Global Scientific JOURNALS

GSJ: Volume 12, Issue 3, March 2024, Online: ISSN 2320-9186
www.globalscientificjournal.com

ON THE SENSITIVITY ANALYSIS OF A MATHEMATICAL MODEL OF THE TRANSMISSION DYNAMICS AND CONTROL OF CERVICAL CANCER DISEASE FOR OPTIMAL HUMAN HEALTH

Dr. Tertsegha Tivde, Emmanuel Onoja Ameh and Reuben Iortyer Gweryina

Department of Mathematics, College of Physical Sciences, Joseph Sarwuan Tarka University, Makurdi
tivde.tertsegha@uam.edu.ng

KeyWords
Sensitivity Analysis, Mathematical Model, Dynamics and Control, Cervical Cancer, Human Papilloma Virus Infections, Effective Reproductive number

ABSTRACT

Human Papilloma Virus which causes Cervical Cancer was studied in terms of its prognosis. A Mathematical Model of the Dynamics and Control of Cervical Cancer Due to Human Papilloma Virus Infections was formulated using compartmental analysis modeling approach. Preventive and treatment control measures were incorporated into the model. The next generation matrix operator was used in computing the effective reproduction number, R_e. The resulting effective reproductive number was used in determining the sensitivity indices of the various parameter of the formulated epidemiological model by applying the normalized forward sensitivity index. The results showed the most sensitive parameter to be vaccinated rate, ω_1 followed by the transmission coefficient β and wanning rate, σ of the vaccinated women. The paper called on women to present themselves for both screening and hence, vaccination for optimal human health.

INTRODUCTION

It is of no doubt that Genital Human Papilloma Virus (HPV) is one of the most common sexually transmitted infections that has constituted a serious health threats to the society and has been proven in epidemiological and molecular studies to be a necessary etiologic agent for cervical cancer. According to Llamazares and Smith (2008)[8], most people who become infected with HPV do not even know that they have it due to several of them being harmless.

The study conducted by Bergot *et al*. (2011)[2] revealed the symptoms of cervical cancer cases to include; abnormal vaginal bleeding, pain during sexual intercourse, increased amount of discharge from the vagina and foul-smelling discharge from vagina. Going by this analogy we can infer that women who have many sexual partners with men who have had many other partners have a greater risk and having a weakened immune system and not getting a regular Pap test.

Earlier stated, Cervical Cancer is an abnormal kind of cancer that develops in women's cervix. The cervix is the entrance to the womb from the vagina; it joins the uterus to the vagina. Blood flows from the uterus through the cervix into the vagina during menstrual period. Cervical cancer may sometimes be a threat to life; it can attack nearby tissues and organs. It may extend to other parts of the body. Cervical cancer is the second most common cancer after breast cancer occurring in Sub Saharan Africa (Lowy and Schiller, 2006)[9].

Cervical cancer cells can spread by breaking away from the cervical tumor. They can transmit through lymph vessels to nearby lymph nodes. The spread of cancer cells occurs through the blood vessels to the lungs, liver, or bones. Although there are wide variations in the burden and incidence between countries (Ranging from 3 – 50 per 100,000), more than 80% of the global burden of Cervical Cancer and related deaths occur in low income countries of South and Central America, sub-Saharan Africa, and south and south-east Asia. Cervical Cancer affects women during the most productive years of their lives, leading to misery, low productivity, and economic hardship on individuals, family and societal levels (Franco and Harper, 2005)[6].

Primary prevention of HPV infection begins with HPV vaccination of girls aged 9-25years, before they become sexually active. After many years of testing, two HPV vaccines have been approved by the USA Food and Drugs Administration (FDA). They are Gardasil and Cervarix which reduces the risk of cancerous or precancerous changes of the cervix and perineum by about 93%. HPV vaccines are typically given to female age 9 to 25 years 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 (WHO, 2005)[11].

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 (Lee and Tameru, 2012)[7].

Getting the HPV vaccine before being exposed to HPV will prevent High risked HPV16-18 types that cause HPV infections. 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, reduces the viral load and consequently transmission (Bogaards *et al*, 2010)[3].

The problem of human papilloma virus (HPV) infection cuts across all gender worldwide but mostly found in the female population. HPV infection results in different human cancers which continue to persist and cause great threat in both developed and developing countries. Most of the governments all over the world are ever trying to their level best to curb such dangerous impacts.

Lee and Tameru (2012), formulated mathematical models, from individual and population perspectives, will help decision makers to evaluate different prevention and mitigation measures of HPV and deploy synergistically to improve cancer outcomes. Integrating the best-available epidemiologic data, computer-based mathematical models used in a decision-analytic framework can identify those factors most likely to influence outcomes and can help in formulating decisions that need to be made amidst considerable lack of data and uncertainty.

Shaban and Hawa (2014)[10] modeled the spread dynamics of HPV infection incorporating into the model screening and vaccination without taking into consideration the varying infectivity and susceptibility of individuals to HPV. This study investigates the impact of vaccination and screening on the dynamics of HPV by studying the impact of public health education programme against HPV transmission dynamics. This has been achieved by formulating a mathematical model therby incorporating into a model, control measure at the varying infectivity and susceptibility states. The paper computed the basic reproduction number for the HPV disease which was used in the determination of the sensitivity of the various model parameters.

Model Formulation

The model is formulated by modifying the model by Shaban and Hawa (2014). In addition to the assumptions of the existing model, the impact of vaccination and screening on the dynamics of HPV as well as the impact of public health education programme against HPV transmission dynamics as suggested by as future work.

Parameters of the modified model

In addition to the parameters of the existing model we present the parameters of the modified model as follows:

Table 1: Variables and Parameters of the Modified HPV Basic Model

Parameter	Definition
$S_\alpha(t)$	The number of susceptible aware individuals at time t
$S_n(t)$	The number of susceptible unaware individuals at time t
$\pi\rho$	Aware Susceptible individuals recruited at a constant rate

$(1-\rho)\pi$	Unaware Susceptible individuals recruited through other means
ϑ_e	Public health awareness campaign
e	Progression rate from unaware susceptible to aware susceptible individual
$\nu(1-u)$	Progression rate from screen individuals to Cancer with control measure
$\epsilon(1-u)$	Progression rate from unscreened individuals to Cancer with control measure

We now explain the dynamics of each compartmental population. The modified model is built on the following assumptions: i) We formulate a basic HPV model with human population at time t, ii) The total population size denoted by N, is divided into seven subclasses namely; Aware Susceptible individuals S_α(t), Unaware Susceptible individuals S_n(t), Vaccinated individuals V(t), Unaware infected individuals I_u(t), Screened infected individuals I_s(t), individuals with cervical cancer C(t) and Recovered individuals R(t), iii) The susceptible individuals are sub divided into aware and unaware. Aware Susceptible individuals are recruited at a constant proportion rate $(1-\rho)\pi$ and Unaware Susceptible individuals are recruited through other means at rate, $\rho\pi$, iv) The susceptible individuals may progress to become infected with HPV when the public health education or public awareness campaign are not implemented at the rate ϑ_e v) The susceptible individuals are vaccinated at the rate of ω and others acquire HPV infection at the rate, λ, where $\lambda = \frac{\beta(I_u + I_s)}{N}$ where, β is the effective contact that may result into HPV transmission and β is defined as the probability that a contact between a susceptible person and an infectious partner leads to a new infection, vi) The screened individuals can modify their behaviour at the rate η which results into reducing the risk of HPV transmission in the population, vii) The vaccinated individuals may also be infected at a reduced rate (1- $\varphi)\lambda$, where $\varphi \in (0, 1)$ measures the efficacy of the vaccine, viii) The vaccinated individuals return to the susceptible class after waning their immunity at the rate σ. The unaware infected individuals are screened and joined to the screened infected class at the rate, ϕ. ix) some of the unaware infected individuals' progress to cancers at the control rate $\varepsilon(1-u)$ and screen individuals also progress from screen individuals to Cancer with control measure $\nu(1-u)$ and others recover through body immune system at the rate δ, x) The screened infected individuals recover after a successful treatment at the rate, γ, xi) recovered individuals revert to the susceptible class after waning their immunity at the rate α and xii) All individuals suffer natural mortality at a rate μ and sick individuals die of cancer at the rate ζ.

The governing equations of the modified model

The governing equations of the modified model are as

$$\left.\begin{aligned}
\frac{dS_n}{dt} &= \rho\pi - [e + \omega_2 + \mu + (1-\vartheta_e)]S_n \\
\frac{dS_\alpha}{dt} &= (1-\rho)\pi + \mathrm{e}S_n + \sigma V + \alpha R - [\omega_1 + \mu + (1-\vartheta_e)\lambda]S_\alpha \\
\frac{dV}{dt} &= \omega_1 S_\alpha + \omega_2 S_n - [\sigma + \mu + (1-\varphi)\lambda]V \\
\frac{d\mathrm{I}_u}{dt} &= (1-\vartheta_e)\lambda S_\alpha + (1-\vartheta_e)\lambda S_n + (1-\varphi)\lambda V - \big(\phi + \delta + \mu + \epsilon(1-u)\big)\mathrm{I}_u \\
\frac{d\mathrm{I}_s}{dt} &= \phi \mathrm{I}_u - \big(\gamma + \mu + \nu(1-u)\big)\mathrm{I}_s \\
\frac{dC}{dt} &= \varepsilon(1-u)\mathrm{I}_u + \nu(1-u) - (\mu + \zeta)C \\
\frac{dR}{dt} &= \delta \mathrm{I}_u + \gamma \mathrm{I}_s - (\alpha + \mu)R
\end{aligned}\right\} \quad (1)$$

The non- negative initial conditions for the model are,
$S_n > 0; S_\alpha > 0;\ V \geq 0; \mathrm{I}_s \geq 0; \mathrm{I}_u \geq 0; C \geq 0; R \geq 0$

Effective Reproduction Number and Sensitivity Analysis

In order to carryout the sensitivity analysis on the model, the basic reproduction number was determined as effective reproduction number. The effective reproduction number so obtained was used in the determination of the various sensitivity indices of the model parameters.

The effective reproduction number, $\mathrm{R_e}$

Basic reproduction number denoted, $\mathrm{R_0}$ is the average number of secondary HPV Infections caused by an infectious individual during his or her entire period of infectiousness. The Basic reproduction number is an important non-dimensional quantity in epidemiology as it set the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies. On the other hand effective or control reproduction number $\mathrm{R_e}$ measures the average number of HPV new infections gen-

erated by a typical infectious individual in a community in the presence of control measure such as public awareness campaign, vaccination, screening and treatment strategies are implemented. The next generation operator approach as described by Van den Driessche and Watmough (2002)[12] was used to determine the R_0.

The conditions on which the effective reproduction number would be implemented are such that;

i. If $R_0 < 1$, then each infected individual with HPV produce on average, less than one new infection during her infectious period and the disease dies out in the population but,
ii. If $R_0 > 1$, each HPV infected individual produces on average more than one new infectious during infectious period, in this case HPV infection can persist in the population.

We compute the basic reproduction number using the next generation operator approach as described by setting $F_i(x)$ to be the rate of the new infections in the compartment I, V_i^- is the rate of transfer of individuals out of compartment I, $V_i^+$is the rate of transfer of individuals into compartment i by all other means, x_0 is the disease-free equilibrium state, and R_0 is the dominant eigen-value matrix of $G = FV^-$. The most dormant eigenvector of $\det(G - \lambda I)$ is the basic reproduction number.

It is assumed that each function (F_i, V_i) is continuously differentiable at least twice in each variable. The disease transmission model consists of non-negative initial conditions together with the following system of equations: Where G is called the next generation matrix. It is comprised of two parts F and V defined by

$$x = f_i(x) = F_i(x) - V_i, i = 1, \ldots . n \tag{2}$$

where,

$$F = \frac{\partial F_I(x_0)}{\partial x_j} \text{and } V = \frac{\partial V_I(x_0)}{\partial x_j} for\ i, j = 1,2,3 \tag{3}$$

Applying this approach on the model in equation (1), the effective reproduction number was obtained and represented by equation (4)

$$R_e = \frac{\beta(\gamma+\mu+\eta\phi)\{(1-\vartheta_e)[(\sigma+\mu)(e+\omega_2+\mu)+\rho\mu(\omega_2-\omega_1)]+(1-\varphi)[\omega_1(e+\omega_2+\mu)+\rho\mu(\omega_2-\omega_1)]\}}{(\gamma+\mu+\nu(1-u))(e+\omega_2+\mu)(\sigma+\omega_2+\mu)(\delta+\phi+\mu+\varepsilon(1-u)} \tag{4}$$

Equation (4) involves the contribution of unaware infected and aware infected individuals in the transmission of HPV infection. Thus,

$$\mathrm{R_e} = \mathrm{R_{e1}} + \mathrm{R_{e2}} \tag{5}$$

where

$$\mathrm{R_{e1}} = \frac{\beta(\gamma+\mu+\eta\phi)(1-\vartheta_e)[(\sigma+\mu)(e+\omega_2+\mu)+\rho\mu(\omega_2-\omega_1)]}{(\gamma+\mu+\nu(1-u)(\sigma+\omega_2+\mu)(\delta+\phi+\mu+\varepsilon(1-u)} \tag{6}$$

and

$$\mathrm{R_{e2}} = \frac{(1-\varphi)[\omega_1(e+\omega_2+\mu)+\rho\mu(\omega_2-\omega_1)]\}}{(\gamma+\mu+\nu(1-u)(e+\omega_2+\mu)(\sigma+\omega_2+\mu)(\delta+\phi+\mu+\varepsilon(1-u)} \tag{7}$$

Equations (6) and (7) are the contribution of unaware infected individuals in the population and the contribution of Public health awareness campaign respectively.

Sensitivity Analysis

Sensitivity analysis was done here to determine how best we can reduce human mortality and morbidity due to HPV. We know that, initial disease transmission is directly related to, R_0. We calculate the sensitivity indices of the basic reproduction number, R_0 to the parameters in the model. These indices tell us how vital each parameter is to disease transmission and prevalence.

The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives governed by equation (8);

$$r_\tau^p = \frac{\partial p}{\partial \tau} \times \frac{\tau}{p} \tag{8}$$

Where r_τ^p is the sensitivity index of τ. Equation (8) was applied on equation (4) and the sensitivity indices results of R_e are given in Table 2 and are arranged from the highest sensitivity value to the lowest value.

Table 2: Sensitivity indices of R_0 with respect to each parameter

S/No.	Parameter	Value	Sign
1	ω_1	1.4264	+
2	β	1.0000	+
3	σ	0.4525	+

4	η	0.2857	+
5	ω_2	0.1399	+
6	ρ	0.0133	+
7	ε	0.0435	-
8	δ	0.1739	-
9	γ	0.2143	-
10	ϕ	0.4099	-
11	e	0.4346	-
12	$1-\vartheta_e$	1.3850	-
13	μ	1.7425	-
14	φ	1.0824	-

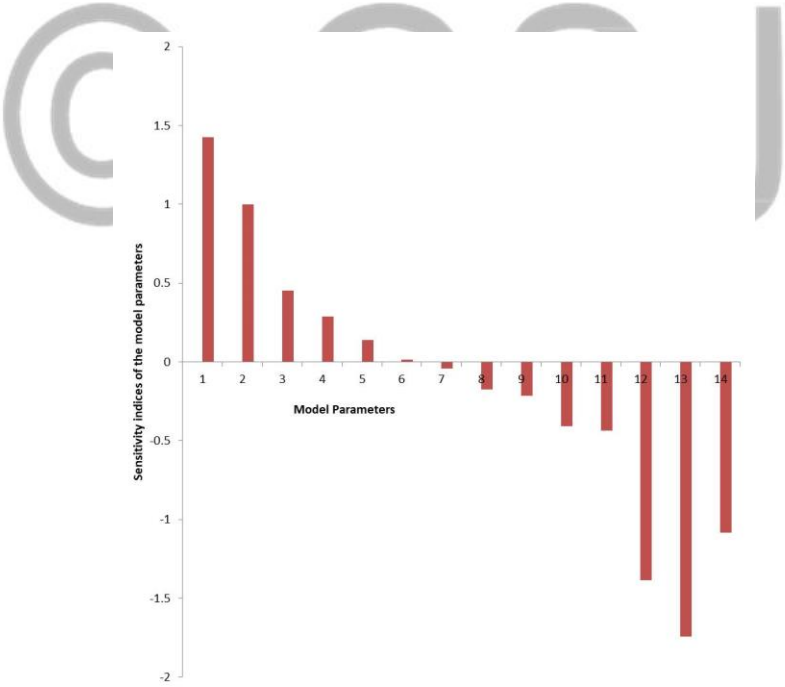

Figure 1: A bar graph showing the sensitivity indices of the model parameters (the numbers 1 – 13 on the horizontal axis represent the various parameters of as shown in Table 2)

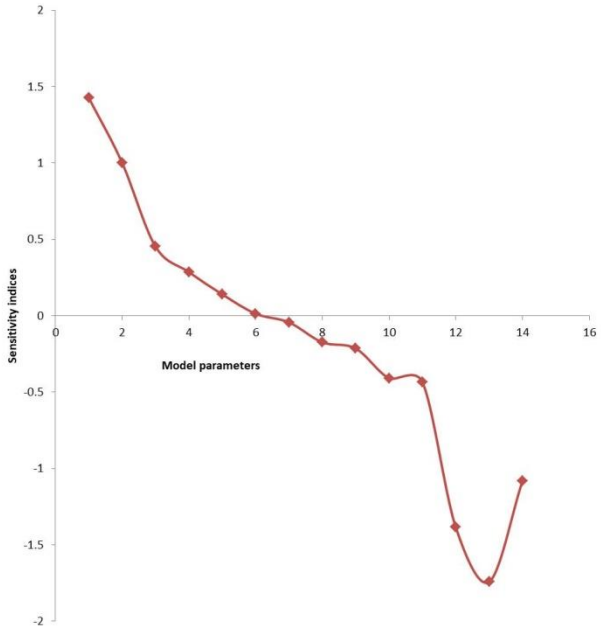

Figure 2: A graph showing the sensitivity indices of the model parameters (the numbers 1 – 13 on the horizontal axis represent the various parameters of as shown in Table 2)

Discussion

The results in Table 2 is plotted in Figures 1 and 2 showing explicitly that the indices with positive signs show that the basic reproductive number, R_e increases when the corresponding parameters are increased. In a similar pattern, those parameters having negative signs of sensitivity indices indicate that the value of R_e decreases when the parameters are increased. The most sensitive parameter here is ω_1= +1.426372025 and the least sensitive is φ = -10.82371226. This shows that the rate at which women are enlightened to get vaccinated is pivotal to the control of HPV. This result is in consonance with CDC (2021)[1] which shows that HPV infections, genital warts, and cervical precancers (abnormal cells on the cervix that can lead to cancer) have dropped since the vaccine has been in use in the United States.

Conclusion and recommendation

A basic deterministic model of HPV transmission dynamics and control was formulated taking the population of women. Preventinve control and treatment control were employed as basic control measures in the model. The HPV model with public awareness campaign, vaccination and screening was used in computing the effective reproduction number, R_e which was employed in in carrying out the sensitivity analysis.

A sensitivity analysis revealed that the most sensitive parameter is the vaccinated rate, ω_1 followed by the transmission coefficient β *and* σ wanning rate of the vaccinated individual. We recommend that palliative care should be incorporated into the model as future work.

References

[1] CDC, Reasons to Get HPV Vaccine, Centre for Disease Control and Prevension, November, 2021.

[2] A. S. Bergot, A. Kassianos, H. Ian and D. Mittal, New Approaches to immunotherapy for HPV Associated Cancers . *OPEN ACESS Cancers*, 11:346-3495, 2011.

[3] J. A. Bogaards, M. Xiridou, M. H. Veerle Coupe, J. L. M Chris, J. Wallinga, and J. Berkhof, Model-Based Estimation of Viral Transmissibility and Infection-Induced Resistance From the Age-Dependent Prevalence of Infection for 14 High-Risk Types of Human Papillomavirus. *American Journal of Epidemology*, 17(7): 817-825, 2010.

[4] O. Diekmann and J. A. Heesterbeek, Mathematical Epidemiology of Infectious Disease Model Building; Analysis and Interpenetration. *International Journal of Epidemiology* 30(1): 186, 2001.

[5] P. V. Driessch and J. Watmough, Reproduction Number and Sup-Thresholds Endemic Equilibrium for compartmental Models of Disease Transmission. *Mathematical Biosciences*, 180: 29-48, 2002.

[6] E. L. Franco and D. M. Harper, Vaccination against Human Papillomavirus Infection: a new paradigm in cervical cancer control. Canada: McGill University 23(17-18):2388-94.,

[7] S. L. Lee and A. M. Tameru, A Mathematical model of Human papillomavirus in the United States and its impact on cervical cancer. *Ivyspring International Publisher Journal of Cancer,* 3:262-266, 2012**.**

[8] M. Liamazares and R. J. Smith, Evaluating Human Papillomavirus Vaccination Programs in Canada: Should provincial healthcare pay for voluntary adult vaccination?. Biomed Centra, Ottawa, Canada. *Journal of public health,* 8(1)1-12, 2008.

[9] D. R. Lowy and J. T. Schiller, Prophylactic Human Papillomavirus Vaccines. *J C Invest*, 116(5):1167-1173, 2006.

[10] N. Shaban and M. Hawa, Modeling the Impact of Vaccination and Screening on the Dynamics of Human Papillomavirus Infection. *International Journal of Mathematical Analysis*, 8 (9): 441-454, 2014.

[11] WHO, Report of the Consultation on Human Papillomavirus Vaccines World HealthOrganization. *Geneva*, (April 2005) https://www.cdc.gov/std/hpv/stdfsct-hpv.html.

[12] P. Van den Driessche and J. Watmough, J. Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission. *Mathematical Bio-sciences*, Volume 180: 29-48, 2004.