning rate	0.17	[35]
ρ	Proportions of the vaccine efficacy waning rate	0.01	Assumed
δ	Rate of moving from exposed to infectious and pre-cancer with lesions compartment	0.45	[39]
α	Rate of moving from infectious and pre-cancer with lesions compartment to cervical cancer compartment	0.15	[40]
η	The rate by which infectious individuals move to treatment group	0.3	Assumed
σ	The rate by which individuals move from cervical cancer compartment to treatment group	0.39	Assumed
θ	Recovery rate of infectious individuals	0.18	Assumed
τ	Recovery rate of individuals from cervical cancer compartment	0.3	[41]
ω	Recovery rate of treated individuals	0.85	[28,29]
ϵ	Disease induced rate of infectious individuals	0.35	Assumed
γ	Disease induced rate of individuals by cervical cancer	0.28	Assumed
μ	Natural death rate	0.01	[4]
λ	Force of infection	0.009	[38]

Based on parametric values, the effective and basic reproduction numbers are:

$$\boldsymbol{R_{eff}} = \frac{\boldsymbol{\lambda\delta[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma][(1-q)(\phi+\mu)^2+\rho\phi q(\phi+\lambda+2\mu)]}}{\boldsymbol{(\phi+\mu)^2(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}} = \mathbf{1.9}$$

$$\boldsymbol{R_0} = \frac{\boldsymbol{\lambda[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma]}}{\boldsymbol{(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}} = \mathbf{21.5}$$

Following the replacement of the aforementioned numerical values for the parameters, we have:

$R_{eff} = 1.9$ and $R_0 = 21.5$. Based on this data analysis, we determine that the fundamental reproduction number is, meaning that throughout an infectious period of an

individual, around 22 healthy individuals are infected if there is not intervention. However, the effective reproduction number indicates that, as a result of HPV vaccination intervention, one infectious individual can infect roughly 2 healthy individuals during the infectious period. Since $R_{eff} = 1.9 > 1$, it indicates that HPV disease persists in a community. So, vaccination of HPV is effective to control the disease

Sensitivity

Definition: The normalized forward sensitivity index of R_{eff} that depends differentiably on a

Parameterpis defined by:

$$SI(P) = \frac{\partial R_{eff}}{\partial p} \times \frac{p}{R_{eff}}$$

The parameter with higher magnitude is/are more influential. The sign of the sensitivity indices of R_{eff} with respect to the parameters show the positive or negative impact of the parameter on R_{eff} . That is, if the sign of the sensitivity indices is positive then the value of R_{eff} increase whenever the value of the parameter increases and if the sign of the sensitivity indices is negative then the value of R_{eff}decrease whenever the value of the parameter increase**[36].**

For this model, $\boldsymbol{R_{eff}} = \frac{\lambda\delta[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma][(1-q)(\phi+\mu)^2+\rho\phi q(\phi+\lambda+2\mu)]}{(\phi+\mu)^2(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}$.

$$SI(\lambda) = \frac{\partial R_{eff}}{\partial \lambda} \times \frac{\lambda}{R_{eff}} = \frac{[(\mathbf{1}-\boldsymbol{q})(\boldsymbol{\phi}+\boldsymbol{\mu})^2 + \boldsymbol{\rho\phi q}(\boldsymbol{\phi}+\boldsymbol{\lambda}+\mathbf{2}\boldsymbol{\mu})](\boldsymbol{\mu}-\boldsymbol{\lambda}) + \boldsymbol{\lambda\rho\phi q}(\boldsymbol{\lambda}+\boldsymbol{\mu})}{[(\mathbf{1}-\boldsymbol{q})(\boldsymbol{\phi}+\boldsymbol{\mu})^2 + \boldsymbol{\rho\phi q}(\boldsymbol{\phi}+\boldsymbol{\lambda}+\mathbf{2}\boldsymbol{\mu})](\boldsymbol{\lambda}+\boldsymbol{\mu})}$$
$$= 0.07$$

$$SI(\delta) = \frac{\partial R_{eff}}{\partial \delta} \times \frac{\delta}{R_{eff}} = \frac{\mu}{\delta+\mu} = 0.02$$

$$SI(\epsilon) = \frac{\partial R_{eff}}{\partial \epsilon} \times \frac{\epsilon}{R_{eff}} = \frac{\epsilon[(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})(\boldsymbol{\alpha}+\boldsymbol{\eta}+\boldsymbol{\theta}+\boldsymbol{\epsilon}+\boldsymbol{\mu})-[\boldsymbol{\epsilon}(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})+\boldsymbol{\alpha\gamma}]]}{[\boldsymbol{\epsilon}(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})+\boldsymbol{\alpha\gamma}](\boldsymbol{\alpha}+\boldsymbol{\eta}+\boldsymbol{\theta}+\boldsymbol{\epsilon}+\boldsymbol{\mu})} = 0.54$$

$$SI(\sigma) = \frac{\partial R_{eff}}{\partial \sigma} \times \frac{\sigma}{R_{eff}} = \frac{-\boldsymbol{\sigma\alpha\gamma}}{(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})[\boldsymbol{\epsilon}(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})+\boldsymbol{\alpha\gamma}]} = -0.04$$

$$SI(\gamma) = \frac{\partial R_{eff}}{\partial \gamma} \times \frac{\gamma}{R_{eff}} = \frac{\alpha(\sigma+\tau+\mu)}{(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})[\boldsymbol{\epsilon}(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})+\boldsymbol{\alpha\gamma}]} = 0.28$$

$$SI(\tau) = \frac{\partial R_{eff}}{\partial \tau} \times \frac{\tau}{R_{eff}} = \frac{-\boldsymbol{\tau\alpha\gamma}}{(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})[\boldsymbol{\epsilon}(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})(\boldsymbol{\phi}+\boldsymbol{\mu}+\boldsymbol{\rho\phi})+\boldsymbol{\alpha\gamma}]} = -0.03$$

$$SI(\alpha) = \frac{\partial R_{eff}}{\partial \alpha} \times \frac{\alpha}{R_{eff}} = \frac{\alpha[\gamma(\eta+\theta+\epsilon+\mu)-\epsilon(\sigma+\gamma+\tau+\mu)]}{[\epsilon(\boldsymbol{\sigma}+\boldsymbol{\gamma}+\boldsymbol{\tau}+\boldsymbol{\mu})+\boldsymbol{\alpha\gamma}](\boldsymbol{\alpha}+\boldsymbol{\eta}+\boldsymbol{\theta}+\boldsymbol{\epsilon}+\boldsymbol{\mu})} = -0.28$$

$$SI(\phi) = \frac{\partial R_{eff}}{\partial \phi} \times \frac{\phi}{R_{eff}} = \frac{\rho\phi q[(\phi+\mu)(\lambda+2\phi+2\mu)-2\phi(\phi+\lambda+2\mu)]}{(\boldsymbol{\phi}+\boldsymbol{\mu})[(\mathbf{1}-\boldsymbol{q})(\boldsymbol{\phi}+\boldsymbol{\mu})^2+\boldsymbol{\rho\phi q}(\boldsymbol{\phi}+\boldsymbol{\lambda}+\mathbf{2}\boldsymbol{\mu})]} = -0.01$$

$$SI(q)=\frac{\partial R_{eff}}{\partial q}\times\frac{q}{R_{eff}}=\frac{\boldsymbol{q[\rho\phi(\phi+\lambda+2\mu)-(\phi+\mu)^2]}}{[(\mathbf{1-q})(\boldsymbol{\phi+\mu})^2+\boldsymbol{\rho\phi q}(\boldsymbol{\phi+\lambda+2\mu})]}=-3.51$$

$$SI(\rho)=\frac{\partial R_{eff}}{\partial \rho}\times\frac{\rho}{R_{eff}}=\frac{\rho\phi q(\phi+\lambda+2\mu)}{[(\mathbf{1-q})(\boldsymbol{\phi+\mu})^2+\boldsymbol{\rho\phi q}(\boldsymbol{\phi+\lambda+2\mu})]}=0.04$$

$$SI(\eta)=\frac{\partial R_{eff}}{\partial \eta}\times\frac{\eta}{R_{eff}}=\frac{\boldsymbol{-\eta}}{(\boldsymbol{\alpha+\eta+\theta+\epsilon+\mu})}=-0.3$$

$$SI(\theta)=\frac{\partial R_{eff}}{\partial \theta}\times\frac{\theta}{R_{eff}}=\frac{\boldsymbol{-\theta}}{(\boldsymbol{\alpha+\eta+\theta+\epsilon+\mu})}=-0.18$$

Table 4: The sensitivity index of parameters

No	Parameter	Sensitivity index
1	q	-3.51
2	ϵ	0.54
3	η	-0.3
4	α	-0.28
5	γ	0.28
6	θ	-0.18
7	λ	0.07
8	σ	-0.04
9	ρ	0.04
10	τ	-0.03
11	δ	0.02
12	ϕ	-0.01

From the table 4 above, we consider that the most sensitive parameter is proportion rate of vaccinated individuals (q) and the least sensitive parameter is the vaccine efficacy waning rate (∅).The proportion rate of vaccinated individuals (q) influences effective reproduction number negatively. That is when the value of proportion rate of vaccinated individual increases, correspondingly the value of effective reproduction number decreases or vice-versa.

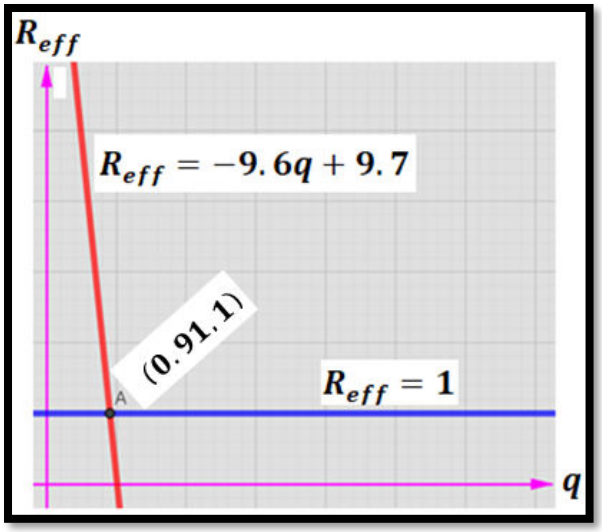

Figure: 5 Graphs of effective reproduction number versus influential parameters (q)

From figure 5 above we observe that, (0.91, 1) is the intersection point of the proportion rate of vaccinated individuals and effective reproduction number. When the value of proportion rate of vaccinated individual (q) is greater than one, then the value of effective reproduction number is less than one. At the point of intersection of $R_{eff} = -9.6q + 9.7$ *and* $R_{eff} = 1$,the value q=0.91 biologically tell us that one infectious individual can infect only one female throughout his infectious period. At this point, the disease cannot be epidemic. For q=0.91, Ethiopia should give HPV vaccine to 7,085,260 females with age 9-14. If the country vaccinates more than 7,085,260 females, then $R_{eff} < 1$.This means, the cervical cancer disease dies out of the country. That is, the prevalence is decreasing and cervical cancer can no more epidemic in the country.

2.7 Results and discussion

Ethiopia has a population of 36.9 million women ages 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 7445 women are diagnosed with cervical cancer and 5338 die from the dis ease. Cervical cancer ranks as the 2nd most frequent cancer among women in Ethiopia and the 2nd most frequent cancer amongwomenbetween15and 44 years of age. Data is not yet available on the HPV bur den in the general population of Ethiopia. However, in Eastern Africa, the region Ethiopia belongs to, about 4.7% of women in the general population are estimated to harbor cervical HPV 16/18 infection at a given time, and 67.9% of invasive cervical cancers are attributed to HPVs 16 or 18. [48]

In order to examine the dynamics of cervical cancer brought on by HPV infection in Ethiopia, I looked at non-linear systems of ordinary differential equations. I applied and expanded the suitable mathematical model on the dynamics of HPV-caused cervical cancer in this work. I found that an important aspect of mathematical epidemiology which is known to be effective reproduction number R_{eff} which determines how the disease spreads in the country and control with vaccination intervention.

To decide if the spread of HPV-caused cervical cancer in Ethiopia is high or low, I used the standard measurement which is known as the effective reproduction numberR_{eff}. In my modified model I derived the effective reproduction number $R_{eff} = \frac{\lambda\delta[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma][(1-q)(\phi+\mu)^2+\rho\phi q(\phi+\lambda+2\mu)]}{(\phi+\mu)^2(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}$and basic reproduction number $\boldsymbol{R_0} = \frac{\lambda[\epsilon(\sigma+\gamma+\tau+\mu)+\alpha\gamma]}{(\lambda+\mu)^2(\delta+\mu)(\sigma+\gamma+\tau+\mu)(\alpha+\eta+\theta+\epsilon+\mu)}$ .Based on some collected data from Ministry of Health of Ethiopia and standard data taken from different journals, I found that the numerical value of the effective reproduction number is $R_{eff} = 1.9 > 1$.This in principle implies that, even if vaccination is given, the disease spreads in the community and one infectious individual infects about two healthy individuals in his/her infectious time. Here, the basic reproduction number, without vaccination intervention, is $R_0 = 21.5$ which told us thatone infectious individual infects about twenty two healthy individuals in his/her infectious time. From this, it possible to see that vaccination intervention is so effective.

From figure 5, it is possible to see that how effective reproduction numberR_{eff} is affected by the proportion rate of vaccinated individuals (q). From the graphical representation, $q = 0.91$is control parameter. If $q < 0.91$then the effective reproduction number is greater than one and HPV-caused cervical cancer disease spreads in the community. If $q > 0.91$then the effective reproduction number is less than one and the disease decreases its spread in the community.

2.8 Conclusion

In many fields of research, particularly health science, mathematical modeling has shown to be an invaluable tool for visualizing complicated systems and unsolved issues in order to simplify the study of their behavior. In this paper, I have applied mathematical modeling of cervical cancer transmission by Human papilloma virus with vaccination intervention. About 6.3 million females take at least the first dose of HPV vaccine and about 5,839,000 take the last doses in Ethiopia. For the proportion rate of vaccinated individuals(q=0.91), where the effective reproduction number is unity, Ethiopia should give HPV vaccine to 7,085,260 females with age 9-14. If the country vaccinates more than

7,085,260 females, then $R_{eff} < 1$.This means, the cervical cancer disease dies out of the country. That is, the prevalence is decreasing and cervical cancer can no more be epidemic in the country.

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