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COMMENTARY

The HPV Vaccination: Retrospective Analysis of the Early First Two Vaccine Alternatives

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Globally, HPV virus infection is the most commonly transmitted sexual disease of all. At the same time, the prevalence of HPV infection varies considerably by country and can change significantly with changes in lifestyle and sexual behavior. Every year, about half a million women worldwide develop cervical cancer, with up to four-fifths being women from developing countries. The lack or underuse of cancer screening programs in developing countries plays a key role in this. It is estimated that approximately 230,000 women die from cervical cancer worldwide each year [1]. Cervical cancer is the eleventh most common cancer in women of all ages in Central Europe. In women up to 45 years of age, it is the second most common malignant tumor, but overall accounts for only 3.2% of all cancers and 1.8% of all cancer deaths in women. A multifactorial cause is propagated, whereby primarily proteins and genome components of different HPV viruses but in contrast also other cofactors such as a young age at initial diagnosis, immunosuppression, smoking and coinfections with herpes simplex virus as well as infections with chlamydia are thought to play a not insignificant role. The long latency between primary HPV infection and cancer suggests that other factors such as sexual behavior, genetic predisposition, nutritional status, and social education status may be influential. HPV vaccines are vaccines designed to protect against specific types of sexually transmitted human papillomavirus (HPV) and to prevent cancer. To date, one bivalent and one tetravalent vaccine exist. Two HPV vaccines are currently licensed: Cervarix and Gardasil. Cervarix is a bivalent vaccine and is only effective against HPV types 16 and 18. Gardasil is a tetravalent vaccine and is directed against HPV types 6,11,16 and 18. However, there are many more HPV viruses with oncogenic potential that are not present in either of these vaccines. Regular screening for early detection of cervical cancer (PAP test) is recommended, as not all carcinogenic HPV types are covered by the vaccine. The vaccines are only preventive and not therapeutic. The aim of the vaccine is to reduce the burden of disease from cervical cancer. Considering the seroconversion rate of both vaccines one month after the third administration, figures of 99.5% are given, with the duration of protection 6 years [2]. In spring 2007, the STIKO issued a recommendation for vaccination of girls aged 12 years - 17 years against the carcinogenic HPV types 16 and 18. In June 2007, the Federal Joint Committee

(GBA) introduced vaccination as a standard benefit of the statutory health insurance. Ongoing intensive and well-founded discussions about legitimacy, benefits and cost-effectiveness of HPV vaccination are the order of the day and justify a statement. Etiology and Pathogenesis of Human Papillomavirus Infection Papillomavirus is a viral particle approximately 55 nm in size that includes a double-stranded circular viral genome of 7904 base pairs. HP viruses belong to the papovavirus family and have an icosahedral protein capsid. There are approximately 100 different HPV types that can infect both the skin and mucous membranes. In the uro-anogenital tract, about 40 different HPV types come to the fore, which are divided into 2 groups. Low-risk HPV types have a low potential to cause malignancy. High-risk HPV types have a high oncogenic potential. Based on Europe, the infection rate without clinically relevant change is between 16-33 million people/year. Infection with human papillomaviruses is one of the most common sexually transmitted diseases worldwide. Approximately 70% of all people have been infected with genital HPV at least once during their lifetime. Among these, women usually become infected between the ages of 20 and 30, with HPV detectable in one in three women two years after their first sexual contact [3]. HPV causes persistent infections in the uterine area with an increased risk of developing precancerous lesions (CIN). In general, the time between primary infection and cancer development can be up to 20 years or longer, with a marked increase in the incidence of cervical cancer after the age of 35 [4]. However, in approximately 10% of chronically infected individuals, the changes progress to high-grade dysplasia (CIN III) within eight years, which is considered a precancerous condition. These changes also still regress in up to 3%, with approximately 812 years remaining between a CIN III and cancer [5]. Molecular biology and oncogenesis of HPV infection the envelope-less virus has a simple structure and is divided into an early region ("early region") that performs regulatory functions and a late region ("late region") that encodes two structural proteins. The capsid of the virus consists of 80% structural protein L1 and 20% capsid protein L2. In the "early region" there are 6 viral genes, 2 of which are called oncogenes. They are responsible for viral replication and transformation of infected cells. Papillomaviruses infect the basal cell layer of the epithelium and initially lead to a latent infection in which the viral genome replicates in parallel with the host cell. Clinically, these infections remain inapparent. In some cells, there is replication of papillomavirus and eventual release of viral capsids in the epithelial layers with sloughed off epithelial remnants. This stage of cellular change with marked viral replication corresponds to a mild-grade cervical lesion (CIN 1) in histologic section with evidence of koilocyte corresponding to vesicular distension of the cells. However, if the oncogenic oncogenes are expressed in cells that replicate their own genome, then malignant transformation may occur. Dysplastic cells develop, which may progress to highly dysplastic lesions. Unregulated and increased cell proliferation sets in, ultimately leading to cancer growth. In addition, this process leads to the increased production of another cell protein, p16INK4a, which, in the course of normal cell division, would prevent the cell from dividing again by means of a strict feedback loop. Detection of this protein indicates advanced HPV infection and is a surrogate marker for activated oncogene expression of HR-HP viruses in dysplastic cervical epithelial cells. In cervical cancer, genetic material from HPV can be detected in 95% of tissue samples, suggesting a causal relationship. However, there are also forms of cervical cancer without the presence of genetic material from HPV. Risks of HPV infection High-risk HPV types 16 and 18 are thought to be responsible for approximately 70% of all cervical cancers in women worldwide [6]. 55.3% of all cervical precancerous lesions of severity CIN 2 and 3 were associated with HPV 16 in 2 studies, 6.4% with HPV 18, HPV 45 was detected in 8.5%, and HPV 31 in 6.4% of cases [7]. In 2005, the WHO classified HPV types

16,18,31,33,35,39,45,51,56,58,59 and 66 as carcinogenic [8]. The so-called low-risk HPV types 6 and 11 are responsible for the development of more than 90% of genital warts. Genital warts are the most common viral sexually transmitted disease worldwide. Frequency, age distribution and progression of cervical cancer In Germany, approximately 6200 women develop cervical cancer. With 1700 deaths, cervical cancer was not one of the most common cancers, nor one of the most common causes of cancer death in women, accounting for 1.8% of all cancer deaths. In the incidence statistics, it currently ranks only 11th. This current status is the result of an effective early detection program. The comparatively low incidence of cervical cancer is accompanied by a much higher incidence of dysplasia found. The EUROCARE-4 trial, published in September 2007, calculated a 5-years relative survival rate of 55% for invasive cervical cancer [9]. Screening options-benefits and risks Since the introduction of cytologic examination of cervical smears for early detection of cervical cancer and its precursors (Pap test) from the age of 20 years in the early 1970s, the incidence of invasive carcinoma in Germany has decreased by approximately two-thirds. The Pap test is a very successful and effective secondary prevention measure against cervical carcinoma. In countries such as England, Sweden, and the Netherlands, screening is much better organized and therefore even more effective, with a 90% reduction in the risk of cervical cancer among participants [10]. In countries without adequate cancer screening programs, cervical cancer contributes significantly to cancer mortality. Developmental Aspects of Prophylactic HPV Vaccines A quadruple vaccine manufactured by Sanofi Pasteur MSD (Whitehouse Station, N.J.) was first approved in the United States in 2006 and by the European Medicines Agency in September 2006 through the centralized approval process in European Union countries. In Europe, the vaccine is marketed under the trade names Gardasil and Silgard, respectively. The vaccine contains purified, recombinantly produced L1 proteins from the capsid of the four papillomavirus types 6, 11, 16, and 18, which spontaneously assemble into virus-like-particles (VLP) [11]. The crucial building block of the HPV vaccine is these L1 proteins, empty viral particles that contain no genetic material but look like real viruses to the immune system. These L1-VLPs induce an astonishingly high immune response when injected intramuscularly. The publication of the first HPV vaccination study in the New England Journal of Medicine in November 2002 caused a furor due to its resounding success and was euphorically commented with the title "The beginning of the end of cervical cancer?". According to the European Medicines Agency, 1.5 million patients had already been vaccinated with Gardasil in Europe by January 2008 [12]. Since October 2009, Gardasil has also been approved in the United States for the prevention of genital warts in men and boys [13,14]. Approval for the bivalent vaccine developed by GlaxoSmithKline (Rixenarts, Belgium), marketed under the trade name Cervarix, was granted in Australia in May 2007 and for the European Union in September 2007. Cervarix also contains recombinant L1 proteins from the capsid in VLP`s, but only of papillomavirus types 16 and 18 [15]. Merck& Co and GlaxoSmithKline have granted cross-licenses to each other, allowing both to use the patent rights for vaccine production. The German Cancer Research Center is a co-patent holder and thus shares in the profits from vaccine sales.

Efficacy aspects of the tetravalent vaccine (Gardasil) The efficacy of the tetravalent vaccine was investigated in four placebo-controlled, randomized and double-blind phase II and phase III trials. In women who were not infected with the corresponding human papillomavirus at the time of vaccination, vaccination prevented infection in 96-100% of cases. In the (so-called) Future II study, the occurrence of CIN II or more severe precancerous

cervical lesions was recorded. While one case of CIN occurred in the group of vaccinated women (n = 5305), 42 cases occurred in the group of women vaccinated with placebo (n = 5260). The independent Data Safety Monitoring Board recommended rapid vaccination of placebo-vaccinated subjects for ethical reasons [16,17]. When including women with existing infections by HPV types 6,11,16 and/or 18 at baseline and also those who received fewer than three required doses of vaccine, the efficacy of Gardasil against precancerous cervical lesions caused by the corresponding HPV types is lower but still present. In the combined interim analysis of the four relevant efficacy studies conducted for approval, Gardasil efficacy was only 39% [11]. Gardasil is known to be cross-protective with phylogenetically related HPV types 45, 52, and 58 [18-20].

Efficacy aspects of the bivalent vaccine (Cervarix) Cervarix is a bivalent vaccine that is effective against HPV 16 and 18. Statistically significant efficacy has been demonstrated for this drug in a large study only for HPV 16, not HPV 18, and clinical data for Cervarix to date are only available over a 5.5-years period [21]. According to new data, Cervarix may also protect against infections with HPV types not included in the vaccine. This cross-protection extends to varying degrees to virus types 31,33,35,39,45,51,52,56,58 and 59, with virus types 31 and 45 having high oncogenic potential [22]. According to data from the PATRICIA (Papilloma Trial against Cancer in young Adults) study, a phase III trial of Cervarix that enrolled 18,644 women aged 15-25 years in 14 countries in North and South America, Europe, and the Asia-Pacific region, a reduction in CIN 2 findings by 70% (33 versus 110 cases), CIN 3 findings, by 87% was found. The rate of conizations was reduced by 68.8% [21,22]. Current data on safety and efficacy According to the data available to date, a follow-up of up to 6.4 years for women who were not infected with the highly carcinogenic HPV types 16 and 18 at the time of vaccination showed almost 100% protection against cervical dysplasia induced by these two HPV serotypes. This fact is supported by a recent German HPV vaccination guideline and a systematic review of 6 randomized trials involving more than 40,000 women and girls aged 15 years to 26 years investigating the efficacy of the vaccines [23-25].

Cost aspects of HPV vaccination Some studies conclude that HPV vaccination is cost-effective [18,26,27]. In Germany, a single injection costs approximately 150 euros, with 3 vaccinations required per patient. Thus, basic immunization with three injections at months 0,2, and 6 costs approximately 450 euros. According to estimates by the Federal Association of Company Health Insurance Funds, this costs the German healthcare system up to one billion euros per year. Should booster vaccinations prove necessary every 5 years or so, the costs of the vaccination program would multiply. In other countries, the vaccine is considerably cheaper (example Australia 96 euros). In the USA, for example, vaccination of women 35 years and older is not cost-effective [28]. Since 2002, the pharmaceutical "vaccination industry" has experienced rapid growth. In 2002, the revenue generated by pharmaceutical companies in the U.S. from HPV vaccination was $135 million; by 2012, it was $1.4 trillion [29]. This is particularly true in developing countries, where cervical cancer is, in some cases, the most common cancer in women [30]. In Kenya, the vaccine costs about half an average annual income [31,32]. In developing countries, where cervical cancer is by far the most common, vaccination is an almost prohibitive cost for the population. Adverse side effects of HPV vaccination Data on the tolerability of HPV vaccination were available from several clinical trials with over 20000 participants at the time of approval. Since the approval of Gardasil, several million girls and women worldwide have been vaccinated. Adverse reactions are registered in special monitoring

programs. Based on the study data available to date, HPV vaccination is considered safe and well tolerated by the German Health Technology Assessment, the U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the European Medicines Agency [18,33]. For both vaccines, the most common adverse reactions encountered in controlled trials were local reactions in 83% of women in the vaccine group and in 73% of women in the placebo group. The most common systemic reactions were headache, fatigue, muscle pain, and nausea; these occurred equally in the vaccine and placebo groups. Serious adverse effects included bronchospasm, hypertension, and severe headache. Since the U.S. approval of the HPV vaccine Gardasil in June 2006, the FDA and the Centers for Disease Control and Prevention have received - 17160 reports of possible adverse events in a total of approximately 26 million doses of vaccine administered as part of surveillance programs through September 2009. The vast majority of adverse reactions, 92%, were classified as not serious. 8% were serious. Serious was defined as resulting in hospitalization, a life-threatening illness, an irreversible disability, or death. For example, cases of Guillain-Barre syndrome (because of its frequency, the synonym "Gardasil-Guillain Barre syndromes" is repeatedly found), thrombosis, and deaths were reported in close temporal relation to vaccination. Unexpectedly, no causal relationship between vaccination and the respective disease has been demonstrated in any case [33]. The US consumer protection group Judical Watch had already published a first list of 1637 reported adverse events after HPV vaccination in the USA in May 2006. In October 2007, they announced a further 1824 vaccine adverse events. Thus, from May 2006 to October 2007, there were 3461 adverse events, including 11 deaths, caused by HPV vaccination alone. On June 20, 2007, a healthy 17-years-old woman was vaccinated with Gardasil for the first time and died the same day. Other isolated deaths have occurred and are known. Causal links with HPV vaccination have always been denied. Call for reassessment of HPV vaccination In November 2008, scientists from various German research institutions called for a reassessment of HPV vaccination on the grounds that efficacy may be significantly lower than assumed [34,35]. In a reassessment by the Robert Koch Institute on August 10, 2009, vaccination was still recommended. However, information media giving the impression that HPV vaccination protects 100% against cervical cancer were judged to be dubious according to the current status [36] In Germany, the initial euphoria of HPV vaccination has quickly subsided. Currently, the vaccination rate is likely to be below 30% In June 2011, vaccine manufacturers were jubilant about an Australian study showing a significant decrease in cervical cell changes in HPV-vaccinated 17-years-old girls [37]. However, lost in the jubilation was the fact that this effect was not detectable in girls over 18 years of age who had also been vaccinated [37]. In addition, the current data do not demonstrate efficacy in girls and women already infected with HPV. One study even raised the suspicion that vaccination might promote the development of cell dysplasia in women already infected with HPV types 16 and 18 [38]. Therefore, vaccine manufacturers and authorities recommend vaccination exclusively before first sexual contact. In France, the French Ministry of Health recommended that virginity be verified before vaccination. Clinical efficacy studies with girls before and during sexual maturity have not yet been conducted-the manufacturers are content with the less meaningful detection of antibodies in the blood in the months after vaccination. The STIKO recommendation to vaccinate all girls before their first sexual contact is therefore on shaky ground and not evidence-based. These data should actually be available, be over an insufficiently studied vaccine is publicly recommended for half of the adolescent population. Conflicts of interest The European Cervical Cancer Society (ECCA) is more than 50 percent funded by vaccine manufacturers Sanofi Pasteur, Roche, and Glaxo Smith Kline. The German Cancer

Research Center is co-owner of the cervical vaccine patents. This means that just about anybody/person that has approved or recommends the vaccination can financially benefit from each individual vaccination. Conclusion For several reasons, HPV vaccination should be viewed critically. The approval of Gardasil was based on 4 trials in advance, and only one phase III trial for Cervarix. This was not sufficient for a meaningful assessment of clinical benefit [39]. Clear evidence of protection from "cervical cancer" has not been conclusively established, only from cervical precancerous lesions. Regulatory agencies have accepted CIN II, CIN III, and carcinoma in situ as surrogate parameters when examining efficacy for potential precancerous lesions. Currently, vaccines are used whose unequivocal efficacy against cervical cancer is not well established.

Long-term studies are lacking. It is assumed that the development of cervical cancer has a duration of 15 years - 30 years. Studies of currently only up to 6.5 years are not able to show any clarity. At the same time, protection is very often proven and determined by the level of antibody titer; whether the level or the presence of high antibodies against HPV provides absolute protection against the development of cervical cancer is rather questionable.

In summary: There is not yet sufficient evidence on long-term side effect risks. Cervical cancer can be adequately controlled by safer sex (good protection against high-risk HPV) and effective screening programs. Its incidence has been declining for years. The vaccine is genetically engineered. What consequences it has for vaccinated people is unclear. Genetically engineered vaccines penetrate the cellular material and change it. What consequences this has for our offspring is unclear.

No direct causal link has yet been shown to prove that HP viruses are indeed the cause of cervical cancer. Even the NCI, the National Cancer Institute in the USA, admits this fact. It is only known that factors such as long-term use of oral contraceptives and the number of births, as well as genetic changes, smoking or an acquired immune deficiency, promote tumor development. It is unknown how long vaccine protection lasts with either current vaccine alternative. No study provides evidence of lifelong immunity; one study demonstrates protection for at least 5 years. In this context, the question of "booster vaccination" will become an issue. It is unknown how vaccination affects the distribution of the remaining HPV types. It is unknown whether other HPV types, which may also cause cancer, will increase instead of HPV 16 and 18. Vaccination creates a "false sense of security" because it reduces motivation for screening and limiting other risks (e.g., smoking). It is unknown what the effect of vaccination is if there has been prior infection with HPV. It is possible that the vaccination may have exacerbating effects if the virus has already been contracted but is still asymptomatic. It is possible that vaccination produces a change in the character of the other types of virus not reached by vaccination. The consequence of this situation is unknown. Whether there is then a benefit or an increase in risk in the final outcome is unknown. HPV vaccines are extremely expensive. Expanding the screening program by foregoing vaccination would save large costs to the health care system that could be invested elsewhere in social projects. Health policy is not always rational. Objective, well-founded and balanced information of the population about the benefits and limitations of HPV vaccination is desirable but probably not feasible.

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