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Three Doses to Finish: A Review on Completion of Human Papillomavirus (HPV) Vaccination among Adolescent Females Aged 12-17 years

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Abstract

Human papillomavirus (HPV) related cancers have become a major public health concern. About 90% of HPV-related cancers are caused by HPV 16 and 18 strains. The virus can cause various cancers, such as oropharyngeal, anal, penile, but most of the HPV related cancers are dominated by cervical cancer. About 70% of all cervical cancers are caused by HPV infection. HPV vaccination in the U.S still remains an important public health challenge with the rate of vaccine initiation of just 50%. Therefore increasing the pattern of HPV vaccine uptake is an important public health issue to increase the overall vaccination coverage. Improving parental awareness among adolescents and their mothers about HPV vaccine and its triple course regimen can significantly reduce later risk of HPV infection and cervical cancer among adolescent females. This article expands the understanding of HPV vaccine's initiation and completion among adolescent females. An intervention called three doses to finish is also proposed in the article, to increase the awareness of HPV vaccine, and completion rates of the vaccination by an educational seminar and text message reminders.

Keywords: Cervical cancer; HPV; Vaccine; Adolescent females; Intervention

The Burden of Cervical Cancer

Cancer is the leading cause of death in developed countries and second leading cause of death in developing world [1]. The burden of cancer is still increasing due to number of reasons including cigarette smoking, physical inactivity, unhealthy diets etc. Certain viruses like (EBV) Epstein Barr virus, (HPV) Human Papillomavirus and (HIV) Human Immunodeficiency virus also have the ability to cause cancer [2]. Although lung, breast and colorectal cancers are the leading cause of mortality among women, and cervical cancer still holds an important place in cancer causing mortality among females [3].

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of mortality in females in the world, contributes to about 9% of the total new cancer cases and 8% of total number of deaths due to cancer among women [4]. Estimates of worldwide burden of cervical cancer indicates that 529,8000 cases and 275,100 deaths occur due to cervical cancer every year [2].

The highest incidence rates of cervical cancer are seen in Eastern and Southern Africa [3]. India, accounts for about 27% of all the disease cases of cervical cancer .3 In United States, the incidence of cervical cancer is getting decreased [3]. However it is still found to show high incidence rates in Hispanics, 4 and African American ethnicities of the country [5]. The incidence rate of cervical cancer is 34% higher and the mortality rate is double in African American women when compared to White American females [4]. Hispanic women in United States show incidence and mortality from cervical cancer about 50-70 times higher than non-Hispanic white females [5].

Risk Factors of the Disease

Some of the most important risk factors of cervical cancer includes early age at first sexual intercourse, infection with Human Papillomavirus, multiple sexual partners, active and passive cigarette smoking, high parity, prolonged use of oral contraceptives (>5 years) [6]. Human Papilloma virus causes almost all cases of cervical cancer. It also causes some non-cervical cancers like vulvar, vaginal, anal, and penile and oropharyngeal cancer [7]. For cervical cancer, the rate of HPV transmission increases with the increase in number of sexual partners, multiparty and early age at first sexual experience [8].

Screening for Cervical Cancer

High quality screening methods for cervical cancer, such as Papanicolaou smear cytology testing (Pap smear) has significantly reduced the morbidity and mortality from squamous cell carcinoma of the cervix that constitutes 90% of all cervical cancers [9]. This reduction in mortality is due to increased detection of the advance disease in early stages, and the detection of pre-invasive lesions that reduces the overall incidence of invasive cancer [5]. It is very much understood now that persistent infection with Human Papillomavirus (HPV) is necessary for the development of cervical cancer.10 Different subtypes of HPV, like HPV 16 and HPV 18 are highly carcinogenic genotypes, and can cause cervical cancer. Thus cervical carcinogenesis proceeds as: acquiring Human Papillomavirus, persistent infection of HPV, progression of the disease to precancerous stage, and the stage of invasive disease [5,10,11].

The importance of cervical cancer screening lies in the fact that one half of cervical cancers in the US are in women who have never been screened. About 10% of cervical cancer occurs in women who have not been screened in the last 5 years [12,13]. According to American Cancer Society, cervical cancer screening should begin at the age of 21

years [14]. For women in the age range of 21-29 years, screening for cervical cancer by cytology is recommended every 3 years [14]. For those in age range of 30-65 years, the proposed screening test is to get cervical cytology and HPV testing done every 5 years or only cytology alone every 3 years [14].

The Development of HPV Vaccination

HPV is the most common sexually transmitted infection in the US. About 20 million men and women in the country are infected with HPV infection [15]. The infection of HPV is very common among men and women in their late teens and early twenties [15].

Although cervical cancer is very rare in adolescent females, yet its prevention in this age group is an important issue. There is no cure for HPV infection and persistent infection can lead to warty lesions on genitalia and various types of cancers (cervical, oropharyngeal, penile etc.) [16]. Therefore, the best way to deal with it is via universal HPV vaccination, a safe, efficacious, cost effective and highly effective method that should be used in adolescent females before they become sexually active [14]. Vaccination against HPV has shown exceptionally promising results in the prevention of genital warts, cervical cancer and other HPV related cancers (Markowitz, 2007) [17].

In 2006, United States became the first country to license HPV vaccine for females aged 9-26 years [18]. US Food Drug and Administration (FDA) approved a quadrivalent vaccine, Gardasil, for protection against four types of HPV (HPV 6, 11, 16 and 18) that are responsible for causing up to 70% cervical cancer cases and 90% genital warts [19]. Gardasil, developed by pharmaceuticals of Merck, is approved for females as well as males in the age range of 9-26 and specifically recommended for males and females in the age group of 11-12 at the time of their regular preventive care visit [19]. In 2009, an approval was given by FDA for bivalent vaccine for protection against HPV, Cevarix developed by GlaxoSmithKline, which covers two cancer causing HPV strains (HPV 16 and 18) for girls aged 9-26 years [19]. Both vaccines are given in the form of three dose schedule. The recommended dose regimen for HPV vaccine is to receive three doses of the vaccine in a way that: 1st dose at time 0, second dose 1-2 months after the first dose, and the final dose within 6 months of the first dose [19]. According to a study by Parkin et al. [16] both Gardasil and Cevarix have the potential to significantly lessen the burden of HPV infection if the population show widespread uptake and administration of these vaccines prior to sexual activity, the ideal time being early adolescent years [16].

Importance of HPV Vaccination in Adolescent females

Administration HPV vaccination among young adolescent females is an important step in preventing HPV infection later in their life. Completion of the HPV vaccination series that constitutes of three doses greatly increases the chances of protection against HPV for the rest of the recipient's life [20]. As the mode of HPV transmission is via sexual intercourse, young adolescent females can get infected just after they become sexually active and experience their first sexual activity [21]. Therefore adolescent females should be vaccinated against HPV before they begin their sexual life [21]. A study from Australia concludes a significant reduction in high grade cervical abnormalities in females less than 18 years after three years of mass HPV vaccination program that targeted adolescent females [22]. According to a study by Dunne et al. [23] a delay in administration of HPV vaccine can show negative effects on adolescent girls' health and about 1/4th of the females in 14-19 age group are found to be infected with at least one strain of HPV and thus have high risk of developing cervical, anal, vaginal and oral cancers [23]. The vaccine of HPV is effective only before the infection is acquired, and has no promising role after the infection has already been occurred [24,25]. A study by Kohli et al. [26] indicates that a powerful and wide-ranged HPV vaccination program which provides a complete 100% coverage can reduce the burden and mortality from cervical cancer by 76% [26].

Completion of HPV Vaccination Course among Adolescent Females

Despite the importance of HPV vaccination, the uptake of this vaccine by the population is still very low compared to what it should be. A recent study reports that only 35.9% young females in Japan are vaccinated against HPV [27]. Even in United States, the uptake of vaccine and its completion has been very slow among adolescents and young adult females.28 Nationwide estimates show that in 2007, only about one-fourth females in the age group of 13-17 received HPV vaccine, and among them only 7% completed the full course of the vaccine.28 According to National Health Survey (NHIS) of 2008, among females age 11-17 years, only 23% received vaccine and 9% completed the triple dose series [28-30]. In 2009, these figures were elevated to about 44% initiated the vaccine course and 27% completed all three doses of HPV vaccination [19]. In 2010, National survey discovered that about 49% adolescent females in the age group of 13-17 years, received at least one dose and only 32% completed the three dose course [18]. Completion of HPV vaccine is a big problem in US [31]. In Utah, although the initiation of HPV vaccine among adolescent females is equal to the country's average of 54%, but the three dose completion is only 41.8%, as compared to US average of 70% in 2010 [18]. California also shows low rate of HPV vaccination among adolescent females when compared to US average [32]. In Florida, HPV vaccine initiation and completion among Medicaid population was found to be 19.8%, which is much lower than 37.2%, the rate of vaccination in general population of the country [28,33]. Disparities also exist in the Appalachian area of the US [34]. Among adolescent females, who belong to the Appalachian area of the US, vaccine initiation is lower than the US average; however rate of completion of the vaccine is higher in this population [34].

Reasons for not Initiating/Completing Vaccination among Adolescents

One of the most important issues in adolescent females' HPV vaccination is that parents, particularly mothers, of these young girls, play an important role in making vaccination decisions [34]. A study indicates that teenagers' choice in joint vaccination decision with their parents has the potential to show both positive and negative effect on vaccine uptake [35]. There are several reasons behind low rate of vaccine uptake and completion of the series among adolescent females. In India, parents desire to vaccine their daughters at older ages, such as after 15 years [36]. A study by Kepka, et al. [31] that studied the HPV vaccination attitudes in Latino population of US, reports that low rate of assimilation with the culture, limited knowledge of HPV, inadequate information about HPV vaccine's 3 doses among Latino parents are the main barriers to vaccine completion [31]. A study by Darden et al. [37] reports that 11-14% parents in National Immunization survey of teens refused HPV vaccination because their daughters were not sexually active at that time, and their perception of the vaccine was that it should be given after a girl has started her

sexual life [37], another set of parents in the survey, regarded the vaccine as un-necessary, which is something frightening for public health professionals [37]. In North Carolina, lack of HPV vaccine completion was found to be higher among teenagers who are not very compliant about their routine visit to their doctor [38]. According to Schluterman et al. [39] HPV vaccine completion was low among African-American female teens compared to Caucasians in their study [39], and population that had public health insurance showed better rate of vaccine initiation and adherence compared to those with private insurance [39]. Lack of health insurance was also found to be a major barrier towards HPV vaccination, in-spite of free vaccination programs; people still have this mentality that the vaccine is not for free [39]. Studies have indicated several factors act as barriers to vaccine uptake and adherence to the completion of the regimen [40,41] these include mother's behaviour towards the vaccine which includes: low understanding of HPV infection and severity of its complications with persistent HPV infection, not aware of daughter's possibility of getting HPV, concerns regarding the side-effect profile and benefits of the vaccine, cost, societal impact and doctor's recommendation of the vaccine [40,41]. Another study reveals that those mothers with past history of STD and less than high-school education were more likely to support their daughters for HPV vaccination and adherence on the regimen [42]. Thus attitude of the parents is very important for the success of this vaccination program in adolescent age group. An interesting study of non-White population of the US comments on the importance of recommendation by the primary care physician in preventing HPV infection just by counseling about HPV vaccination among the minority groups of the country [43]. Hispanic population in this study shows more vaccination rates after they discuss it with their primary care providers [43], a result consistent with findings by Freed et al. [44] which reported increase pediatric vaccinations among Hispanic minority after it was advised by their primary care physician [44] A study on African-American adolescent females [45]describes that few reasons of non-vaccination among adolescent girls were that their mothers were not familiar with the term HPV, had doubts and questions about the vaccine's safety, regarded vaccine to be less urgent, and showed exasperation over inadequate information in advertisements and broadcasts regarding Gardasil vaccine [45] Public health departments of Appalachia,46 reports lack of knowledge of HPV, concerns and worries about the side-effects of vaccine and newness of vaccine in the country, as three important factors that acts as barriers to HPV vaccine's initiation and completion in that population [46].

Evidence Based Interventions

Several interventions have been used to increase the initiation and completion of HPV vaccine among adolescent girls. One intervention that has been widely used is the school based vaccination program. In Scotland [47], a school based intervention of HPV vaccine's all three doses has achieved very high uptake of the vaccine by adolescents [47]. According to a large cohort by Tabrizi et al. [48], a large government funded public school based free HPV vaccination program was done to vaccinate girls aged 12-17 years between 2007-2009 [48], and the same girls were followed over the next couple of years from 2010-2011 and it was found that the prevalence of HPV genotypes 6, 11, 16 and 18 infections was significantly lower in these young women [48].

Literature review has brought our attention towards another important intervention that was done to increase the adherence rate of adolescent female for HPV vaccinations. A study from Duke University, North Carolina by Matheson et al. [49] supports the fact the vaccination reminders for 2nd and 3rd vaccine dose via text message improves the vaccine completion rates among adolescent females [49]. Thus, text message reminders can play an effective role for vaccine's completion for those who enroll themselves in this approach [49]. Text message reminders can be favourable to both parents, as well as adolescent girls as people tend to check their text message inbox, more than emails or voice messages. This approach has also been successfully used for influenza vaccination reminders [50].

The Department of CDC also recommends that the primary healthcare providers can play an important role in increasing the completion rates of HPV vaccines, [15] by administering HPV vaccine to adolescent girls by the time they come for their other vaccinations like Tdap [15].

There are number of research papers published on the effectiveness of education based type of interventions for increasing the adherence to multi-dose series of HPV vaccine. Some studies have used the written handouts, [51] while others have used the school based immunization programs that also promote awareness among parents and young girls [52]. It is always beneficial to educate young girls and their mothers about HPV vaccine, [53] and its total number of doses that should be given before the onset of sexual activity [54]. Encouraging communications between mothers and their young daughters also increase the completion rate of the vaccine.54 The importance of effective education of adolescent girl about HPV infection and vaccine resides in the fact, [55] that those adolescent girls who receive the vaccine before the beginning of sexual activity are more likely to follow safe sex guidelines like using a condom during sexual intercourse [55].

Therefore, after looking at all above interventions, it is noted that the importance of educational programs and the reminder of the vaccine to the population carries huge importance.

Proposed Intervention

There is a need to have an intervention that is the mixture of these two actions i.e. educational program, and the reminder of the vaccine completion. This paper proposes an intervention with the title of "Three Doses to Finish". The first part of the intervention deals with the education of both, mothers as well as young adolescent girls, about HPV infection, the consequences of its persistence in the body that can lead to cervical, vaginal, anal and oral cancer, increasing their knowledge about the importance of cervical cancer screening and barrier methods and finally, educating them about Human Papillomavirus vaccine, its accessibility, its total doses, side-effects, level of protection by the vaccine and most importantly, the timing of the vaccine administration, which is, before the onset of sexual activity by young adolescent girls. The second part of this intervention is to increase the adherence to multi-dose regimen by using text message service to both, adolescent girls and their mothers at 3 and then 6 months after the educational seminar is done. In a study by Matheson et al. [49] text message reminders proved highly effective in promoting on-time receipt of HPV vaccination's 2nd and 3rd doses. Among the participants who received text message reminders, 14% completed the vaccine series on time, compared to only 3% of the standard care group that did not receive any text message reminders [49].

There are two goals attached with this proposed intervention. Goals of this program are: 1) to increase the awareness about Human

Papillomavirus infection and its dangerous outcomes, to educate mothers and daughters about the HPV vaccine, its access, and increase the awareness among the targeted population about vaccine's doses and the importance of completing all the doses before the onset of sexual activity; 2) to promote and increase the adherence to vaccines multi-dose regimen.

Health Promotion Setting for Intervention and the Target Audience

Three doses to finish, is proposed as a school based intervention that can target any public school of the country. The education about HPV infection, its vaccination and the importance of adherence to the regimen can best be delivered at the school. The school is selected as the target place because it provides a safe and relax environment and participants would not have to worry about the location of the intervention. Also, the school provides the location where CDC and other organizations can promote their free vaccination programs regardless of the insurance status. Because the first part of intervention is education based, therefore this portion should be conducted in the main auditorium of the school. As the target population includes adolescent girls aged 11-17 and well as their mothers, hence the seminar can be conducted over the weekend, such as on Saturday, when girls and their mothers can gather in the main auditorium of the school. The program planning team can deliver important information to the target audience and distribute pamphlets that contain information about HPV vaccine and answer some basic questions about the vaccine such as when it should be given, such as how many doses are there?, what are the possible side-effects? And where can we get a free vaccine from?. Next, a video should be played based on the similar information about HPV and vaccine. The video will help the audience in remembering more about the issue. The whole session should be made as interactive as possible. In order to attract more audience, the school authorities can also get involved and they may give extra credit to the students who attend the seminar along with their mothers. Finally, the wrap up session should include lunch and during the lunch, participants should be informed about the second section of the intervention, which is, to enrol the maximum number of participants in the text messaging campaign by noting down the cell-phone numbers of mothers as well as their teenage daughters. All participants can be given an empty sheet of paper that will gather young girls' history of vaccination, how many doses are given to her and the cellular phone numbers of both mother and daughter. The text message reminders should be sent to all numbers after 3 months of the educational seminar. Thus, the whole intervention looks feasible and cost effective and will effectively coordinate with the mission of Three Doses to Finish.

Adaptability of the above proposed intervention will increase the awareness about Human Papillomavirus infection and its dangerous outcomes, educate mothers and daughters about the HPV vaccine, its access, and increase the awareness among the targeted population about vaccine's doses and the importance of completing all the doses before the onset of sexual activity. The intervention shall also promote and increase the adherence to vaccines multi-dose regimen.

Conclusion

The completion of HPV vaccination among adolescents is still an important issue. This review article provides an overview of the rate of completion of the triple-dose regimen and the possible barriers to completion. This article suggests that educating mothers and their teenage daughters on HPV, its vaccine, importance of the vaccine completion and the reminder text messages will improve the vaccination's completion rate and will reduce the rate of HPV infection among young adult females. This will also increase young girls' compliance towards practicing safe sex practices after the onset of their sexual activity.

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