Myths and fake messages about human papillomavirus (HPV) vaccination: answers from the ESGO Prevention Committee

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Received 15 May 2022
Accepted 20 May 2022
Published Online First 12 July 2022

To cite: Taumberger N, Joura EA, Arbyn M, *et al*. *Int J Gynecol Cancer* 2022;**32**:1316–1320.

INTRODUCTION

Vaccine hesitancy is a global challenge. This has become even more visible during the COVID-19 pandemic. In most European countries with a sufficient vaccine supply, public programs failed to achieve coverage of more than 80%. There are various reasons for this phenomenon: in addition to political positions and religious beliefs, many would rather rely on opinions than facts. These opinions are nurtured by myths, repeated over social media and the internet. Vaccines preventing infections, disease, and cancer caused by human papillomavirus (HPV) have been available for more than 15 years. After clinical trials provided data from tens of thousands of study participants, we now have the experience and observational data from hundreds of millions of vaccine doses distributed worldwide.[1] These vaccines have demonstrated that they prevent not only HPV infections and pre-invasive disease, but also invasive cervical cancer.[2–4]

We have identified nine myths (summarized in Table 1) that we wish to discuss and dispel in this review article. This article will help support anyone who wants to give the best protection to children, adolescents, and adults by providing facts that can be used in discussions with individuals who might feel insecure after having heard various myths about HPV vaccination.

Myth #1: PAP Smears and Annual Check-ups are Effective So There is No Need for Vaccination

The introduction of cervical cancer screening programs using cytology significantly reduced the incidence of cervical cancer, but these programs have limitations and do not make complete elimination feasible. However, screening programs only address cervical cancer and not all HPV-associated diseases. These programs are only a secondary prevention method since their goal is the early detection of pre-cancerous lesions. Primary prevention of cervical cancer—which means avoiding an HPV infection altogether—can be effectively accomplished by HPV vaccination. Furthermore, the implementation of screening programs has been shown to be challenging in low-income countries where, together with middle-income countries, approximately 85% of cervical cancer deaths occur.[5]

Based on our knowledge of the efficacy of HPV vaccination, the goal should be not only to detect HPV-related pre-cancerous lesions early but to avoid them totally. The elimination of cervical cancer will only be possible with the combination of vaccination and screening, preferably with HPV testing, including self-sampling for some women.[6] HPV vaccination may also prevent other HPV-related malignancies that cannot be prevented through the detection and treatment of pre-invasive lesions, such as vaginal, vulvar, anal, penile, or oropharyngeal cancer.[7]

Myth #2: HPV Vaccines are New So There are No Safety and Efficacy Data on the Long-Term Side Effects

The vaccines we use today have been thoroughly studied for decades now. The principle of these vaccines was described 30 years ago. The first vaccine trials with a monovalent HPV 16 vaccine—the very same component used in the currently available vaccine—started in 1997 and the results were published in 2002. The first vaccine to be licenced was the quadrivalent HPV 6/11/16/18 vaccine which became available in 2006, followed by the bivalent HPV 16/18 vaccine in 2007. Meanwhile, the second generation of vaccines with the nonavalent HPV vaccine has been available in Europe since 2016.[8] To date we have more than 25 years of experience with these vaccines as well as observational data from hundreds of millions of distributed doses worldwide and several tens of thousands of study participants. The possible side effects are well documented and the safety of these vaccines has been confirmed by the World Health Organization (WHO), the US Centers for Disease Control and Prevention, and many other authorities.[9 10]

Myth #3: HPV Vaccination Can Cause Ovarian Failure

The concern about ovarian failure is primarily based on different case reports, animal models, and

Table 1 Summary of nine myths and fake messages about human papillomavirus vaccination

Myth		Fact	
#1: PAP smears are also effective: no need for a vaccination	X	The only screening available is for cervical cancer, not other cancers Five other cancers (affecting both women and men) are caused by HPV Screening is a secondary prevention method to detect pre-cancerous lesions or cancer early HPV vaccination is effective in the primary prevention of disease	✓
#2: HPV vaccines are new so there are no safety and efficacy data on long-term side effects	X	We have 25 years of experience with the vaccines We have 15 years of real-life experience with several hundred million doses distributed worldwide The possible side effects are well documented Vaccine safety has been confirmed by WHO, CDC, and many other authorities	✓
#3: HPV vaccination can cause ovarian failure	X	No connection between HPV vaccination and ovarian failure has been observed, following observation of 1 million females	✓
#4: Vaccines cause autoimmune diseases, neurological disease, and death	X	The incidence of autoimmune or neurological conditions and death is the same in HPV-vaccinated and unvaccinated populations	✓
#5: Children are not sexually active so there is no need to vaccinate them early	X	The earlier you vaccinate, the better the immune response Fewer doses are needed when individuals are vaccinated under the age of 15 years The earlier you vaccinate, the better the strength of the prevention	✓
#6: Boys and men do not get cervical cancer so they do not need a vaccine	X	HPV is linked to at least five malignancies other than cervical cancer: vulvar, vaginal, anal, penile, and oropharyngeal cancers Gender-neutral vaccination provides the best protection for all individuals regardless of gender and (future) sexual orientation	✓
#7: After the first sexual intercourse the vaccine does not work any longer	X	In clinical trials most young women were sexually active and the level of protection was >90% Efficacy data up to the age of 45 years are available Even after treatment for HPV-related disease, the vaccine potentially reduces the risk of subsequent disease	✓
#8: Natural HPV infection already creates a protective antibody response so there is no need for vaccination	X	Antibody response after natural HPV infection is low HPV vaccination provides a strong immune response and gives robust protection against disease	✓
#9: HPV vaccination increases risky sexual behavior and promiscuity	X	There is no evidence that HPV vaccination increases promiscuity or promotes risky sexual behavior	✓

CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus; PAP, Papanicolaou; WHO, World Health Organization.

analyses which evaluated pregnancy in populations vaccinated against HPV.[11 12] Nevertheless, an evaluation in 2018 of nearly 20 000 women aged 11–34 years found no connection between adolescent vaccination and ovarian failure—only 1 of 46 patients with confirmed primary ovarian failure received an HPV vaccine.[7] Furthermore, recent data from Denmark also showed no association between HPV vaccination and primary ovarian insufficiency among more than 950 000 Danish women and girls.[13]

Myth #4: There are Several Vaccinations that Induced Severe Adverse Events Like Autoimmune Diseases and Death

There have been many studies to evaluate the reasons among parents for making the decision to not vaccinate their children against the HPV virus, with one of the most commonly reported reasons being "safety concerns".[14–16] In no small part because of media reports about a few cases of individuals who died shortly after—but without causality from—the HPV vaccination, the population has been sensitized with false and unproven information about the vaccine. To sum up the main safety concerns that have been reported, these involve fear of death after the vaccination, autoimmune disease and neurological syndromes,[17] and premature ovarian insufficiency as discussed above.[11 12 18–21]

Addressing this myth, it must first be stated that numerous clinical trials and post-licensure studies have been published which reported a very good safety profile of the current approved and used HPV vaccines with no associations with serious adverse events. Summarizing the published recommendations of the US

Food and Drug Administration and the European Medicines Agency, acute injection site reactions such as pain, swelling, and redness were higher in the vaccination group compared with the placebo recipients in pre-licensure clinical trials. Systematic adverse events such as headache and nausea were similar among both groups as well as autoimmune disease incidence. Concerning the deaths in a temporal context with HPV vaccination, none of these were considered to be vaccine-related according to the existing, published data based on clinical trials that included tens of thousands of participants.[8 9 22–25] Furthermore, numerous studies have investigated the potential risk for autoimmune or neurological conditions which, among others, included more than 3 million adult females,[26] nearly 1 million adolescent females[27] and 600 000 boys,[28] as well as a little more than 250 000 girls.[29] Although minor risks have been reported for some conditions such as Reynaud's disease, type 1 diabetes, vitiligo, or narcolepsy,[26 28 30] no proven association with any of the conditions according to the investigated HPV vaccine could be made in those studies.[26–29 31]

Myth #5: Children are Not Sexually Active So Why Vaccinate Them Against Something That Does Not Concern Them at This Age?

A question that often arises when discussing HPV vaccination at the recommended age of between 9 and 12 years is whether this is too young since sexual intercourse is not an issue at this age. One of the main parental concerns about earlier sexual activity and promiscuity (the final myth considered here), but also the concern about unnecessary vaccination against something that is not happening yet, is often mentioned.

The fact is that adolescents vaccinated under the age of 15 years showed much higher HPV antibody titers than their older peers. They had a better immune response. This, together with the results of clinical trials showing persistent high antibody titers after receiving two doses of HPV vaccination at younger ages, led to the recommendation of two doses in adolescents under the age of 15 years.[32] Furthermore, one-dose regimes are currently being evaluated. The available data on the long-term effect shows almost complete effectiveness up to 14 years after vaccination. Also, the possibility of combining HPV vaccination with other recommended vaccines at this age by concomitant administration has been shown to lead to higher vaccine coverage in adolescents.[33]

Finally, we know that vaccination prior to the onset of sexual activity is most effective and that the age of first sexual contact differs among people, countries, and cultures. Although HPV is the most common sexually transmitted infection, non-sexual ways of contagion such as fomites, shared clothing, and horizontal as well as vertical transmission have been reported.[34 35] Vaccination is designed to give long-term protection and, like other vaccines, it should not be administered close to a possible infection. The earlier you vaccinate teenagers the better, starting from the age of 9 years. You can never vaccinate too early but rather, unfortunately, sometimes you can vaccinate too late.

Myth #6: Boys and Men Do Not Get Cervical Cancer So They Do Not Need a Vaccine

In addition to cervical cancer, HPV is linked to at least five other malignancies: vulvar, vaginal, anal, penile, and oropharyngeal cancer. The last three also occur in males. Thus, national and also many international vaccination regimes nowadays recommend HPV vaccination for girls and boys alike.[36 37] As the overall genital HPV infection prevalence among men aged between 18 and 59 years in the United States was reported at approximately 45%, it is crucial to raise awareness about prevention of HPV-related cancers in young boys and men. Furthermore, men act as carriers for the virus and so the goal needs to be herd immunity of at least ideally 80% in girls-only vaccination and 60% in gender-neutral vaccination. Gender-neutral vaccination provides the best protection for all individuals regardless of gender and (future) sexual orientation and is a great opportunity to double the coverage. Also, male in addition to female vaccination will result in achieving cervical cancer elimination earlier.

Myth #7: After the First Sexual Intercourse the Vaccine Does Not Work Anymore

One persistent and false myth is the missing efficacy and benefit of the HPV vaccination if given after the first sexual contact or intercourse. Randomized trials have demonstrated lower but still substantial and significant protection among young women regardless of prior HPV exposure against cervical pre-cancer compared with HPV-naïve women, in whom protection is excellent. However, in women vaccinated at an older age (>25 years), protection at the population level is low.[22] A benefit of vaccinating women after treatment for cervical intraepithelial neoplasia is additional protection against recurrent disease compared with treatment without HPV vaccination.[38] Nevertheless, high-level evidence from prospective randomized trials addressing this effect is needed and should be available soon, before a general recommendation for HPV vaccination adjuvant to treatment of pre-cancerous lesions can be given.[39]

Myth #8: Natural HPV Infection Already Creates a Protective Antibody Response, So There is No Need for Vaccination

HPV reaches the basement membrane through fissures and infects basal cells. One characteristic of HPV infection is that the virus does not enter into the body's circulation and does not cause local inflammation. Thus, an antibody response is low to absent. Studies have shown that recurrent, natural HPV infections were seen equally in women after years of follow-up, regardless of the type-specific serological status. In a meta-analysis of 14 eligible studies that included >24 000 individuals from 18 countries that examined HPV natural immunity, the authors observed moderate protection against subsequent infection in female subjects of the order of 30%, but not in male subjects.[40] The natural immune response is insufficient to control for new infections and is far lower when compared with the high levels of seroresponse and the high efficacy observed against persistent infections after HPV vaccination.[41]

Myth #9: HPV Vaccination Increases Risky Sexual Behavior and Promiscuity

A myth that repeatedly arises in the context of HPV vaccination is possible sexual disinhibition in adolescents. This can lead to lower vaccination rates in earlier years because of parents' concerns about possible promiscuity and increased risky sexual behavior.[42 43] Because of this reported issue, two systematic reviews have been performed that address this issue. These reviews reported an increased need for precise information about HPV-related diseases and HPV vaccination as well as lower rates of sexual intercourse

without condoms and without contraception in the cohort of vaccinated adolescents.[44 45] Furthermore, the rate of chlamydia was higher in the unvaccinated cohort.[45] To date, several studies have addressed this question and found no evidence for an impact on sexual behavior in adolescents after receiving HPV vaccination compared with an unvaccinated cohort.[43 46–48]

Rysavy et al[48] also highlighted the need for early vaccination as their investigated cohort suggested sexual activity at a young age. Real-world experience has clearly demonstrated that early vaccination is more effective than vaccination after the age of 15–17 years.[1 3] Finally, the necessity of better information and education of adolescents and their parents regarding HPV-related diseases and HPV vaccination to resolve all doubts is needed.[49] The aforementioned findings strongly suggest that there is no evidence that HPV vaccination increases promiscuity and that these concerns should not deter parents from giving consent for their children to be vaccinated at a young age.

CONCLUSIONS

HPV vaccines are highly effective in girls and young women and likely also in boys and young men, in particular among those individuals that are HPV DNA-negative at the time of HPV vaccination. Moreover, licenced HPV vaccines have demonstrated balanced occurrence of severe adverse effects through trials and real-life surveillance activities. There is a need to continue to publicize, clearly communicate, and disseminate these data to further reduce HPV-related pre-invasive and invasive disease.

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Acknowledgements We acknowledge the work and effort of all co-authors and participating colleagues.

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Contributors All the authors participated in the conception, writing, and reviewing of the final version of this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MA and MG were supported by the Horizon 2020 Framework Programme for Research and Innovation of the European Commission through the RISCC Network (Grant No. 847845).

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

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