**Thesis**

# Does Targeted Education about HPV Have a Positive Effect on HPV Vaccination Intention in a Sample of 12- to 14-Year-Old Students?

## Report from a High School in Graz


submitted by

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in partial fulfillment of the requirements for the degree of

**Doktorin der gesamten Heilkunde**

**(Dr$^{in}$. med. univ.)**

at the

**Medical University of Graz**

executed at the

**University Department of Obstetrics and Gynecology**

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Graz, 6$^{th}$ November 2024

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*Graz, 6th November 2024* *Maria Katharina Louisa Rissner m.p.*

# Note to the Reader

For the present medical research question, only the anatomical gynecologic reproductive organs are relevant; personal gender affiliation is not. Accordingly, this thesis refrains from using language with strong social connotations and from non-inclusive language, except for direct quotations from the literature. Readers are encouraged to apply this purely medical perspective to these quotations as well.

All citations from (World Health Organization, 2020a) are paraphrased or directly quoted form the original work. The following is true for all adaptations “This is an adaptation of an original work “[Global strategy to accelerate the elimination of cervical cancer as a public health problem]. Geneva: World Health Organization (WHO); [2020]. Licence: CC BY-NC-SA 3.0 IGO”. This adaptation was not created by WHO. WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition” (World Health Organization, 2024a).

# Acknowledgements

Ich bedanke mich herzlich bei Dr. Dr. Nadja Taumberger für ihre kompetente, lehrreiche und empathische Betreuung! Vielen Dank für all die Korrekturen, die Ratschläge, die Weitergabe ihres Wissens und die ständige Inspiration durch ihre wertvolle medizinische und menschliche Arbeit. Ich habe in der Zeit sehr viel von ihr gelernt, Freude am wissenschaftlichen Arbeiten entwickelt und mit ihr ein großes ärztliches Vorbild gefunden. Ich bedanke mich bei Prof. Dr. Tamussino für die freundliche Betreuung, Beratung, Unterstützung und Korrektur dieser Arbeit! Ich danke Ihnen beiden für die ansteckende Begeisterung in den Bereichen Gynäkologie und Public Health und die Motivation diese Begeisterung in Zukunft aufzugreifen.

Ich möchte Mag. Edda Berger-Cian für die Möglichkeit danken, diese Studie an der Graz International Bilingual School (GIBS) durchzuführen, für die organisatorische Hilfe, sowie für die jederzeitige Beantwortung aller Fragen bezüglich der GIBS.

Ich bedanke mich von ganzem Herzen bei Rosi für das jederzeit offene Ohr, all die wertvollen, in Sekundenschnelle erfolgenden, wissenschaftlichen Ratschläge und die Bereitschaft mit mir über genderadäquate Sprache zu diesem Thema zu beraten. Für die große Geduld für all meine Fragen, die Hilfe bei der Datenkontrolle im Endspurt, die viele Zeit und (unter anderem finanzielle) Unterstützung beim letzten Feinschliff der Arbeit und insgesamt für die stetige Unterstützung in meinen Studienjahren. Ich bin zutiefst dankbar, mit einem Menschen wie dir all meine Gedanken teilen zu können. Die Erfahrung der letzten Monate, dass du dich ihnen unhinterfragt annimmst, ist Balsam für meine Seele – Danke.

Vielen Dank an Elli für all die wissenschaftlichen Tipps, das Korrekturlesen und deine innige Freundinnenschaft. Ich bedanke mich auch bei Moritz, für Rat und Tat, sowie für die aufwendige Korrektur.
Danke an Clara, Guido und Mara für die gemeinsamen Diplomarbeits-Schreibtage und die geteilte Gaude! Danke an meine lieben, in den letzten Jahren dazu gewonnen, Studienfreund*innen für die intensiven, bunten Jahre! Ganz besonders will ich mich bei Gregor, Tamara, Amelie und Clara für die nach wie vor so lebendige Freund*innenschaft bedanken.

Vielen herzlichen Dank an meinen lieben Freund Jürgen, für die professionellen Ratschläge, das geduldiges Anhören meiner offenen Fragen und die liebevolle Rundumversorgung in den letzten Schreib-Monaten. Es ist ein Segen, dich als Partner im Leben zu haben.
Liebe Mama, lieber Papa, ich bin euch von ganzem Herzen dankbar, dass ihr uns Kindern die Startbedingungen für unsere wunderbare Leben und unsere großartigen Ausbildungen gesetzt habt. Vielen Dank für all die tiefgehende Unterstützung auf meinem Weg. Ich bin über alle Maßen dankbar, in unserer Familie zu sein. Liebe Mama, vielen Dank für die seelische, kulinarische, finanzielle, aber vor allem liebende Zuwendung über die letzten Jahre und im Besonderen über die letzten Monate.
Und Papa: Ich wünsch mir, du wärst da, um das mit mir zu erleben. Danke für dein tiefes Vertrauen in meinen Weg.

# Zusammenfassung

**Einleitung:** Die WHO (World Health Organization) hat 2018 das Ziel formuliert, das Zervixkarzinom weltweit zu eliminieren. Da ca. 99% aller Zervixkarzinome durch Infektionen mit HPV (Humanen Papillomaviren) ausgelöst werden, wirkt der HPV-Impfstoff Gardasil®9 präventiv gegen bis zu 90% aller HPV-assoziierten Karzinome. Um das Ziel der WHO zu erreichen, ist eines der drei festgelegten Subziele eine 90% Durchimpfungsrate aller weiblichen Personen bis zum 15. Lebensjahr, die bis 2030 erfüllt werden müssen. Der österreichische Impfplan empfiehlt Gardasil®9 ab dem vollendenden 9. Lebensjahr für alle Geschlechter. Jedoch wird die HPV-Impfquote (2 Dosen) der 14-Jährigen in Österreich im Jahr 2022 auf lediglich ca. 53% geschätzt. Daten zur Geschlechterverteilung der HPV-geimpften Bevölkerung liegen nicht vor. Die (min.) Durchimpfungsrate (insgesamt und pro Geschlecht) in einer Stichprobe von Schüler*innen eines Grazer Gymnasiums wurde erhoben, sowie der Einfluss einer gezielten Aufklärung über HPV auf die Impfbereitschaft von Schüler*innen mit negativem oder unklaren Impfstatus analysiert.

**Methodik:** Im Juni 2021 wurde eine prospektive Fragebogenstudie an einem Grazer Gymnasium durchgeführt. 135 Einverständniserklärungen wurden an die Intention-to-treat-Population ausgeteilt. Schüler*innen mit elterlich unterschriebener Einverständniserklärung füllten einen Fragebogen zu ihrem HPV-Impfstatus, ihrem HPV-Wissen und ihrer Impfbereitschaft aus. Dann wurde eine gezielte Aufklärung zu HPV und der HPV-Impfung durchgeführt. Danach füllten die Schüler*innen einen zweiten Fragebogen aus. Die Inklusionskriterien beinhalteten eine elterlich unterzeichnete Einverständniserklärung und Alter zwischen 12 und 14 Jahren. Die Daten wurden mit deskriptiver Statistik ausgewertet.

**Ergebnisse:** 55/135 (41%) Schüler*innen aus der Intention-to-treat Population brachten unterschriebene Einverständniserklärungen und 54 Schüler*innen wurden letztendlich inkludiert. 38/54 (70%) Schüler*innen waren immunisiert, was in der gesamten Intention-to-treat-Population eine minimale Durchimpfungsrate von 28% (38/135) ergibt. 3 Schüler*innen (6%) hatten zum Zeitpunkt der Studie eine Dosis erhalten. 77% (26/34) aller weiblichen Schüler*innen gaben an geimpft zu sein, 85,3% (29/34) erhielten zumindest die 1. Dosis.

Zu Beginn der Studie waren 18 Schüler*innen (33%) über HPV, und 27 Schüler*innen (50%) über die HPV - Impfung informiert. Nach der Aufklärungsstunde wussten 54 Kinder (100%) über HPV und 53 Kinder (98%) über die HPV-Impfung Bescheid.

Vor der Aufklärung waren 10/13 (77%) Schüler*innen mit negativem oder unklaren Impfstatus bereit, sich in einem Catch-Up Impfprogramm impfen zu lassen. Nach der Aufklärung erhöhte sich diese Zahl auf 11/13 (85%) Schüler*innen.

**Zusammenfassung:** In der untersuchten Kohorte war nach gezielter Aufklärung eine zusätzliche Schüler*in dazu bereit sich impfen zu lassen. Die Ergebnisse der Studie erlauben keine schlüssigen und eindeutigen Empfehlungen darüber, ob gezielte Aufklärung die HPV-Impfbereitschaft erhöhen kann. Jedoch führte gezielte Aufklärung in dieser Studie zu einem Zuwachs an Schüler*innen mit Wissen bezüglich der Primärprävention von HPV-assoziierten Malignomen. Folglich könnte Aufklärung zu einer Steigerung des Wissens in Bezug auf HPV und die HPV-Impfung führen; ein indirekter Effekt, der langfristig zu einer Erhöhung der HPV-Impfbereitschaft führen könnte, ist möglich. Des Weiteren ist es nicht möglich, Aussagen über die tatsächliche Durchimpfungsrate der Intention-to-treat Population (n=135) zu treffen, da wir nur die Durchimpfungsrate der Per-Protocol Population (n=54) kennen.

Um weitere Aussagen über die untersuchten Themen treffen zu können, sind weitere Studien mit größeren Stichproben aus multiplen Schulen in unterschiedlichen Settings, Randomisierung in Interventions- und Kontrollgruppen und eine Analyse des demographischen Hintergrunds notwendig.

# Abstract

**Background:** In 2018, the WHO (World Health Organization) called for the elimination of cervical cancer. About 99% of cervical carcinomas are caused by HPV (human papillomavirus) infection and the nonavalent vaccine Gardasil®9 is thought to prevent up to 90% of HPV-associated carcinomas. To reach the WHO´s goal, a 90% vaccination coverage of all females by age 15 is one of the measures required to be taken until 2030. The Austrian Vaccination Plan recommends the 9-valent HPV vaccine to all genders starting from the age of 9. However, in Austria, in 2022 the HPV vaccination coverage (both doses) is estimated to be approximately 53% for children aged 14. No data on gender distribution amongst the vaccinated population exists. Therefore, this study investigated the (minimal) vaccination coverage (total and per gender) in a predefined sample group of high school students in Graz. Furthermore, it aimed to explore if targeted education on HPV can improve the willingness to receive the vaccine amongst students with a negative or uncertain vaccination status.

**Material & Methods:** In June 2021, we conducted a prospective questionnaire-based study in a high school in Graz. 135 consent forms were handed out to the intention-to-treat population. Students with parentally signed consent forms filled out a questionnaire concerning their HPV immunization status, HPV knowledge and willingness to get vaccinated. Then we conducted a targeted education class about HPV and HPV vaccination. Successively, they filled out a second, similar, questionnaire. Inclusion criteria were a parentally signed consent form and age between 12 – 14 years. The questionnaire data was analyzed via descriptive statistics.

**Results:** 55/135 students from the intention-to-treat population (41%) handed in signed consent forms. 54 students (40%) were included. 38/54 students (70%) were vaccinated, which leads to a minimal vaccination coverage (full immunization with two doses) within the overall intention-to-treat population of 28% (38/135 students). 3 students (6%) had received one dose by the time of the study. 77% (26/34) of all female students were vaccinated, 85% (29/34) received the 1st dose.
Before receiving targeted education, knowledge about HPV and the HPV vaccine was reported by 18 (33%) and 27 students (50%), respectively. After the educational class, 54 (100%) students knew about HPV and 53 (98.15%) knew what the HPV vaccine was.
Before the educational class, 10/13 (77%) students with a negative or uncertain immunization status, would choose to get vaccinated in a cost-reduced vaccination program.

After being educated, 11/13 (85%) students would get vaccinated.

**Conclusion:** In our cohort, only one of 13 unvaccinated or uncertain whether vaccinated students was willing to get vaccinated after targeted education. Our results do not permit conclusive recommendations on whether targeted education can raise HPV vaccination intention. However, targeted education did lead to an increase in the number of students with knowledge regarding primary prevention of HPV-associated cancers. Therefore, education may increase knowledge regarding HPV and the vaccine, which might possibly have an indirect effect and lead to increased HPV vaccination intention in the long run. Furthermore, as we only know the rate of vaccination of the study participants (n=54), we cannot state the actual vaccination rate within the group that was intended to be investigated (n=135).
Further studies with larger sample sizes, in multiple schools from diverse settings, randomization into interventional and control groups and analysis of demographic background data would be necessary to answer these questions more conclusively.

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# Abbreviations

| | |
|---|---|
| ACIS | Adenocarcinoma in situ |
| AGO | Arbeitsgemeinschaft Gynäkologische Onkologie |
| AIN | Anal intraepithelial neoplasia |
| AIS | Adenocarcinoma in situ |
| CA | Condyloma acuminatum |
| CIN | Cervical intraepithelial neoplasia |
| CIS | Carcinoma in situ |
| COVID-19 | Coronavirus disease 2019 |
| ECC | Endocervical curettage |
| EMA | European Medical Agency |
| EB | Endocervical biopsy |
| EU | European Union |
| FEH | Focal epithelial hyperplasia |
| GIBS | Graz International Bilingual School |
| HIC | High Income Country |
| HIV | Human immunodeficiency virus |
| HP | Human papilloma |
| HPV | Human Papillomavirus |
| HSIL | High-Grade Squamous Intraepithelial Lesion |
| IARC | International Agency for Research on Cancer |
| LLETZ | Large loop excision of the transformation zone |
| LIC | Low Income Country |
| LSIL | Low-Grade Squamous Intraepithelial Lesion |
| MIC | Middle Income Country |
| MEH | Multifocal epithelial hyperplasia |
| OEGGG | Österreichische Gesellschaft für Gynäkologie und Geburtshilfe |
| OPSCC | Oropharyngeal squamous cell carcinoma |
| PAP | Papanicolaou |
| RRP | Recurrent respiratory papillomatosis |
| SCC | Squamous cell carcinoma |
| SCP | Squamous cell papilloma |
| SIL | Squamous intraepithelial lesion(s) |

| | |
|---|---|
| SIR | Standardized incidence ratio |
| STI | Sexually transmitted infection |
| U.S. | United States |
| VAIN | Vaginal intraepithelial neoplasia |
| VIN | Vulvar intraepithelial neoplasia |
| VLP | Virus-like-particles |
| WHO | World Health Organization |

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# 1 Introduction

## 1.1 Human Papillomavirus (HPV)

The Papillomavirus is part of the Papovavirus - group (Agaimy *et al.*, 2019; Lax *et al.*, 2019). It is exceptional for being the only virus in this family with a double-strand DNA, an icosahedral, non-enveloped capsid and a virion (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007; Stanley, 2010; Agaimy *et al.*, 2019; Lax *et al.*, 2019). HPV is epitheliotropic and causes species-specific infection of mucosal and cutaneous tissues (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007; Agaimy *et al.*, 2019; Lax *et al.*, 2019) in higher vertebrates (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007). Types differ from each other by their DNA sequence (particularly the E6-, E7- and L1-sequence) (Agaimy *et al.*, 2019; Lax *et al.*, 2019). Papillomaviruses causes papillomas (due to typical epithelial proliferation) that carry the potential to transform into malignancies (ibid.).

At least 100 human papillomavirus (HPV) types are known to exist (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007; Agaimy *et al.*, 2019; Lax *et al.*, 2019). Three groups can be distinguished:

- The mucocutaneous group, affecting skin and oral mucosa
- The epidermodysplasia verruciformis group
- The anogenital group (Agaimy *et al.*, 2019; Lax *et al.*, 2019).

More than 40 HPV types belong to the anogenital group (Agaimy *et al.*, 2019; Lax *et al.*, 2019). There are three oncogenic risk groups are distinguished in the anogenital group:

- low-risk HPV types: 6, 11, 42, 43, 44, 53
- intermediate-risk HPV types: 31, 33, 35, 39, 51, 52, 59, 68 (less often detected in invasive cervical cancer)
- high-risk HPV types: especially 16 and 18, but also 45, 56, 58; (high risk types are most commonly detected in invasive squamous cell carcinoma (Agaimy *et al.*, 2019; Lax *et al.*, 2019).

The International Agency for Research on Cancer (IARC) classifies the HPV high-risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 as carcinogenic (*RKI - RKI-Ratgeber - Humane Papillomviren*, 2018) for the cervix (*RKI - RKI-Ratgeber - Humane Papillomviren*, 2018; IARC, 2023, 2024g).

The majority of females will obtain a high-risk HPV infection throughout the course of life,

but as most infections resolve spontaneously within 1-2 years, only few females will develop a malignant disease (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020). Viral persistence occurs only in small share of infections; however, viral persistence may result in the development of dysplasia up until cancer (ibid.).

A study analyzed a cohort of female college students over a follow-up period of 5 years and found that 80% of participants showed HPV infection at some point (Winer *et al.*, 2003a; Kurman, Ellenson and Ronnett, 2019, pp. 253–254). Most HPV infections are of transient nature and become latent or resolve 1-2 years after being detected (Burchell *et al.*, 2006; Schiffman *et al.*, 2011a; Moscicki *et al.*, 2012; Kurman, Ellenson and Ronnett, 2019, p. 254). After a persistence of 36 months, the potential for the infection to undergo clearance in the future is substantially reduced (Schiffman *et al.*, 2007; Kurman, Ellenson and Ronnett, 2019, p. 254). However, the longer the duration of persistence of an infection, the higher the probability for developing a high-grade precursor lesion (Schiffman *et al.*, 2007; Elfgren *et al.*, 2017; Moscicki *et al.*, 2012; Kurman, Ellenson and Ronnett, 2019, p. 254). Persistence of HPV infections for ≥2 years occurs in about 10% (Kurman, Ellenson and Ronnett, 2019). Consequently, high-risk type HPV infections with persistence ≥2 years represent the greatest risk for females; these HPV infections might advance "to a high-grade cer-vical [sic] cancer precursor or even an invasive cervical cancer" (Kurman, Ellenson and Ronnett, 2019, p. 254).

### 1.1.1 Mechanisms of Malignant Transformation

Two proteins, E6 and E7 (with a transforming and growth-stimulating effect) are built by high-risk HPV types (for example by type 16 and type 18) (Agaimy *et al.*, 2019; Lax *et al.*, 2019). This distinguishes these types from low-risk HPV types (ibid.). E6 and E7 complement each other and build necessary components for malignant transformation (in cell cultures) (ibid.). Adhesive processes occur between E6 and p53 and between E7 and distinctive cell cycle proteins, such as retinoblastoma protein (ibid.). These interactions cause cellular dysfunction (ibid.). Therefore, p53 does not mutate, but is deactivated in cervical neoplasia (ibid.). Lastly, by inhibiting the expression of E6 and E7, malignant transformation can also be inhibited (Agaimy *et al.*, 2019; Lax *et al.*, 2019). The incubation period for HPV infection spans from a few weeks to months (ibid.). HPV infections mostly occur in the proliferatively active epithelial region of the transformation zone (ibid.). HPV

virions first interact with basal cells or immature metaplastic epithelium, which results in either productive or non-productive infection (ibid.):

- non-productive infection: HPV-DNA is in the infected cell´s nucleus in its episomal form (ibid.).
- productive infections: virus synthesis and cellular DNA synthesis occur separately (Agaimy *et al.*, 2019; Lax *et al.*, 2019). Koilocytes and dyskeratocytes (two cytopathogenic effects caused by infection with HPV) develop as a result of the extensive proliferation of proteins and HPV-DNA in epithelial intermediate and surface cells (ibid.).

Subsequently, the viral DNA is integrated into the chromosomal DNA which is histologically visible as a precancerous lesion (Agaimy *et al.*, 2019; Lax *et al.*, 2019). No histological changes are seen in latent epithelial HPV infection (ibid.).

## 1.2 Transmission of HPV

HPV is transmitted through direct contact from skin to skin (Kaufmann, Costa and Scharl, 2013; Scharl and Göhring, 2013a; Petca, Borislavschi, M. Zvanca, *et al.*, 2020) or skin to mucosal tissue (Petca, Borislavschi, M. Zvanca, *et al.*, 2020, p. 2) with sexual intercourse being the main mechanism in horizontally transmitting anogenital HPV (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007). Transmission through sexual activity has been documented most, nevertheless studies gave rise to the assumption of non-sexual transmission routes (Petca, Borislavschi, M. Zvanca, *et al.*, 2020).

Since HPV (pseudotype HPV type 16 and bovine papillomavirus type 1) has shown resistance against desiccation (Roden, Lowy and Schiller, 1997), transmission through fomites might be possible as well (Roden, Lowy and Schiller, 1997; Kaufmann, Costa and Scharl, 2013; Scharl and Göhring, 2013a). Moreover, vertical transmission from birthing person to child and self-inoculation are possible transmission modes (Petca, Borislavschi, M. Zvanca, *et al.*, 2020). Waterborne HPV transmission is still a topic to be investigated (Ding *et al.*, 2011; La Rosa, 2016a, 2016b; Petca, Borislavschi, M. Zvanca, *et al.*, 2020).

### 1.2.1 Sexual Transmission

Sexual intercourse involving interaction with infected vulvar, vaginal, cervical, anal or penile epithelial tissue is the main horizontal transmission route of anogenital HPV (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007). Infection of the basal cells can occur through microabrasions in the epithelial tissue (Agaimy *et al.*, 2019; Lax *et al.*, 2019). Thus, the virus replicates and is released again (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007; Agaimy *et al.*, 2019; Lax *et al.*, 2019). However, as explored in a study on female homosexual intercourse and HPV-associated lesions, the data suggests that penetrative sexual activity with an HPV-infected penis entering the vagina is not required (Marrazzo *et al.*, 2001; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007). Consequently HPV-related lesions were found in female subjects who have only engaged sexually with others females (Marrazzo *et al.*, 2001).

Furthermore, the main transmission route for HPV-related head and neck cancers is oral sexual contact with oral sex being described (in a review by Tumban) as oral-anogenital (anal, vaginal, penile) interaction (Tumban, 2019). Moreover, activities as simple as open-mouthed kissing seem to be possible HPV transmission modes (D'Souza *et al.*, 2009; Fu *et al.*, 2015; Tumban, 2019). As a result, a higher number of open-mouth kissing partners (D'Souza *et al.*, 2009; Fu *et al.*, 2015; Tumban, 2019) or oral sex partners (D'Souza *et al.*, 2009) increased the probability of HPV detection/infection (D'Souza *et al.*, 2009; Fu *et al.*, 2015). However, Fu et al. did not find a significant connection between "lifetime number of oral sex partners and oral HPV" (Fu *et al.*, 2015, p. 7).

### 1.2.2 Nonsexual Horizontal Transmission

HPV is also transmitted horizontally through non-sexual skin contact, mouth, fingers and fomites (Petca, Borislavschi, M. Zvanca, *et al.*, 2020). Studies investigated that HPV maintains around 30% (31% of infectious units of in-vitro generated pseudotype HPV type 16 and 34% of infectious units of purified wart-derived bovine papillomavirus type 1) of its contagiousness after 7 days of room temperature desiccation (Roden, Lowy and Schiller, 1997; Casalegno *et al.*, 2012a; Petca, Borislavschi, M. Zvanca, *et al.*, 2020). This becomes a relevant matter as, for example, gynecological equipment can cause HPV transmission (Petca, Borislavschi, M. Zvanca, *et al.*, 2020). In a study which tested various gynecological tools and objects in the gynecological environment for HPV, 18% of samples were tested

positive, with the colposcope having the highest contamination risk (Gallay *et al.*, 2015a). Similarly a study conducted from 1988 to 1989 found that within the investigated virginal group, 51% showed signs of colposcopic HPV infection (Tay, Ho and Lim-Tan, 1990; Liu, Rashid and Nyitray, 2016a). Out of the virginal, HPV-infected cases, 86% cases were HPV positive (Tay, Ho and Lim-Tan, 1990). In conclusion, the study proposed not to conceive HPV as a solely sexually transmitted disease, but rather an ubiquitous matter (Tay, Ho and Lim-Tan, 1990). Symptoms of HPV infection in the investigated virginal group were either microwarts, condylomata acuminata or subclinical infection (Tay, Ho and Lim-Tan, 1990; Liu, Rashid and Nyitray, 2016a), however the study did not explore non-vaginopenetrative sexual contact as a possible infection route for virgins (Frega *et al.*, 2003; Winer *et al.*, 2003b).

### 1.2.3 Vertical Transmission sub partu

HPV can be vertically transmitted from mother to infant during delivery (Fredericks *et al.*, 1993; Puranen *et al.*, 1996; Smith *et al.*, 2010). However, Smith et al. found in a study in 2004 that the probability of HPV infection in infants was low compared to the relatively high infection rate in their mothers´ cervix (Smith *et al.*, 2004). In a study by Smith et al., 30% of people who gave birth were tested positive for HPV-DNA, whereas HPV-DNA was detected in only 1.5% of their newborn babies; HPV samples were drawn from genital and oral regions as well as from cord blood (Smith *et al.*, 2010). In contrast, another study found that HPV transmission rate from HPV-positive females to their vaginally born neonates´ oropharyngeal epithelium was 30% (Tenti *et al.*, 1999, p. 475)(Tenti *et al.*, 1999). Still, the authors stated, that HPV-positive babies should be seen as "contaminated rather than infected" (Tenti *et al.*, 1999, p. 475), as virus elimination has been observed months after birth (ibid.).

In contrast, Cason et al. studied whether newborns contaminated with HPV types 16 and 18 at birth were still contaminated at 6 months (Cason *et al.*, 1995). Of 61 pregnant people 69% were HPV 16 and 21% HPV 18 positive (ibid.). 24 hours after delivery, transmission rates to the newborn were around 73% (ibid.). After 6 weeks 80% of the babies positive at birth were still contaminated with HPV-DNA (ibid.). At 6 months, HPV type 16 DNA was found in 83% of the babies, however HPV type 18 DNA was detected in only 20% of cases (Cason *et al.*, 1995).

### 1.2.4 Waterborne Transmission

HPV has been detected in water environments but HPV transmission through water has never been confirmed (Petca, Borislavschi, M. Zvanca, *et al.*, 2020). HPV types 16, 18 and 53 were detected in wastewater sludge in 2013 by Bibby and Peccia (Bibby and Peccia, 2013a, 2013b; Petca, Borislavschi, M. Zvanca, *et al.*, 2020).

The foundation for the non-sexual HPV transmission hypothesis (La Rosa, 2016a; Petca, Borislavschi, M. Zvanca, *et al.*, 2020) stems from 2011 when Ding et al. reported that HPV capsids in various reconstitutions were still contagious for a minimum of seven days after being exposed to wet surroundings (Ding *et al.*, 2011; La Rosa, 2016b; Petca, Borislavschi, M. Zvanca, *et al.*, 2020).

## 1.3 Risk Factors for HPV Infection

A study on risk factors for anogenital HPV infection found that in a male population current smoking, in comparison to lifelong smoking abstinence, is related to a positive result for any HPV type as well as for an oncogenic HPV type (Nielson *et al.*, 2007). The association between detection of any HPV type (and oncogenic as well as non-oncogenic HPV types) and smoking 10 or more cigarettes daily was even stronger (Nielson *et al.*, 2007). Furthermore, an association was found between sexual behavior variables and positive HPV testing in the investigated male population (ibid.):

> "Factors statistically significantly associated with any HPV infection were increasing lifetime number of female sex partners, number of female sex partners during the past 3 months, and increased frequency of intercourse during the past month and during the past 3 months." (Nielson *et al.*, 2007, p. 1140)

The same factors were associated with the detection of oncogenic HPV types. Additionally, the use of condoms during half of all sexual contacts is related to a lower probability of HPV detection (Nielson *et al.*, 2007).The presence of genital warts is associated with oncogenic as well as any HPV type (ibid.). History of intercourse with a female partner with a pathological PAP smear was also associated with detection of oncogenic HPV in men (Nielson *et al.*, 2007).

Castellsagué et al. (2002), using data from IARC studies found that male circumcision is related to a lower risk of penile HPV-infection (Castellsagué *et al.*, 2002). Furthermore, females in monogamous relationships with male circumcised partners with a history of several sex partners (≥6), had a decreased risk of cervical cancer compared to females whose partners were not circumcised (Castellsagué *et al.*, 2002).

A meta-analysis/ systematic review looked at risk factors for oral HPV infection (Shigeishi and Sugiyama, 2016). A significant association ($p < 0.0001$) was observed between oral HPV infection and oral sex (Shigeishi and Sugiyama, 2016). Moreover, smoking is a further risk factor for oral HPV infection ($p = 0.0024$) (Shigeishi and Sugiyama, 2016). Additionally, that relation was significant in females ($p = 0.0058$) (Cook *et al.*, 2014; Shigeishi and Sugiyama, 2016).

Tobacco exposure was found to cause an increase in the production of proinflammatory cytokines as well as lower anti-inflammatory cytokine levels (Arnson, Shoenfeld and Amital, 2010; Kreimer *et al.*, 2013), which might lead to a higher probability of HPV infection and persistence, especially in the oral cavity where direct interaction between oral epithelium and tobacco carcinogens takes place (Kreimer *et al.*, 2013).

In females, oral contraception, smoking, rising cumulative number of sexual partners and having a male sex partner, especially one known for a period shorter than 8 months before intercourse and their number of previous sexual partners, were significantly predictive factors for HPV infection (Winer *et al.*, 2003b). Contraception with male condoms in new sexual relationships did not show protection (ibid.). The study reported that although genital HPV infection in virginal females was rare, nonpenetrative sexual intercourse was correlated with higher infection risks in virgins (Winer *et al.*, 2003b).

It remains unclear which factors influence viral persistence and elimination subsequent to anogenital HPV infection (Agaimy *et al.*, 2019; Lax *et al.*, 2019). However, HPV type and immunological factors, such as a smoking habit, malnutrition and HIV infection with immunodeficiency seem to play a role (ibid.).

## 1.4 HPV-associated Diseases

HPV causes various benign and malignant diseases at numerous sites (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020). HPV-induced tumors are grouped into tumors affecting

the skin, the anogenital mucosa and the non-genital mucosa, predominantly the oropharyngeal and laryngeal mucosa (ibid.).

Infection with HPV can lead to different symptoms at the affected locations. Tumorous lesions such as skin warts, epidermodysplasia verruciformis (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020) and oral benign epithelial lesions such as Morbus Heck (focal epithelial hyperplasia), oral condylomata, warts and (a large share of) papillomas belong to the group of HPV-induced diseases (Agaimy *et al.*, 2019; Agaimy, Noske and Baumhoer, 2019). Recurrent respiratory papillomatosis, HPV-positive head and neck cancers (especially of the oropharyngeal region) and anogenital condylomata acuminata are also caused by HPV (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020). Most importantly, HPV can lead to cervical, penile, vulvar, vaginal as well as anal intraepithelial neoplasias (CIN, PIN, VIN, etc.) as well as to cancer of the mentioned organs (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020).

## 1.5 HPV-associated Lesions in all Genders

### 1.5.1 Skin: Benign Lesions

#### 1.5.1.1 Skin: Skin Warts

Skin warts are benign lesions induced by specific HPV types such as HPV 1, HPV 2 and HPV 3 (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020):

- Verrucae vulgares are common and occur after an incubation period of two to four months (ibid.). They affect mostly hands and feet. Most of these lesions regress spontaneously (ibid.). The facial area (e.g. eyelid) can also be affected by filiform verrucae vulgares (ibid.). Pringle suggested that verrucae vulgares were mainly associated with HPV 2 and HPV 4 and were mostly found on childrens´ hands and fingers (Pringle, 2014).
- Verrucae planae juveniles, another type of HPV-induced warts, are found on facial areas such as the forehead and the perioral region, but also on the legs and arms (Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020).
- Plantar warts are observed on the soles of the feet and are extremely prone to relapse

(Ganzenmüller and Iftner, 2020; Suerbaum *et al.*, 2020).

### 1.5.2 Skin: In-situ Carcinoma

#### 1.5.2.1 Bowen´s Disease

Bowen´s disease describes a carcinoma/carcinoma in situ, located in the epidermis that occurs as a red, squamous, flat, sharply limited and partly keratotic lesion on the extremities and the trunk (Terhorst, 2019; Terhorst-Molawi, 2019). The disease predominantly affects people over the age of 40 (ibid.). Dyskeratotic, atypical cells, that are frequently associated with HPV, are found in the disorganized epidermal layer (ibid.). Bowen´s disease can transform to Bowen´s carcinoma (ibid.).

### 1.5.3 Oral Cavity: Benign Epithelial Lesions

Morbus Heck (focal epithelial hyperplasia), enoral warts, condyloma and a big share of papillomas belong to the group of mucocutaneous wart diseases caused by HPV (Agaimy *et al.*, 2019; Agaimy, Noske and Baumhoer, 2019). The mentioned lesions are predominantly caused by the genital HPV types 6 and 11 and the main transmission mode is through smear infection and sex (ibid.). Oral HPV lesions are located predominantly on the tongue and palate but can arise anywhere in the oral cavity (ibid.).

#### 1.5.3.1 Oral Cavity: Verruca Vulgaris

Although verruca vulgaris is often found on children´s hands and fingers, it is rarely observed in the oral cavity (Pringle, 2014). However, oral verrucae vulgaris show clinical and microscopical similarities to the common skin wart and the main transmission route is through autoinoculation of the fingers to the oral cavity (Pringle, 2014). Testi et al stated that HPV types 2 and 57 were detected in enoral warts (Testi *et al.*, 2016). However, Betz (2019) and Pringle (2014) listed HPV types 2 and 4 to be associated with oral verruca vulgaris (Pringle, 2014; Betz, 2019a). They are generally located on the tongue, hard palate,

gingiva or labial mucosa (Testi *et al.*, 2016).

#### 1.5.3.2 Oral Cavity: Squamous Cell Papilloma

Syrjänen recorded oral squamous cell papilloma (SCP) to the list of benign HPV lesions (Syrjänen, 2018a). Both, SCP and condyloma accuminata (CA) are linked to HPV types 6 and 11 (Betz, 2019a). Syrjänen describes SCP as the most frequent benign tumor located in the oral epithelium (Syrjänen, 2018b). SCPs are most observed in children and have a second peak in the fourth and fifth life decade (Syrjänen, 2018a). Moreover, acrodermatitis enteropatica, nevus unius lateralis, Down syndrome, focal dermal hypoplasia syndrome, Costello syndrome and Cowden syndrome are linked to the occurrence of multiple oral papillomas (Syrjänen, 2018a).

#### 1.5.3.3 Oral Cavity: Condyloma Accuminata

Condyloma acuminatum (CA) is usually seen as a venereal disease of the anogenital skin and mucosa (Syrjänen, 2003). Syrjänen reported that oral CA, apart from oral sexual transmission, can be caused via autoinoculation with fomites (Betz, 2019b; Syrjänen, 2003; Eversole *et al.*, 1987a). Moreover, maternal transmission can lead to oral CA (Syrjänen, 2003). CA is most frequently observed in adults, reaching a peak incidence during the third and fourth life decade (Eversole *et al.*, 1987b; Zunt and Tomich, 1989; Panici *et al.*, 1992; Betz, 2019b).

#### 1.5.3.4 Oral Cavity: Multifocal Epithelial Hyperplasia

Multifocal epithelial hyperplasia (MEH), also known as focal epithelial hyperplasia (FEH) or Heck´s disease, is an uncommon, benign disease of the oral cavity (Bendtsen *et al.*, 2021; Sethi *et al.*, 2022). MEH/FEH is caused by infection with HPV types 13, 32 or both (Pfister *et al.*, 1983; De Villiers *et al.*, 1986; Beaudenon *et al.*, 1987; Chang *et al.*, 1991; Borborema-Santos *et al.*, 2006; Kumaraswamy and Vidhya, 2011; Bendtsen *et al.*, 2021; Sethi *et al.*, 2022), however other HPV types like HPV 6, 11, 16, 18, 31, 39, 40, 51, 52, 55, 58, 66, 68,

69, 71 and 74 were also found to be causing or co-causing agents for these lesions (González *et al.*, 2005; Khanal *et al.*, 2015; Bozca, Ozbudak and Alpsoy, 2020; Bendtsen *et al.*, 2021; Jiménez Aguilar *et al.*, 2023a, 2023b). Moreover, Bendtsen et al. reported a case of a 56-year-old female with a FEH lesion caused by HPV 90 infection (Bendtsen *et al.*, 2021).

Nowadays, cases of FEH are seen across the globe (Sethi *et al.*, 2022), however initially cases of the disease were seen among Inuit, some African populations and Native Americans (Witkop and Niswander, 1965; Jarvis and Gorlin, 1972; Sethi *et al.*, 2022). FEH has been proposed to be linked to ethnicity (Orfanos, Strunk and Gartmann, 1974; Axéll, Hammarström and Larsson, 1981) (Praetorius-Clausen, 1972; Sethi *et al.*, 2022) and genetics (Sethi *et al.*, 2022). In 2004, García-Corona et al. found, that 19 (86%) out of 22 patients, who were histologically and clinically diagnosed with FEH, were positive for human leukocyte antigen DR4 (García-Corona *et al.*, 2004; García and Espinosa, 2011; Akoğlu *et al.*, 2015; Bendtsen *et al.*, 2021; Sethi *et al.*, 2022).

FEH appear as multiple lesions ranging from 0.2 to 3 cm (Ledesma-Montes and Mendez-Mendoza, 2017). These oral lesions present as soft nodular or papular, white to mucosa-colored elevations (Nartey, Newman and Nyako, 2003; Ledesma-Montes *et al.*, 2005; Said *et al.*, 2013; Syrjänen, 2018b; Bozca, Ozbudak and Alpsoy, 2020; Bendtsen *et al.*, 2021) (Agnew, Alexander and Prabhu, 2017; Bendtsen *et al.*, 2021).

### 1.5.4 Aerodigestive Tract: Benign Lesions: Laryngeal Papillomas/Papillomatosis

Laryngeal papillomas/papillomatosis are caused by HPV types 6 and 11 (Franzen and Coordes, 2022; Gürkov, 2022). Lesions may either present solitary (in the vocal fold area) or primarily multiple (supra/subglottic occurrence, up into the tracheobronchial tree is possible) (ibid.). They are primarily benign lesions with a potential for malign transformation (ibid.). Although the pathogenesis is similar, an adult and a juvenile form need to be distinguished (Franzen and Coordes, 2022). A distinction is necessary due to the clinical and prognostic differences between the two entities (ibid.).

The juvenile form presents before the age of 5 (Franzen and Coordes, 2022; Gürkov, 2022), lesions may be recurrent until adulthood (Gürkov, 2022). They mostly present as multiple, multilocular lesions and are not keratinized (Franzen and Coordes, 2022; Gürkov, 2022). Papillomas occurring during childhood rarely transform into cancer (Franzen and Coordes,

2022). However, malignant transformation is possible, especially in papillomas caused by HPV type 11 (ibid.).
Adult laryngeal papillomas appear as solitary, keratinized lesions in the vocal fold region, findings range from different stages of dysplastic changes up to carcinoma in situ (Franzen and Coordes, 2022, p. 230; Gürkov, 2022). Franzen and Coordes describe the adult form as a facultative precancerous lesion, with a malign transformation rate of 20% (Franzen and Coordes, 2022, p. 230).

### 1.5.5 Head and Neck: Malignant Epithelial Lesions

#### 1.5.5.1 HPV-associated Head and Neck Carcinoma

Head and neck cancer include epithelial malignant neoplasias in the upper aerodigestive tract, more specifically in the nasal cavity, paranasal sinuses, oral cavity, larynx and pharynx (Mourad *et al.*, 2017). These lesions are typically detected in elderly patients and are associated with alcohol and tobacco consumption (Blot *et al.*, 1988; Global Burden of Disease Cancer Collaboration, 2017; Mourad *et al.*, 2017; Chow, 2020). Partly because tobacco consumption is declining, head and neck cancers are gradually decreasing globally (Global Burden of Disease Cancer Collaboration, 2017; Mourad *et al.*, 2017; Chow, 2020; Nogues *et al.*, 2021; Surveillance Research Program, National Cancer Institute, 2024). A review by Sturgis and Cinciripini from 2007 concludes that the incidence of squamous cell carcinoma of the head and neck decreased in the past two decades (point of view: 2007), which is largely attributable to a decrease of tobacco habit prevalence starting 4 decades ago (Sturgis and Cinciripini, 2007).
Conversely, in the past decades, the OPSCC reappeared due to infection with HPV (Van Dyne *et al.*, 2018; Nogues *et al.*, 2021) and as data of the Centers of Disease Control and Prevention, which "analyzed data from population-based cancer registries that participate in the CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program" (Van Dyne *et al.*, 2018, p. 918), found, it superseded cervical cancer as the leading cause of HPV-associated cancer in the United States in 2015 (Sturgis and Cinciripini, 2007; Van Dyne *et al.*, 2018; Nogues *et al.*, 2021). Chaturvedi et al., using data from the Cancer Incidence in Five Continents database (Chaturvedi *et al.*, 2013 using data from; International Agency for Research on Cancer,

2010), found that between 1983 to 2002 the incidence of oropharyngeal carcinoma rose significantly (in several countries worldwide), particularly affecting people in several developed countries (using United Nations definitions for development (De Martel *et al.*, 2012; Chaturvedi *et al.*, 2013)) "and at younger ages" (Chaturvedi *et al.*, 2013, p. 4550), the "results underscore a potential role for HPV infection on increasing OPC incidence, particularly among men" (Chaturvedi *et al.*, 2013, p. 4550) (De Martel *et al.*, 2012; Chaturvedi *et al.*, 2013 using data from; International Agency for Research on Cancer, 2010).

HPV has been linked to three cancer locations in the head and neck: the oropharynx and, to a way lesser degree, to the larynx and the oral cavity (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015). Worldwide, HPV is attributable for around 38 000 cases of head and neck cancer (de Martel *et al.*, 2017 deriving from ; Plummer *et al.*, 2016)[1]. HPV - attributable head and neck cancer is a bigger burden in more developed than in less developed countries and, with that, showing a diametrically opposed geographical distribution to cervical cancer (de Martel *et al.*, 2017)[1].

HPV type 16 and 18 are attributable for 85% of HPV-associated head and neck cancer worldwide, with HPV type 16 being predominant in comparison to cervical cancer (de Martel *et al.*, 2017 deriving from; Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016)[1].

### 1.5.6 Anal Cancer

De Martel et al. found, that in the year 2012, HPV was attributable for around 35 000 cases of anal cancer around the world (de Martel *et al.*, 2017 deriving from; Plummer *et al.*, 2016)[1], making HPV the attributing agent for approximately 90% of all anal cancers (de Martel *et al.*, 2017)[1]. On a global scale, HPV – attributable anal cancer is equally distributed amongst

[1] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

females and males (de Martel *et al.*, 2017)[2]. However, the disease affects females in more developed countries slightly more frequently than it affects males (de Martel *et al.*, 2017)[2]. Nevertheless, in less developed countries, the disease occurs slightly more frequently in males (de Martel *et al.*, 2017)[2].

The relative contribution of HPV types 16 and 18 to HPV-attributable anal cancers is 87% (de Martel *et al.*, 2017 deriving from; Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016)[2]. HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 are together responsible for 96% of the disease (de Martel *et al.*, 2017 deriving from; Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016)[2].

HPV type 16 is an especially important contributor in anal cancer (Lin, Franceschi and Clifford, 2018; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020a), as Lin, Franceschi and Clifford found it to be the most carcinogenic HPV type at this location (Lin, Franceschi and Clifford, 2018), detecting enrichment of this type from high-grade intraepithelial to invasive lesions (Lin, Franceschi and Clifford, 2018).

The same systematic review shows that in all groups analyzed HPV prevalence was reported to be 80% or more in patients with anal malignancy and, regardless of gender, was even higher in HIV-positive anal cancer (100%), than in HIV-negative anal cancer (Lin, Franceschi and Clifford, 2018).

### 1.5.7 Anogenital Warts (Condylomas)

Anogenital warts, also known as condyloma and condyloma acuminata (CA), are caused in particular by HPV types 6 and 11 (Steben and Garland, 2014a, 2014b). In a study of 8800 females in the placebo arm of two randomized trials of a quadrivalent HPV (types 6, 11, 16, 18) vaccine, 298 subjects (3.4%) developed condyloma acuminata associated to HPV types 6 or 11, with HPV type 6 predominating (Garland *et al.*, 2009). In total, 520 different lesions were identified as genital warts (Garland *et al.*, 2009) and HPV-DNA was found in 472 (90.8%) of said warts, however it is possible that the lesions, that were tested negative (14 HPV types were tested), could have been positive for HPV types that were not tested

[2] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

(Garland *et al.*, 2009). HPV type 6 and 11 were found in 447 (86.0%) of these 520 lesions, making up for 94.7% of the 472 HPV-DNA positive genital warts (Garland *et al.*, 2009). Moreover, in 161 (31.0%) of 520 lesions high-risk HPV types were detected (Garland *et al.*, 2009).

CA clinically appear as visible mucosal or skin growths in the anogenital region (Steben and Garland, 2014a, 2014b). The anogenital skin region and/or mucosa can be affected by multiple warts (Steben and Garland, 2014a, 2014b). Anogenital warts appear as exophytic, asymmetric and polymorphic fronds in anogenital regions irritated by shaving, friction or trauma (Steben and Garland, 2014a, 2014b). Most people affected by condyloma acuminata notice the warts during self-examination, as, CA in general, do not cause a lot of pain or discomfort (Steben and Garland, 2014a, 2014b). However, symptoms that may occasionally arise are pruritus, or seldomly, if secondarily infected, CA can lead to local discharge and/or bleeding (Steben and Garland, 2014a, 2014b)

Hartwig et al. reported that the estimated number of new cases of condyloma acuminata per year in Europe in females ranged from 379 330 to 510 492 cases and in males ranged from 376 608 to 427 720 (Hartwig *et al.*, 2017).

Based on health claims data from the United States (US) in 2004, the projected incidence of CA for 2004 in the US was 1.1/1000 male individuals and 1.2/1000 female individuals and incidence rate peaked in males between the ages of 25 – 29 (2.7 per 1000) and in females between the ages of 20 – 24 (4.6/1000) (Hoy *et al.*, 2009; Markowitz *et al.*, 2014).

Pirotta et al. detected a significant psychosocial burden for females either receiving a diagnosis of or screening for HPV-associated genital condition, with the greatest impact, among others, being observed in subjects with extragenital warts (Pirotta *et al.*, 2009). Moreover, subjects diagnosed with CA were concerned about “partner and transmission” (Pirotta *et al.*, 2009, p. 510). Pirotta et al. conclude that health workers offering PAP smears and discussion of said results should be aware that the impact of HPV is larger than the lesions it causes, with even patients being screened and receiving normal findings potentially suffering from “negative psychosocial repercussions” (Pirotta *et al.*, 2009). The authors summarize that HPV vaccination will reduce the psychosocial impact on females as well as health expenses by enabling “less frequent cervical cytology screening” (Pirotta *et al.*, 2009, p. 513).

## 1.6 HPV-associated Diseases in Females

### 1.6.1 Cervical Precancerous Lesions

The junction of the non-keratinized squamous epithelium of the vagina and the portio vaginalis uteri to the endocervical cylindrical epithelium is often the origin of preinvasive as well as invasive cervical lesions (Gossmann, Oettling and Kreienberg, 2013). The squamocolumnar junction shifts throughout the course of life: at puberty it is usually localized slightly external to the cervix, however with sexual maturity the vagina acidifies and the cylindrical epithelium is progressively replaced by squamous epithelium (Gossmann, Oettling and Kreienberg, 2013). This replacement is partly caused by the squamous epithelium´s growth towards the cervix and partly by a metaplastic transformation originating from the cylindrical epithelium´s reserve cell into squamous epithelium (ibid.).
The transformation zone refers to the region between the current and original line between the cylindrical and squamous epithelium (Gossmann, Oettling and Kreienberg, 2013). The location of this line also changes throughout the course of life: during sexual maturity it is usually in the ectocervix (and accessible in colposcopy/examination via specula) whereas after menopause, the squamocolumnar junction is in the endocervical canal (and hence is usually not visible) (ibid.). The transformation zone´s vulnerability is increased due to the regions´ transformative and regenerative processes (ibid.). Due to being subject to mechanical and chemical microtrauma, the reserve and basal cells become especially susceptible to agents with oncogenic potential, such as HPV (ibid.). Thus, it is therefore likely that the transformation zone is a preferred localization for neoplastic processes (ibid.)

Infection with certain HPV types can induce malfunction of growth and differentiation processes of squamous epithelium in the transformation zone, called cervical intraepithelial neoplasia, dysplasia or squamous intraepithelial lesions (SIL) (Gossmann, Oettling and Kreienberg, 2013; Mills *et al.*, 2020). Cervical SILs are defined as squamous cell proliferations with atypical maturation and/or viral cytopathic abnormalities (described below), that are caused by HPV; they do not cross the basement membrane (Mills *et al.*, 2020). SILs occur on the cervical squamous mucosa, and they mostly appear in the transformation zone (ibid.). Especially high-grade squamous intraepithelial lesions arise preferably at the squamocolumar junction (ibid.).
Dysplastic cells appear more immature and similar to basal/ parabasal cells (Gossmann,

Oettling and Kreienberg, 2013). These processes can gradually lead to the development of invasive cervical carcinoma (ibid.) They are categorized according to their level of severity (ibid.).

- **Cervical intraepithelial neoplasia (CIN) I or Low-Grade Squamous Intraepithelial Lesion (LSIL):** in CIN I lesions (mild dysplasia), maturation disorder and basaloid, neoplastic cells occur only in the basal third of squamous epithelium, the layers above are still able to differentiate nearly physiologically (Tavassoli and Devilee, 2003; Girardi *et al.*, 2015, p. 33; Gossmann, Oettling and Kreienberg, 2013; Kohlberger *et al.*, 2017; Reich *et al.*, 2018b, 2018a; Girardi *et al.*, 2015; Kurman, Ellenson and Ronnett, 2019).
- **CIN II or High-Grade Squamous Intraepithelial Lesion (HSIL):** in moderate dysplasia, the two basal thirds of epithelium are affected at the most (basaloid cells are in the basal third up to second third) (ibid.).
- **CIN III or High-Grade Squamous Intraepithelial Lesion (HSIL):** Due to similarities in histopathology and prognosis, this category concludes two entities: severe dysplasia and carcinoma in situ (ibid.). In severe dysplasia almost the entire epithelium is affected (basaloid cells occur in two-thirds up to the entire epithelium), only little differentiation can be seen (ibid.) Carcinoma in situ is characterized by maturation disorders affecting the entire epithelium, no residual differentiation can be detected, and stratification may be lost entirely (ibid.).

Cytologic abnormalities, atypical cell proliferation and maturation are characteristic for dysplastic epithelium in SIL (Girardi *et al.*, 2015; Kurman, Ellenson and Ronnett, 2019). Further features of SIL are varying proportions of cells and nuclei, hyperchromatic and augmented nuclei, nuclear pleomorphism, atypical chromatin distribution, increased mitosis and N/C ratio (ibid.). Nuclear atypia is the prominent characteristic of SIL: filamentous, coarse or granular chromatin and irregular nuclear limits can be seen (Kurman, Ellenson and Ronnett, 2019). The epithelial architecture is no longer preserved: cells lose their polarity, keratinization and parakeratosis may occur on the epithelial surface and a total loss of stratification may take place and "the full thickness of the epithelium is made up of a uniform population of atypical cells" (Girardi *et al.*, 2015, p. 32). Borders between healthy epithelium and dysplasia, as well as between distinct forms of dysplastic epithelium, are sharp (Girardi *et al.*, 2015)

Dysplastic processes are thought to develop continuously, with CIN I and CIN II often being able to regress (Gossmann, Oettling and Kreienberg, 2013). CIN III (Carcinoma in situ and severe dysplasia) however, rarely is reversible and can often progress to invasive cancer without treatment (ibid.).

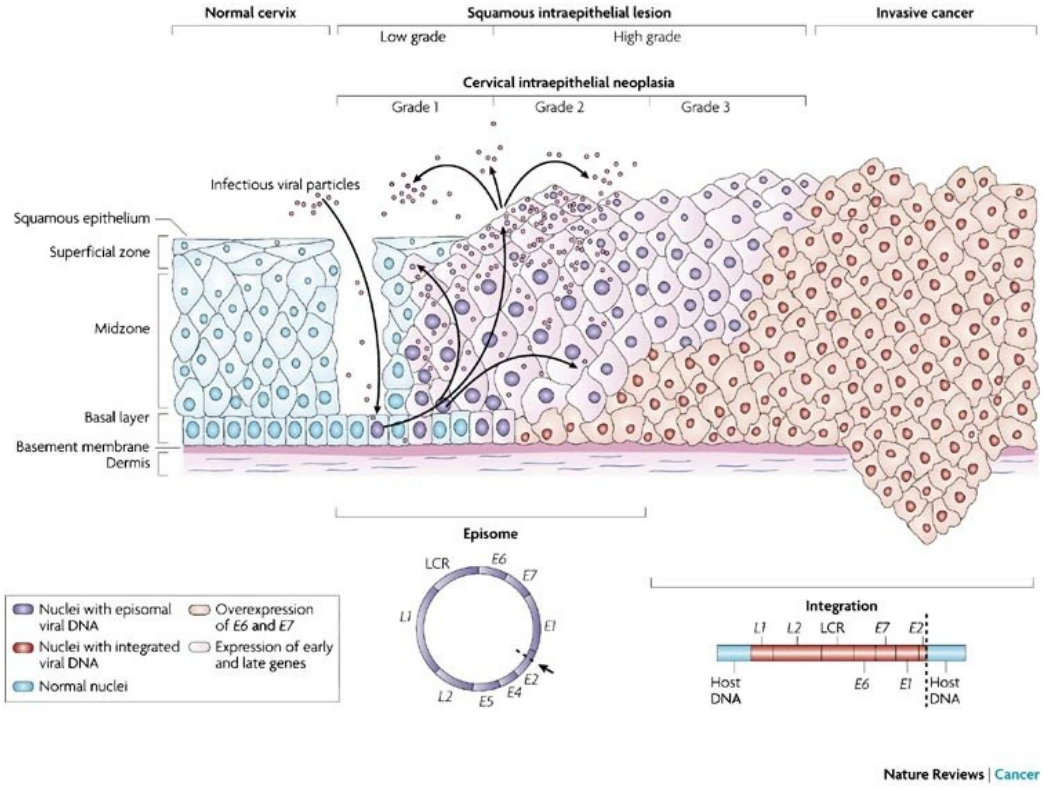


*Figure 1: "HPV-mediated progression to cervical cancer."* *(Used with permission from Springer Nature/ Woodman, Collins and Young, 2007, p. 13)*

Macroscopically, high-risk HPV-related cervical SILs are flat lesions, which can usually not be distinguished from the normal mucosa by the naked eye (Mills *et al.*, 2020). Coexistence of LSIL and HSIL is possible and cannot be differentiated grossly (ibid.). A colposcope and acetic acid allow macroscopic visualization (ibid.). However, as the identification of SIL can be difficult, the sensitivity of colposcopic sampling is imperfect and a negative biopsy finding "does not negate or override concern prompted by a cytologically detected lesion" (Mills *et al.*, 2020, p. 343).

Squamous intraepithelial lesions may grow horizontally and therefore the transformation zone may be entirely involved, an extension "onto the native portio epithelium" (Kurman, Ellenson and Ronnett, 2019, p. 256) is unusual (Kurman, Ellenson and Ronnett, 2019). Dimensions and endocervical distribution of SIL seem to depend on the lesion´s

severity/grade (ibid.). SIL can grow unrestrictedly into the endocervix and, although rarely, it may extend throughout the whole endocervical canal up to the uterus (ibid.). Therefore, HSIL more often extends into the endocervical canal and normally also presents with the largest surface area (ibid.).

The "S3-Leitlinie zur Prävention des Zervixkarzinoms" (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b) states, that since the publication of „WHO classification of tumours of the female reproductive organs" (Kurman *et al.*, 2014a; Stoler *et al.*, 2014; Wilbur *et al.*, 2014), the three-stage categorization of cervical squamous intraepithelial neoplastic lesions (CINI – III) was replaced by a two-stage classification (low-grade/ high-grade lesions) (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, p. 31, 2020b) (Kurman *et al.*, 2014b, 2014a; Girardi *et al.*, 2015, p. 32). However, the possibility of three-stage classification according to CIN – terminology, in either parenthesis or commentary, is pointed out (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, 2020b):

1.) Squamous intraepithelial lesion
    - Low grade, CIN I
    - High grade, CIN II/ CIN III
2.) Adenocarcinoma in situ (AIS/ACIS) (ibid.).

This classification of dysplastic epithelial lesions is based on the Bethesda system (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, p. 31, 2020b; 'The (1988) Bethesda system for reporting cervical/vaginal cytologic diagnoses. Developed and approved at a National Cancer Institute Workshop, Bethesda, 12-13', 1988; Solomon *et al.*, 2002; Kurman, Ellenson and Ronnett, 2019, p. 244).

- **Low-grade squamous intraepithelial lesions (LSIL)** include minor dysplasia, previously called CIN I, condylomas and koilocytic atypia (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, 2020b; 'The (1988) Bethesda system for

reporting cervical/vaginal cytologic diagnoses. Developed and approved at a National Cancer Institute Workshop, Bethesda, 12-13', 1988; Solomon *et al.*, 2002; Kurman, Ellenson and Ronnett, 2019, p. 244; Mills *et al.*, 2020)

- **High-grade squamous intraepithelial lesions (HSIL)** include moderate and severe dysplasia, previously called CIN II and CIN III (ibid.).

The classification, which is valid since 2014, firstly aims to extend the "classic" dysplasia categorization, based on cellular and structural atypia, by including the cell-biologically and pathogenetically relevant characteristics of HPV-association (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, 2020b). Secondly it thus aims to consider the lesions´ distinct tendencies to progress, depending on whether an infection with a low-risk or high-risk HPV type took place (ibid.). p16 (as a marker for high-risk HPV infection) preferably combined with Ki67, is used as a tool to differentiate metaplastic, hyperplastic, and (post-) inflammatory lesions from true precancerous lesions (ibid.). This also enables the detection of most glandular precancerous lesions of the cervix, also known as adenocarcinoma in situ (AIS/ACIS) or high-grade cervical glandular intraepithelial neoplasia (HG-CGIN) (ibid.). Subgroups of glandular precancerous cervical lesions can be distinguished similarly to subgroups of cervical adenocarcinoma: endometrioid, intestinal (with goblet cells), endocervical, "gastric type" (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, p. 31), serous, tuboendometrioid, SMILE (adenosquamous/ "stratified mucin producing intraepithelial lesion" (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b, p. 31) and clear cell (Stoler *et al.*, 2014; Wilbur *et al.*, 2014; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b).

The "S3-Leitlinie Prävention des Zervixkarzinoms" advises German-speaking countries to use the original three-stage classification (CIN I/II/III) and the WHO two-stage classification should be added commentary or in parentheses (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b).

### 1.6.2 Cervical Cancer

The World Health Organization (WHO) states in its publication "Global strategy to accelerate the elimination of cervical cancer as a public health problem":
"Cervical cancer is a preventable disease. It is also curable if detected early and adequately treated. Yet it remains one of the most common cancers and causes of cancer-related death in women across the globe." (World Health Organization, 2020a, p. 7).

Globally, cervical cancer was the fourth most common neoplasia among females in 2022 (IARC, 2024a), with an incidence of 662 301 cases (Ferlay *et al.*, 2021; Sung *et al.*, 2021; Ferlay *et al.*, 2024a; IARC, 2024a) and 348 874 deaths worldwide in 2022 (Ferlay *et al.*, 2021, 2024a, 2024b; Sung *et al.*, 2021; IARC, 2024b). The highest incidence of the disease is in low and middle-income countries (LIC/MIC) (World Health Organization, 2020a; Ferlay *et al.*, 2024b; Sung *et al.*, 2021 and; Ferlay *et al.*, 2021). Eswatini leads with an age-standardized incidence rate of 95,9 cases per 100 000 (Ferlay *et al.*, 2021, 2024b; Sung *et al.*, 2021; IARC, 2024c), age-standardized incidence rate in lowest-risk countries is less than 10 cases per 100 000 people (World Health Organization, 2020a; Ferlay *et al.*, 2021; Sung *et al.*, 2021; Ferlay *et al.*, 2024b).
In Austria the age-standardized incidence rate is 5.9 per 100 000 people (IARC, 2024c).

De Martel et al., using data from GLOBOCAN 2012 (Ferlay *et al.*, 2012), found 530 000 new cases of cervical cancer annually, amounting for the vast majority of HPV-associated cancer cases globally (de Martel *et al.*, 2017)[3]. In 2012, nearly 50% of cervical cancer cases were found in females under the age of 50 (de Martel *et al.*, 2017a using data from Ferlay *et al.*, 2012)[3] and more than two-thirds of cases are found in less developed countries (de Martel *et al.*, 2017)[3]. Most of cervical cancer cases are seen in South America, sub-Saharan Africa and South-Eastern Asia, where India is especially strongly affected (de Martel *et al.*, 2017)[3]. An age-standardized incidence rate of over 30 per 100 000 is mostly observed in countries in sub-Saharan Africa, Oceania and South America (de Martel *et al.*, 2017)[3].
Globally, in 2018 approximately 90% of the 311 000 deaths caused by cervical cancer took place in low and middle-income countries (World Health Organization, 2020a).
The worldwide burden of cervical cancer is predicted to continue to rise, reaching 760 082 cases (IARC, 2024f) and a mortality of 411 035 by the year 2030 (IARC, 2024e). The

[3] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

WHO´s "Global strategy to accelerate the elimination of cervical cancer as a public health problem" uses data from 2018 to 2030 to predict incidence and mortality with the same IARC tool (World Health Organization, 2020a). The WHO elaborates that most of these rises will be seen in females in LICs and MICs, which reflects "the severity of the global divide in cervical cancer morbidity and mortality" (World Health Organization, 2020a, p. 12).

Worldwide, HPV types 16 and 18 cause 71% of all cervical cancer cases, together with HPV types 6, 11, 31, 33, 45, 52, 58, they are responsible for 90% of cervical cancers (de Martel *et al.*, 2017a derived from Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016)[4].

Histologically, more than 80% of invasive cervical cancers are squamous cell carcinoma (Gossmann, Oettling and Kreienberg, 2013). Adenocarcinomas account for 15% of all cervical cancers (Gossmann, Oettling and Kreienberg, 2013). Small et al. describe that neoplasia originating from the ectocervix most frequently are squamous cell carcinoma, making up for a share of 75% of all invasive cervical cancer cases, and neoplasia originating from the endocervix more often are adenocarcinomas (Ries *et al.*, 2007; Small Jr *et al.*, 2017; Cohen *et al.*, 2019). Rare histological subtypes are serous papillary, small cell or neuroendocrine, adenosquamous and clear cell cervical carcinomas (Small Jr *et al.*, 2017).

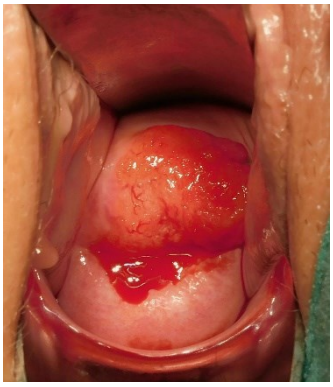

*Figure 2: Adenocarcinoma of the cervix (Universitätsklinik für Frauenheilkunde Graz)*

[4] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

#### 1.6.2.1 Risk Factors for Cervical Cancer

Carcinogenesis is a multifactorial process with different valency and interactions between the influencing factors (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2022). Therefore, the S3-Leitlinie "Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom" distinguishes groups of risk factors for the development of cervical cancer (ibid.).

- Infection with HPV, predominantly with types 16 and 18, and precancerous stages/dysplasias (LSIL, HSIL and AIS) are main risk factors (ibid.). Cervical cancer is almost always caused by HPV infection (Bosch *et al.*, 2002; Schiffman *et al.*, 2011b; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2022). Etiologically carcinogenesis is linked to infection with high risk HPV, mostly types 6, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 70, 73, 82 (Bouvard *et al.*, 2009; Schiffman *et al.*, 2011b; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2022, p. 46). However, the infection usually resolves spontaneously and persists in only 5 – 10% of patients and only approximately 3% of patients with HPV infection develop cervical cancer (Wright and Schiffman, 2003; Rodríguez *et al.*, 2008, 2010; Sycuro *et al.*, 2008; Schiffman *et al.*, 2011b; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2022, p. 46).
- Co-factors are smoking more than 15 cigarettes a day, onset of sexual activity before the age of 14, immunosuppression (HIV, medication), more than 4 partners in 10 years, poor sexual hygiene, other infections (for example chlamydia, gonococcus, genital herpes), poor socio-economic status, multiparity and long-term use of oral birth control >5 years (possible confounder effect) (Castellsagué, Bosch and Muñoz, 2002; Moreno *et al.*, 2002; Franceschi, 2005; Appleby *et al.*, 2007; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; Su *et al.*, 2018; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2022, p. 45).

HPV is seen as a "(virtually) necessary but (generally) not sufficient cause of cervical cancer" (Schiffman *et al.*, 2011c, p. 368), due to its important part in the development of nearly all cervical carcinoma cases (Schiffman *et al.*, 2011c). Except for HPV-negative

cervical cancer, which is rare, the development of cervical carcinoma follows a certain order of sequential steps (Schiffman *et al.*, 2011c). Firstly, the cervix is acutely infected "with carcinogenic HPV types(s)" (Schiffman *et al.*, 2011c, p. 368). Then, instead of being eliminated, the viral infection persists detectably, which is linked to developing precancerous and invasive lesions of the cervix (Schiffman *et al.*, 2011c).

### 1.6.3 Vaginal Precancerous Lesions

Isolated primary precancerous vaginal lesions, called vaginal intraepithelial neoplasias (VAIN), are very uncommon and need to be differentiated from primary vulvar and cervical lesions, that commonly spread to the vagina (S. Costa, 2013). Low grade lesions conclude VAIN I and VAIN II (ibid.). VAIN I affects the lowest third of the mucosa, in VAIN II the lowest and middle third of the mucosa are affected (ibid.). The entire mucosa is affected in VAIN III, which equals vaginal carcinoma in situ (ibid.). Compared to CIN, little is known on the etiology and natural course of vaginal intraepithelial neoplasia (ibid.).

VAIN can be localized anywhere in the vagina, however it occurs more frequently next to the cervix in the upper vaginal third (S. Costa, 2013). VAIN often occurs in a multilocular pattern (ibid.).

A meta-analysis by De Vuyst et al. found that overall prevalence of HPV in VAIN was 93.6% (De Vuyst *et al.*, 2009). Breaking that down into grades, HPV prevalence in VAIN I was 100%, in VAIN II/III 90.1% and 69.9% in invasive vaginal carcinomas (De Vuyst *et al.*, 2009; S. Costa, 2013). The most common HPV type in VAIN I was HPV 16 (23.4%) (De Vuyst *et al.*, 2009). The predominant HPV types in VAIN II/III were HPV 16 (57.6%), HPV 18 (6.9%) and HPV 58 (5.9%) (ibid.). In invasive vaginal carcinoma HPV type 16 (53.7%) predominated (ibid.). Multiple-type infections were prevalent in 10.3% in VAIN I and reduced to a prevalence of 3.4% in vaginal cancer (ibid.). The authors conclude that 60% of vaginal carcinoma could be prevented by vaccination against HPV type 16/18 (De Vuyst *et al.*, 2009; S. Costa, 2013).

### 1.6.4 Vaginal Cancer

In 2017 de Martel et al., using data from GLOBOCAN 2012 (Ferlay *et al.*, 2012) and the

Cancer Incidence in Five Continents (CI5-X) database (Forman D *et al.*, 2014), concluded that 12 000 (78%) out of 15 000 cases of vaginal cancer were attributable to HPV (de Martel *et al.*, 2017 deriving from; Plummer *et al.*, 2016; de Martel *et al.*, 2017 using data from ; Forman D *et al.*, 2014)[5] with HPV type 16 and 18 accounting for about 7400 (63.7% of 12 000) cases (de Martel *et al.*, 2017 deriving from; Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Plummer *et al.*, 2016)[6].

The current incidence of vaginal cancer is 18 819 (Ferlay *et al.*, 2024c using data from, 2021; Sung *et al.*, 2021).

Squamous cell carcinoma (SCC) is the most common type of vaginal carcinoma (80%), (S. Costa, 2013). Around 14% are adenocarcinomas, 6% are malign melanoma and rhabdomyosarcomas (in children) (ibid.). The preferred localization of most vaginal malignancies is the upper third of the posterior vaginal wall (ibid.).

Early vaginal cancer is usually asymptomatic (S. Costa, 2013). Symptoms can include vaginal (in particular postmenopausal) bleeding and discharge (ibid.). Vaginal cancer initially grows into the paravaginal connective tissue, therefore pelvic pain and bladder/bowel-symptoms arise in advanced disease stages (ibid.).

Vinokurova indicated that “high-grade dysplastic lesions in the female lower genital tract may emerge primarily as monoclonal lesions from a transformed cell population derived from the uterine cervix” (Vinokurova *et al.*, 2005, p. 1816; Karam, Berek and Kidd, 2024). These findings were supported by a population-based cohort study of 132 293 females in Sweden with CIN III or severe dysplasia who received treatment during 1958 – 2002 (Strander *et al.*, 2007; Karam, Berek and Kidd, 2024). In this study, females with previous CIN III showed a standardized incidence ratio (SIR) of 6.82 (95% CI 5,61 – 8,21) for vaginal cancer, however, ≥25 years after diagnosis, SIR decreased to 2.65 (Strander *et al.*, 2007; Karam, Berek and Kidd, 2024). Similarly, out of 153 female patients with vaginal cancer or carcinoma in situ treated at the Princess Margaret Hospital, 44 had previous gynecological cancer and from these 34 females had cervical carcinoma (Kirkbride *et al.*, 1995; Karam, Berek and Kidd, 2024).

[5] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

[6] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

### 1.6.5 Vulvar Precancerous Lesions

Vulvar intraepithelial neoplasia (VIN) are precancerous vulvar lesions (S. D. Costa, 2013). Dysplasia grading is differentiated into VIN I (mild), VIN II (moderate) and VIN III (carcinoma in situ/severe) dysplasia (ibid.). Similar to vaginal precancerous lesions (described in Chapter 1.6.3), VIN I affects the lowest mucosal third (ibid.). VIN I also includes vulvar condylomata acuminata, caused by HPV type 6 and 11 infection (ibid.).

VIN II spreads to the lowest and middle third of the mucosa and VIN III affects the entire epithelium (ibid.). Pigmented papules, Buschke-Löwenstein tumors, flat condylomatous papules and Bowenoid papulosis are caused by HPV type 16 and 18 infection and are concluded as atypical condylomata (S. D. Costa, 2013). They vary in their tendencies for malign transformation (ibid.). This group is classified as either VIN II or VIN III, depending on their severity of atypical epithelial proliferation (ibid.).
HPV high risk types are assumed to be the cause of vulvar intraepithelial neoplasia (ibid.). Insinga et al. reported in their systematic review using U.S. data, that HPV type 16 accounted for 77.7% of VIN III disease cases (Insinga *et al.*, 2008; S. D. Costa, 2013).
After introducing the new nomenclature, the histological diagnoses Morbus Bowen, extramammary Paget´s disease of the vulva and erythroplasia of Queyrat, have become obsolete (S. D. Costa, 2013). Since they are clinically and therapeutically indistinguishable from carcinoma in situ (CIS), they are considered as variants of CIS (ibid.).
As extramammary Paget´s disease of the vulva is often associated with adenocarcinoma in other organs (cervix, urethra, breast, Bartholin glands, rectum), a thorough examination of said structures is necessary (S. D. Costa, 2013).

VIN is asymptomatic in about half of the cases (S. D. Costa, 2013). If symptoms show, they are of non-specific character, as for example, paresthesia, vulvar pruritus, dyspareunia, oozing and burning or stabbing pain (ibid.).

Incidence trends of VIN are described in Chapter 1.6.6. It is assumed, that the rising incidence trends are linked to HPV and a viral pathogenesis of the disease (S. D. Costa, 2013).

### 1.6.6 Vulvar Cancer

The current global incidence of vulvar cancer is 47 336 cases with an age-standardized rate of 0.83 per 100 000 (Ferlay *et al.*, 2024d using data from; Sung *et al.*, 2021; Ferlay *et al.*, 2021). Vulvar cancer is uncommon and mostly affects females above the age of 60 years, however around 15% of vulvar cancer cases are among females aged younger than 40 (S. D. Costa, 2013). Costa mentions the incidence to be stable since decades at around 1.5 per 100 000 and prevalence to be increasing due to a general populational age increase (ibid.). While a study by Joura et al. for one supports the observation, finding the overall incidence of vulvar squamous cell carcinoma to stay stable over the time of a decade (study period 1985 – 1988 and 1994 – 1997), for another, an increase of vulvar carcinoma and VIN was observed in females ≤ 50 years (Joura *et al.*, 2000). Moreover, an increase in incidence of overall VIN was detected (Joura *et al.*, 2000). Although Costa et al. report the incidence of vulvar cancer to be stable (S. D. Costa, 2013), different studies have found VIN and vulvar cancer incidence rates to be increasing in European countries and in New Zealand, this trend has been especially evident in younger females (Jones, Baranyai and Stables, 1997; Hampl *et al.*, 2008; Baandrup *et al.*, 2011; Pils *et al.*, 2017; Wakeham *et al.*, 2017).

Considering the topic and aim of this thesis, this overview will focus only on HPV-associated cases of vulvar cancer.

De Martel et al. reported that 8500 out of 34 000 cases of vulvar cancer in 2012 were attributed to HPV infection (de Martel *et al.*, 2017 using data from; Ferlay *et al.*, 2012; Forman D *et al.*, 2014)[7], HPV´s attributable fraction for vulvar cancer is 24.9% (de Martel *et al.*, 2017 using data from; Forman D *et al.*, 2014)[8]. However, the National Cancer Institute describes HPV to be the cause of vulvar malignancy in 69% of cases (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023a; National Cancer Institute, 2023a).

A meta-analysis by De Vuyst et al. found HPV in 40.4% of 1873 vulvar carcinomas (De

[7] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

[8] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

Vuyst *et al.*, 2009). Another meta-analysis, including 91 studies, found the prevalence of HPV DNA in vulvar malignancy to range from 0% to 88.9%, the overall prevalence being 39.1% (Zhuang Li *et al.*, 2023). HPV16 was the most common genotype (78.1%), HPV type 33 (7.5%) and type 18 (4.4%) followed (ibid.).

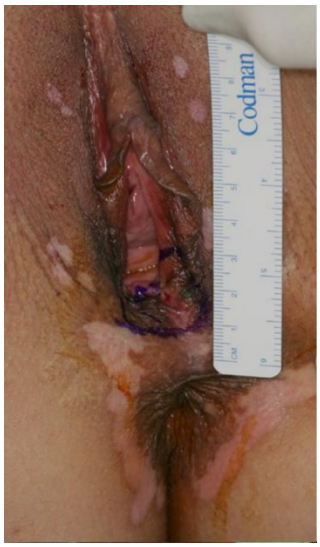


*Figure 3: HPV-associated vulvar disease (Universitätsklinik für Frauenheilkunde Graz)*

Pils et al. examined HPV prevalence in vulvar cancer in Austria (Pils *et al.*, 2017). Out of 177 cases of vulvar cancer, 41 (23%) were HPV positive (ibid.). Moreover, HPV positive cases of vulvar cancer were significantly younger (mean: 63.9 years) than HPV negative cases (mean: 71.6 years) (ibid.). The most frequent HPV type among HPV-DNA positive vulvar cancer cases showing single infection, was HPV 16 (76%), (ibid.).

De Martel et al. examined HPV type contribution on a global matter, with HPV type 16 and 18 making up for approximately 6200 (72.6% of 8500) cases of vulvar cancer (de Martel *et al.*, 2017 derived from; Serrano *et al.*, 2015; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Plummer *et al.*, 2016)[9].

As in vaginal cancer, Vinokurova et al. advanced the hypothesis that "high-grade dysplastic lesions in the female lower genital tract may emerge primarily as monoclonal lesions from a transformed cell population derived from the uterine cervix" (Vinokurova *et al.*, 2005, p.

[9] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

1816).

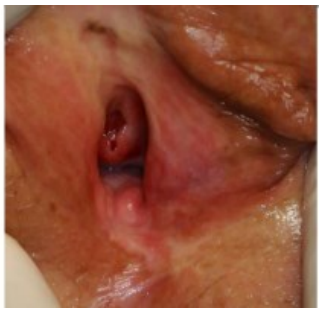

*Figure 4: HPV-associated vulvar disease (Universitätsklinik für Frauenheilkunde Graz)*

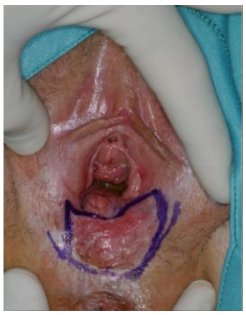

*Figure 5: HPV-associated vulvar disease (Universitätsklinik für Frauenheilkunde Graz)*

Concerning histological type, squamous cell carcinoma make up for the vast majority (90%) of vulvar cancer (S. D. Costa, 2013, p. 421).
Similarly, in a Dutch study investigating on 5680 patients with vulvar cancer between 1989 and 2010, squamous cell carcinoma (81%) was most common, followed by basal cell carcinoma (8%), melanoma of the vulva (6%) and other histological subtypes (5%) (Schuurman *et al.*, 2013).

De Vuyst et al. conclude that around 40% of vulvar carcinoma and 75% of VIN2/3 could be prevented by vaccination against HPV type 16/18 (De Vuyst *et al.*, 2009).

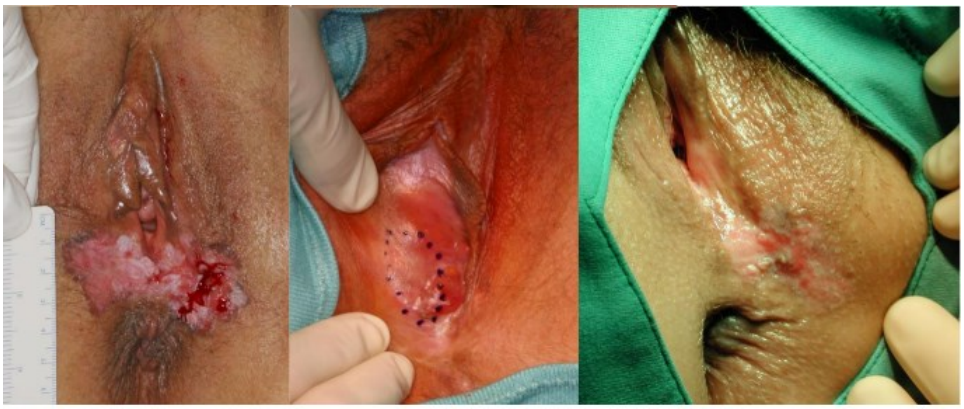

*Figure 6: HPV-associated vulvar disease (Universitätsklinik für Frauenheilkunde Graz)*

## 1.7 HPV-associated Diseases in Males

### 1.7.1 Precancerous Lesions and Penile Cancer

Penile precancerous lesions usually precede penile malignancy (Hammes, 2022). In detail, penile precancerous lesions conclude leukoplakia, lichen sclerosus and atrophicus and CIS of the transitional epithelium and the mucosa (ibid.). Penile mucosal CIS and CIS of the transitional epithelium are defined as Erythroplasia de Queyrat (ibid.). Erythroplasia de Queyrat is histologically equivalent to Morbus Bowen (ibid.).

Current global incidence of penile cancer amounts to 37 700 cases and an age-standardized incidence rate of 0.79 (Ferlay *et al.*, 2024e; Sung *et al.*, 2021; Ferlay *et al.*, 2021). Latin America and the Caribbean lead with an age-standardized incidence rate of 1.3/100 000, in Europe, the age-standardized incidence rate is 0.9/100 000 (IARC, 2024d). The vast majority of penile cancer are SCC (95%) (Hammes, 2022). Penile cancer is a rare in industrialized nations (ibid.).

Penile cancer mainly occurs starting with the $5^{th}$/$6^{th}$ life decade and the prepuce and the glans penis are the most commonly involved sites (Eberli, 2023). The patients´ main reason for medical consultation is a supposedly “inflamed” penis (Eberli, 2023), but also purulent-watery discharge and contact bleeding are possible signs of the disease (Hammes, 2022). As patients commonly suppress symptoms mentally for longer periods of time, consequently the disease spreads (Eberli, 2023).

Risk factors for penile malignancy are poor personal hygiene, phimosis, increasing number of sexual partners, smoking and dermatological UV-A treatments (Hammes, 2022). Poor

personal hygiene may lead to chronic inflammation caused by smegma bacteria, progression to intraepithelial neoplasia and consequently cancer is possible (ibid.). The disease is almost non-existent in ethnic groups practicing circumcision (ibid.). An association of penile malignancy with HPV type 16 or type 18 infection has been observed in some cases (ibid.). Eberli describes that smegma showed carcinogenic behavior in animal testing (Eberli, 2023). Moreover, the malignancy can be covered by a penile phimosis (Eberli, 2023).
The National Cancer Institute describes most penile malignancies to be attributable to HPV (63%) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023a; National Cancer Institute, 2023b). However, De Martel et al., using data from GLOBOCAN 2012 (Ferlay *et al.*, 2012) and from the Cancer Incidence in Five Continents (CI5-X) (Forman D *et al.*, 2014), found that then 50% of penile cancers were attributable to HPV (13 000 out of 26 000 cases of incidence) (de Martel *et al.*, 2017 using data from; Ferlay *et al.*, 2012; Forman D *et al.*, 2014)[10]. HPV type 16 and type 18 make up for around 70.2% (9100 out of 13 000 cases) of penile cancer and together with HPV types 6, 11, 31, 33, 45, 52, 58 they contribute to around 84.6% (11 000 out of 13 000 cases) of penile cancer cases (de Martel *et al.*, 2017 derived from ; Plummer *et al.*, 2016; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)[11].

## 1.8 Primary Prevention: HPV Vaccination

A global 90% vaccination coverage with the HPV vaccine amongst females until age 15 is the first pillar of the WHO strategy to eradicate cervical cancer (World Health Organization, 2020a). Austria has committed to achieving this goal (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024).

The HPV genome´s late region carries two open reading frames, called “L1 and L2 which encode capsid proteins” (Kurman, Ellenson and Ronnett, 2019, p. 251, 2019). The protein

[10] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)
[11] (de Martel *et al.*, 2017 using data from; Plummer *et al.*, 2016; Ferlay *et al.*, 2012; Forman D *et al.*, 2014; UNDP (United Nations Development Programme), 2013; Alemany *et al.*, 2016; Castellsagué *et al.*, 2016; Serrano *et al.*, 2015)

which is encoded by L1 builds the major capsid protein, the protein which is encoded by L2 builds a minor capsid protein (Kurman, Ellenson and Ronnett, 2019). The HPV capsid is built by two proteins, L1 and L2 (Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020; Yadav, Zhai and Tumban, 2019; Kirnbauer *et al.*, 1992; Hagensee, Yaegashi and Galloway, 1993; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., 2007; Scharl and Göhring, 2013b). The immunogenicity of HPV is mainly caused by the L1 protein, which functions as a strong antigen without and with an adjuvant (Kirnbauer *et al.*, 1992; Harro *et al.*, 2001; Koutsky *et al.*, 2002; Lowy and Schiller, 2006; Scharl and Göhring, 2013b). L1 has the ability to congregate as empty virus-like-particles (VLP´s) (Kirnbauer *et al.*, 1992; Lowy and Schiller, 2006; Scharl and Göhring, 2013b; Kurman, Ellenson and Ronnett, 2019). However, they do not carry any DNA, which makes them non-infectious (Scharl and Göhring, 2013b). The only viral component that is present in the vaccines is L1 (Kirnbauer *et al.*, 1992; Lowy and Schiller, 2006; Scharl and Göhring, 2013b; MSD, 2024a). The bivalent vaccine uses purified L1 for HPV type 16 and HPV type 18 (Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020). Additionally to L1 for HPV type 16 and 18, the nonavalent vaccine uses purified L1 for seven further HPV types: 6, 11, 31, 33, 45, 52, 58 (Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020; MSD, 2024b).
The vaccines´ proteins are generated via recombinant DNA-technology to form virus-like structures that are unable to replicate and cause disease (European Medicines Agency, 2014, 2016a, 2016b; Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020). Serum antibody titers are higher after immunization with either of the two vaccines than after natural HPV infection (Harper *et al.*, 2006; Harper and DeMars, 2017; Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020). The antibodies attach to the viral capsids, neutralize the HP-virus, and prevent HPV infection of the epithelial cells (Schiller and Lowy, 2012, 2018; Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020). Adjuvants are added to the vaccines to enhance the body´s immunological response (European Medicines Agency, 2014, 2016a, 2016b; Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020).

In Europe three vaccines - a bivalent, quadrivalent and nonavalent HPV vaccine - are currently approved by the European Medical Agency (EMA) (The FUTURE II Study Group, 2007; Gaskins and Werner, 2020, pp. 8–9; European Medicines Agency, 2016b, 2016a, no

date a; Gaskins and Werner, 2020; Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (PEG), 2020; European Medicines Agency, 2024c, 2024b, 2024a). The bivalent vaccine Cervarix® (GlaxoSmithKline Biologicals S.A.) holds antigens for HPV type 16 and 18 to prevent (pre-) cancerous lesions is approved for females (European Medicines Agency, 2024a, no date b). The quadrivalent vaccine Gardasil® (Merck Sharp & Dohme B.V.) additionally holds antigens of the HPV types 6 and 11, protects against (pre-)cancerous lesions in the cervix and anus, as well as against condylomata acuminata and is approved for females and males (European Medicines Agency, 2024b, no date b). The nonavalent vaccine Gardasil 9® (Merck Sharp & Dohme B.V.) was approved in 2015 (European Medicines Agency, 2024c, no date b). Gardasil 9 holds antigens of 9 HPV types: 6, 11, 16, 18, 31, 33, 45, 52 and 58 (MSD, 2024c; European Medicines Agency, no date b). The HPV vaccines are implemented in numerous national immunization programs (European Medicines Agency, no date b).
In Austria, the nonavalent vaccine Gardasil 9® is recommended (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024).

The efficacy of the quadrivalent HPV vaccination was investigated in two large, double-blind, randomized landmark trials (Garland *et al.*, 2007; The FUTURE II Study Group, 2007). In both studies vaccine efficacy was evaluated comparing a group that received the full immunization regime with a placebo group (ibid.). The study subjects were observed for on average for three years after the first vaccine/placebo dose was given (ibid.). In the FUTURE I study, that included 5455 females subjects (Garland *et al.*, 2007), vaccine efficacy was 100% for the incidence of condyloma acuminata, VIN or VAIN, perianal and perineal intraepithelial lesions and CIN and ACIS that were related with HPV types 6, 11, 16, 18 (Garland *et al.*, 2007). In the intention-to-treat population, which includes female subjects independent of their HPV infection status at baseline, vaccine efficacy was 55% for "when all grades of cervical lesions were combined" (Garland *et al.*, 2007).
The FUTURE II study, including 12 167 females, prophylactic vaccine efficacy was 98% for high-grade cervical lesions associated with HPV types 16 and 18 (The FUTURE II Study Group, 2007). In an intention-to-treat population with all randomized females, with and without prevalent CIN and HPV infection (vaccine and nonvaccine types) at baseline, vaccine efficacy was estimated at 44% for the same endpoint (The FUTURE II Study Group, 2007).

Joura et al. investigated the nonavalent vaccine compared to the quadrivalent vaccine in a double-blind, randomized, international study with 14 215 females (Joura *et al.*, 2015). The efficacy of the nonavalent vaccine was 96.7% for high grade vulvar, vaginal and cervical disease associated with HPV types 31, 33, 45, 52 and 58 in the "per-protocol efficacy population" (Joura *et al.*, 2015, pp. 711, 714, 718).

### 1.8.1 HPV Vaccination in Austria

As at May 2024 the Austrian immunization program includes the nonavalent HPV vaccine Gardasil9 from 9th birthday until the 21st birthday (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). The vaccination scheme for this age group is 1+1, the second vaccine dose should be given in a 6 – 12 months interval after the first vaccine dose (ibid.). HPV vaccination is also administered to (preferably) 4th grade – students, as a part of school immunization programs (ibid.).
A recent update in the HPV immunization program makes the HPV vaccine available free of charge for adults until the age of 30 (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). This free catch-up vaccination offer is scheduled until end of 2025 (ibid.). As decided on the 7th of June 2024, adults between the age of 21 and 30 can profit from free catch-up HPV vaccination in Austria between the 1.7.2024 until the 31.12.2025 (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, no date).

The optimal age for the HPV vaccine is between the 9th and 11th birthday, due to the prophylactic effect of the HPV vaccine (Kirnbauer *et al.*, 1992; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). At this time, the prophylactic effect is especially strong because this is usually before the onset of sexual activity because the vaccine has an optimal immunogenic effect in this age group (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024).

The Austrian immunization plan recommends the HPV vaccine to all people regardless from gender from the 9th birthday until the 30th birthday and optionally after the 30th birthday (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK),

2024). The general recommendation for the best time of vaccine administration is between the 9th and 12th birthday, after that catch-up vaccination is recommended until the 30th birthday (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). Amongst other indications for the HPV vaccine after the 30th birthday are personal desire to be vaccinated and risk of exposure due to sexual behaviour (sexual partner is infected with HPV, changing sex partners) (ibid.).

The vaccination should be given in 2 doses in a 1+1 scheme (Meites, Kempe and Markowitz, 2016a; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024, p. 43) for the age group 9 – 30 years, the second dose is recommended 6-12 months after the first vaccine dose (Iversen *et al.*, 2016a; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). The 2-dose schedule for people aged 15 to 30 is off-label but the Austrian immunization plan states that taking immunological considerations and available data into account the 2-dose vaccination regime may be recommended to a healthy and immunocompetent population (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). A period of at least 6 months should be kept between the first two vaccine doses, for the vaccine to achieve appropriate efficacy in this population group (ibid.).
After age 30, the Austrian immunization plan recommends a three-dose-regime (0/2/6-8) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024; Iversen *et al.*, 2016a).

In June 2021, when our study was conducted, the Austrian immunization plan included the free-of-charge nonavalent HPV vaccine only for children aged 9 – 12 years, regardless of gender (scheme 1+1) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2021). Children up to the age of 15 could receive the vaccine at reduced cost as part of the catch-up-program (ibid.). Due to the COVID-19 pandemic, this catch-up program was extended for children up to the age of 16 (ibid.). In 2021, the 3-dose regime was valid starting from age 15 (ibid.).

## 1.9 Secondary Prevention of Cervical Cancer: Cervical Screening

Secondary prevention seeks to decrease incidence and mortality of cervical cancer by

identifying and treating females with precancerous cervical abnormalities (World Health Organization, 2020a). Various options for secondary prevention exist: 1.) cytology-based screening, 2.) visual cervical examination with acetic acid and treatment (the screen and treat approach) and 3.) HPV testing (World Health Organization, 2020a).

Cytology-based screening, as part of high-coverage national programs, has been successful in reaching said aims (ibid.). However, successful cytologic screening requires the capacity to follow-up on patients, order additional diagnostics like colposcopy and pathology, and provide disease management (ibid.). This can work in HICs but can be difficult in LICs and MICs. Accordingly, the realization of cytology-based national programs has been challenging in LICs and MICs (World Health Organization, 2020a) and in countries where they have been realized, low screening coverage has been observed (ibid.).

In these resource-limited settings, the second screening option, "screen and treat" (World Health Organization, 2020a, p. 28), has been less difficult to establish (ibid.). The screen and treat method combines visual cervical examination with the application of acetic acid and abnormalities are treated (ibid.). However, sensitivity of this method varies, and the accuracy of visual examination is highly dependable on the examiner (ibid.).

Thirdly, HPV testing, having higher specificity and a "strong negative predictive value" (World Health Organization, 2020a, p. 28) can be used for cervical cancer screening (World Health Organization, 2020a). These qualities enable a minimum five-year testing interval, meaning that for females that were tested HPV negative, retesting will only be necessary after 5 years minimum (ibid.). Moreover, HPV testing can be performed via self-sampling, which makes this option more accessible and raises acceptability (ibid.). To enable fast scale-up, countries can use technology platforms, that are already used for testing of other infections (tuberculosis, HIV (human immunodeficiency virus), etc.), for HPV testing (ibid.).

Accordingly, the WHO recommends nations to switch to HPV testing as the main course of action in cervical cancer screening (World Health Organization, 2020a). To evaluate and manage females tested positive for HPV, evidence-based approaches exist (World Health Organization, 2020a).

The PAP smear (short for Papanicolaou) was developed by Papanicolaou and Traut in the 1940s (Papanicolaou and Traut, 1941; Ahr and Scharl, 2013; Gossmann, Oettling and Kreienberg, 2013). In 1941, Papanicolaou and Traut described their technique as „so simple and inexpensive that it may be applied to large numbers of women" (Papanicolaou and Traut,

1941, p. 194).

They stated in their publication that:

> "In presenting this method of diagnosis at this time, we hope that it may prove to be a dependable means whereby the principal malignant diseases of the uterus can be recognized; and further that because of its simplicity, it may eventually be applied widely so that the incipient phases of the disease may come more promptly within the range of our modern modes of treatment which have been proved highly effective in early carcinoma." (Papanicolaou and Traut, 1941, p. 205)

The PAP smear has since then been successfully established in various cancer screening programs, for example in Germany, Canada and Austria (Ahr and Scharl, 2013; Gossmann, Oettling and Kreienberg, 2013; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, Abteilung Kommunikation und Öffentlichkeitsarbeit, 2019; Bundesministerium für Gesundheit (BMG) and Referat L7 'Presse, Internet, Soziale Netzwerke', 2024).

In Austria, the PAP smear is part of the national health screen program and should be performed yearly starting at the age of 18 (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, Abteilung Kommunikation und Öffentlichkeitsarbeit, 2019).

Gossmann et al. describe the association between relative risk for cervical cancer and health screen intervals: cervical screening every three years raises the relative cancer risk by a factor of 4 and a 10-year or more interval makes the relative risk 12 times higher than when screening is carried out 1x/year (Gossmann, Oettling and Kreienberg, 2013).

### 1.9.1 HPV-based Screening

The WHO recommends HPV testing as the primary screening approach (World Health Organization, 2020a). The second pillar of the WHO´s strategy to eliminate cervical malignancy is to screen 70% of all females with a high-performance testing method ("a test that would have performance characteristics similar or better than a HPV test" (World Health

Organization, 2020a, p. 20), new technology might be available in the future) at 35 and 45 years old (World Health Organization, 2020a, 2014).
HPV-testing uses molecular techniques to detect high-risk HPV-DNA in samples (World Health Organization, 2014). For cervical malignancy to develop, persistent HPV infection is almost always necessary (ibid.). The WHO recommends to not use HPV testing in females under 30 (ibid.). The approach to not test females under 30 and detect infections, that are often transient, avoids unnecessary treatment and its negative psychological and financial consequences (ibid.). However, females over 30, that are tested HPV positive might have corresponding cervical lesions or be at risk for future precancerous lesions and cervical cancer (ibid.). The treatment of such "screen-positive" (World Health Organization, 2014, p. 142) females can thus drastically decrease their risk for future cervical malignancy (ibid.). Therefore, the WHO recommends to use HPV testing in females above the age of 30 "or the age specified in updated national guidelines" (World Health Organization, 2014, p. 142). The recommendations made by the Austrian guidelines will be described below.

The WHO states that HPV testing is established as a main screening method in "cervical cancer prevention programmes" (World Health Organization, 2014, p. 142) in resource-rich settings (ibid.). Additionally, self-sampling is possible (World Health Organization, 2014). This option also makes HPV testing an attractive screening option in resource-limited settings as females can self-sample their HPV test and for those with positive results, further examination will be scheduled (Ahr and Scharl, 2013; Stewart *et al.*, 2007).

Moreover, a negative HPV high risk testing result "has a high negative predictive value" (Reich *et al.*, 2018b, p. 1234) and cervical dysplastic lesions that need treatment over longer periods of time can largely be ruled out (Reich *et al.*, 2018b). Further prognostic value can be drawn from subtype specific HPV testing (HPV type 16 and 18) (ibid.).

HPV-based screening can be used alone or in combination with cytology (so-called cotesting) (Ahr and Scharl, 2013; Braune *et al.*, 2015; Reich *et al.*, 2018b; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b). The combination of these methods has a positive effect on screening sensitivity (Ahr and Scharl, 2013). A third strategy is the use of HPV detection as a marker for disease progression in suspicious cytological findings (ibid.).

The first strategy, HPV testing alone as the primary screening method, builds on the hypothesis that HPV high risk infection is necessary for cervical cancer to develop (Ahr and Scharl, 2013). Ahr and Scharl describe screening models, where females over 30 were included for HPV high risk testing (ibid.). Those tested positive in the screening, were then further examined via colposcopy and cytology (ibid.). Screening interval is extended to five years, when tested negative (annual screening → every five years) (ibid.).
Mayrand et al. found in their study that the sensitivity of HPV testing alone (94.6%) outperforms the sensitivity of the cytological smear (55.4%) in detecting CIN2 and 3 (Mayrand *et al.*, 2007; Ahr and Scharl, 2013; Braune *et al.*, 2015). This screening model´s weakness is that HPV testing (94.1%) has lower specificity than cytological testing (96.8%) (Mayrand *et al.*, 2007; Ahr and Scharl, 2013). Additionally, as HPV tests only test for a certain panel of HPV types, a negative result cannot exclude HPV infection with types that the patient was not tested for (Ahr and Scharl, 2013).
Ronco et al. followed-up four large European randomized controlled trials and found that HPV-based screening offers 60 – 70% higher protection against invasive cervical malignancy in comparison to cytological screening (Ronco *et al.*, 2014). The authors recommend implementing "HPV-based cervical screening with triage from age 30 years at intervals of at least 5 years" (Ronco *et al.*, 2014, p. 530).

The strength of the second strategy, cytology combined with HPV testing as a primary screening method, lies in its sensitivity: Mayrand et al. observed 100% sensitivity and 92.5% specificity for the combination of these two screening methods (Mayrand *et al.*, 2007; Ahr and Scharl, 2013). Ahr and Scharl describe, that within this screening model females between 20 and 30 would still be screened via cytology alone (1x/year), as, due to high HPV infection rates in this age range, HPV testing only makes sense beyond this age (Ahr and Scharl, 2013).

The third strategy, using HPV testing as a marker for progression in suspicious cytological findings, is also based on the hypothesis, that infection with high-risk HPV is a requirement for cervical cancer and precancerous lesions to develop (Ahr and Scharl, 2013). Thus, conspicuous cytological findings that are consequently tested positive for HPV have a different prognostic significance, than abnormal cytology that is tested negative (Ahr and Scharl, 2013). Conspicuous cytology and a negative HPV test are either "false-positive cytological findings" (Ahr and Scharl, 2013, p. 362) or they have a high tendency for

remission (Ahr and Scharl, 2013). Abnormal cytology and positive HPV test results on the other hand, are very unlikely to regress and normalize (ibid.).
In the opportunistic Austrian cervical cancer screening program, HPV testing is recommended to females ≥ 30 years, regardless from HPV vaccination status, at minimum this is to be repeated every three years (Reich *et al.*, 2018b). Both testing methods can be performed alternately, however, routine co-testing should not be performed (Braune *et al.*, 2015; Reich *et al.*, 2018b; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2017).

Moreover, the Austrian (OEGGG) HPV task force states that the availability of primary HPV testing for early detection of cervical cancer and precancerous lesions should be enabled in Austria (Braune *et al.*, 2015). After consulting with the patient, the attending gynecologist decides which method is applied: HPV testing as a replacement of conventional cytological testing or both methods alternating (ibid.). In any case a routinely combination of both tests should not be done (ibid.). At present, public insurance in Austria does not cover HPV-based screening.
In the future, HPV testing as a preventative screening method should be implemented for females that were vaccinated within the national vaccination program (Braune *et al.*, 2015). This measure should include a sufficiently long observation interval for the period of implementation (ibid.).

The OEGGG task force proposed that HPV testing should be available to all women > 30 and to those with a history of HPV-associated disease, for example conization, genital warts, St.p. PAPIII+, VIN, AIN (anal intraepithelial neoplasia) or a partner with HPV-associated disease (Braune *et al.*, 2015). Additionally, primary HPV screening should be offered to females over 30 at first consultation and especially to those who have not taken part in annual screening in over two years (ibid). Lastly, all females with whom it is unclear whether they participate in annual screening, should be offered primary HPV screening (ibid.). HPV tests should not be done routinely on females < 30 years (ibid.). Positive HPV test results require follow-up via cytology and colposcopy (ibid.). Cytology shifts from being a preventative screening method to a diagnostic method (ibid). Braune et al. conclude that this way profit can be drawn from cytology´s high specificity and additionally the positive predictive value is raised strongly (Braune *et al.*, 2015).

### 1.9.3 Diagnostic Tests

Not every positive cervical screening result means that the female tested has (pre-) cancer (World Health Organization, 2014). Ensuing diagnostic tests, such as colposcopy and biopsy are required to establish a diagnosis (ibid.).

Colposcopy is usually performed on females who tested positive in cervical screening (World Health Organization, 2014). This test, that examines the vulva, vagina and cervix, is performed to confirm "the presence, extent and type" (World Health Organization, 2014, p. 150) of precancerous or invasive lesion (ibid.). Moreover, colposcopy is performed to "guide biopsies of" (World Health Organization, 2014, p. 150) conspicuous areas and to aid in choosing the right treatment method (ibid.).

The definitive diagnosis is made through a biopsy (World Health Organization, 2014). Cervical samples of suspicious tissue are taken from areas that are positive in visual inspection with acetic acid or that look suspicious for cancerous lesions and are then examined via microscope (ibid.). Colposcopy can help in locating lesion(s) that require biopsy if they cannot be seen with the eye (ibid.). The purpose of biopsies is to assess "the degree of abnormality of the cell changes and to rule out cancer" (World Health Organization, 2014, p. 151). The biopsy results are categorized as normal, CIN (low-grade/CIN I or high-grade/CIN II and CIN III) or invasive cervical cancer (ibid.). This classification aids in treatment recommendations (ibid.).

Endocervical curettage (ECC) is useful if a lesion is suspected but the squamocolumnar junction is not visible in its full extent and if the PAP smear showed a glandular cervical lesion, that typically emerges from the endocervical canal´s columnar epithelium (World Health Organization, 2014). Moreover, ECC is performed in the case of suspected cancer and screening/colposcopy were not appropriate as the transformation zone could not be fully visualized (ibid.). Lastly, if the screening test implies a (pre-)cancerous lesion that cannot be seen in colposcopy, which raises the suspicion that they are located in the cervical canal, ECC is performed (ibid.).

## 1.10 Management and Treatment of Cervical Intraepithelial Neoplasia in Austria

As this thesis focuses on the preventative aspects of HPV associated malign disease, in particular cervical disease, this chapter describes management and treatment of precancerous cervical lesions, as a part of secondary prevention, according to the joint guideline by Reich et al. (Reich *et al.*, 2018). This goal is also integrated in the "Global strategy to accelerate the elimination of cervical cancer as a public health problem" (World Health Organization, 2020a, p. Cover1): 90% of all females with precancerous lesions should receive treatment (World Health Organization, 2020a).

Firstly, the Austrian Joint Guideline states, that, in line with "internationally accepted quality standards" (Reich *et al.*, 2018, p. 1237) the patient needs to be examined via colposcopy before conization or superficial tissue destruction is performed (Reich *et al.*, 2018).

Histologically diagnosed CIN I (LSIL) should be re-evaluated via colposcopy and ECC/EB (endocervical biopsy) in six to twelve months' time (Reich *et al.*, 2018). A resection CIN I lesions is indicated if the lesion persists > 2 years (ibid.).
In Austria, Germany and other European nations, CIN II lesions are, contrary to the concept used in the United States, not categorized as HSILs that need to be treated immediately (Reich *et al.*, 2018; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2020b). In the case of histologically verified CIN II, the patient should be re-evaluated in a maximum period of six months via colposcopy and ECC/EB, however, the observational period should not be longer than a year (Reich *et al.*, 2018). Large loop excision of the transformation zone (LLETZ) and ECC can become necessary (ibid.).
Histologically confirmed CIN III and AIS require treatment with LLETZ and ECC, in case of AIS, conization is always necessary (Reich *et al.*, 2018).

Patients < 25 years of age with HSIL can be observed for up to two years with examinations being performed in 6-month intervals (ibid.).
No suspicion of an invasive lesion in colposcopy and an entirely visible lesion (transformation zone type I or II) are necessary preconditions (ibid.).
If early invasion or AIS are suspected, conization is indicated (Reich *et al.*, 2018). "Recurrent pathological cytology without a histological corre-late [*sic*]" (Reich *et al.*, 2018, p. 1238)

also requires resection (ibid.). Lastly, resection is necessary if HPV high-risk type infection persists for over two years and additional indications apply ("divergent findings" (Reich *et al.*, 2018b, p. 1238)) (Reich *et al.*, 2018b; Kjær *et al.*, 2010).
The recommended resection method is electrosurgical loop conization (LLETZ, LEEP, loop conization/excision, loop cone biopsy) (Reich *et al.*, 2018).
In Austria, approximately 7000 conizations/year are performed (BMSGPK - Diagnosen- und Leistungsdokumentation der österreichischen KA 2002-2023 and GÖG - eigene Berechnungen, 2023).
HPV vaccination after conization could decrease recurrence risk, as some literature indicated (Joura *et al.*, 2012; Kang, Choi and Kim, 2013; Reich *et al.*, 2018). In Austria, insurance covers HPV vaccination after conization due to HSIL (CIN II/III) for females up to 45 years of age (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023a).

If the biopsy findings show a LSIL lesion (CIN I/ condyloma), superficial destruction can be the therapy of choice (Reich *et al.*, 2018b). For superficial destruction, the lesion must be located on the ectocervix, and the transformation zone must be visible in its entire extent (ibid.). A follow-up monitoring after six months is necessary and should include colposcopy and cytology (ibid.).

## 1.11 WHO: Global Strategy for Cervical Cancer Elimination

In 2018 the WHO issued a Global Call for Action to eradicate cervical cancer (World Health Organization, 2018b, 2020a, no date a). In 2020, the World Health Assembly enacted the "Global Strategy of Cervical Cancer Elimination" (World Health Organization, no date a). The strategy proposes "a vision of a world where cervical cancer is eliminated as a public health problem" (World Health Organization, 2020a, p. 7). For the eradication of this cancer as a public health issue nations should aim to reach an incidence < 4 per 100 000 women-years (World Health Organization, 2020a). To be on the road to succeed in that goal, all nations need to fulfill the 90-70-90 targets:

- 90% HPV vaccination coverage of females until aged 15
- 70% screening coverage via a high-performance test at age 35 and 45 years
- 90% of females with a diagnosis of cervical (pre-)cancer receive treatment:

- 90% of females with precancerous lesions are treated
- 90% of females with invasive cervical cancer diagnosis are managed (World Health Organization, 2020a).

The advantages of reaching the 90-70-90 targets until 2030 in LIC´s and lower-middle-income countries were shown by a mathematical model (Brisson *et al.*, 2020; Canfell *et al.*, 2020; World Health Organization, 2020a). By that model, that used the scenario of 90% vaccination coverage of 9-year old females in 2020 ("with a 1-year multi-age cohort catch-up to age 14 years" (Brisson *et al.*, 2020, p. 578)) and 90% screening coverage at ages 35 and 45 by the year 2045, median cervical malignancy incidence rate will decrease by around 42% until 2045 (Brisson *et al.*, 2020; World Health Organization, 2020a). The authors of that study discuss that in case scale-up of HPV immunization in combination with cervical screening is achieved, their results imply "that cervical cancer elimination could be achieved in all countries by 2100" (Brisson *et al.*, 2020, p. 586; World Health Organization, 2020a). Therefore, cervical cancer incidence would be decreased by 97% "and more than 74 million cases would be averted over the next century" (Brisson *et al.*, 2020, p. 586; World Health Organization, 2020a)
Combining vaccination with scale up of screening (twice/life) and treatment (modelled scenario details are to be found in Canfell´s study (Canfell *et al.*, 2020)) would result in a median cumulative number of prevented cervical malignancy deaths of 300 000, more than 14 million and more than 62 million until 2030, 2070 and 2120, respectively (Brisson *et al.*, 2020; Canfell *et al.*, 2020; World Health Organization, 2020a).

Additionally, as part of "Europe´s Beating Cancer Plan", in the fight against cervical cancer and other HPV-associated cancers, the European Commission pursues not only to reach a minimal vaccination coverage of 90% amongst EU target population of females, but also to considerably raise HPV vaccination of males by 2030 (World Health Organization, 2020b; EUROPEAN COMMISSION, 2021; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b; Directorate-General for Communication, 2024a). Among others, one of the measures to reach vaccination goals is to scale-up outreach and communication (Directorate-General for Communication, 2024a). Additionally, the World Health Organization states, that, among others, "vigorous health promotion at all levels" (World Health Organization, 2020a, p. 8) will be necessary to eradicate cervical cancer as a public health challenge (World Health Organization, 2020a). Moreover, bold

strategic actions to increase community awareness and to nationally expand "organized, population-based prevention and treatment platforms" (World Health Organization, 2020a, p. 19), among others, will be necessary to pave the way to cervical cancer elimination (World Health Organization, 2020a).
The World Health Organization´s strategy requests governments to engage with key partners who can stand up for accessible and acceptable health services and products and raise awareness on the topics of prevention and control of cervical cancer in their communities (ibid.).

Addressing especially primary prevention through HPV vaccination, the WHO indicates that the implementation of HPV vaccine programs needs to be complemented with "strong communication strategies for advocacy and social mobilization" (World Health Organization, 2020a, p. 26) to build awareness on the advantages, efficacy and safety of the HPV vaccine, so that long-lasting coverage and a high acceptance level are possible (World Health Organization, 2020a). Moreover, strategies that target the growing anti-vaccine movement need to be developed (ibid.).
Furthermore, apart from vaccination against HPV, a comprehensive prevention strategy should educate on sexual and reproductive health, safer sex, and the importance of tobacco cessation (ibid.). The promotion of a healthy lifestyle to adolescents regardless from their gender, is crucial if it is to achieve a healthier population and sustainable development (ibid.).

As mentioned above, scale-up of outreach and communication are critical to achieve vaccination goals (Directorate-General for Communication, 2024b). Outreach aims at reaching target populations, for example adolescents, outside of health-care facilities, for example in schools, to build and raise health specific knowledge, for example prevention of cervical cancer (World Health Organization, 2014). Moreover, health service access should be ameliorated by that (ibid.). Additionally, outreach aims at reaching maximum coverage and uptake of cervical cancer preventative and control services (ibid.). One of the five target population groups that should be approached with outreach strategies are teenagers (including their families) (ibid.). As per WHO recommendation, young females between 9 and 13 years are the target group for vaccination against HPV (ibid.). Nevertheless, campaigns that spread knowledge and awareness should also include males (ibid.).
Apart from in health-care facilities, health education can be brought to the population

through community education (World Health Organization, 2014). Community education can be carried out in various settings and by various chosen community members, for example by medical professionals, community health workers and teachers (ibid.). Schools, community centers and sports events are some of the possible settings listed by the WHO (World Health Organization, 2014). Information about the HPV vaccine needs to be tailored for the target group (adolescents, regardless of gender, and their parents or legal guardians) (ibid). Community health education, providing educational sessions taught by medical providers or trained community health workers have the potential to raise uptake of cervical cancer preventative and control services (World Health Organization, 2014).

## 1.12 Vaccination Rates Worldwide and in Austria

A 90% HPV vaccination coverage of females by age 15 is one of the WHO´s three targets that have to be met until 2030 for worldwide cervical cancer elimination (World Health Organization, 2020a). Globally, in 2022, HPV vaccination coverage for females by age 15 with the first vaccine dose and the last vaccine dose was estimated to be 21% and 17%, respectively (World Health Organization, 2023a). HPV vaccine coverage for males by age 15 with the first dose and the last vaccine dose was estimated to be 7% and 5%, respectively in 2022 (ibid.). In comparison, in 2018, when the WHO called for action to eradicate cervical cancer, HPV vaccination coverage for females by age 15 with the first dose and the last dose was estimated to be 13% and 10%, respectively and for males by age 15 3% and 2%, respectively (World Health Organization, 2018a, 2023a, no date b).

"HPV Vaccination program coverage" (World Health Organization, 2023a) with the first vaccine dose in females worldwide was 16% in 2021 and increased to 21% in 2022 (World Health Organization, 2023a, 2023e). The World Health Organization describes that this increase was "driven in particular by the effect of new introductions and programmes that resumed after interruptions" (World Health Organization, 2023e). However, in 2019 "HPV vaccination program coverage" with the first dose in females was 19% (World Health Organization, 2023a).

Spayne and Hesketh estimated the global vaccination coverage in 2018 for females aged 15 years old at 12.2% (Spayne and Hesketh, 2021)[12]. Through extrapolation from these

[12] (Spayne and Hesketh, 2021 using data from ; World_Bank, 2020; IARC, 2020; Ferlay *et al.*, 2019; World Bank, 2020, no date; Unicef, 2020, no date, 2019; Huh *et al.*, 2017)

numbers, they found that, 7041 of the around 61 million 15-year-old females in 2018, will probably die from cervical malignancy (ibid.)[13]. Almost all of these deaths are expected in poorer countries (ibid.)[13]. However, in this study only 78 of 195 countries reported on their HPV immunization programs and two countries only reported on the first dose coverage (ibid.)[13]. For the calculation/estimation of the global HPV immunization rate, the lack of reporting was seen as an indicator for a lack of immunization, which the authors stated as unclear if this is actually the case (Spayne and Hesketh, 2021)[13].

In Europe the vaccination rate for females and males by age 15 in 2022 is estimated at 38% and 18% with the first dose and at 29% and 14% with the last vaccine dose, respectively (World Health Organization, 2023b).

A striking example of high HPV vaccination coverage is Uzbekistan, where in 2019 the HPV vaccination was first implemented in the national immunization plan (World Health Organization, 2022) and vaccination coverage in females with the final dose reached 98.6% the same year (World Health Organization, 2023c). In 2023, the HPV vaccination rate peaked even further with 99.8% (females, last dose) (World Health Organization, 2023c). According to the World Health Organization, the communication plan, built by the country itself and aided by the WHO and UNICEF, was crucial to the success of the vaccine implementation (World Health Organization, 2022). Moreover, constant monitoring of the vaccination uptake and addressing problems with adequate measures helped to keep the vaccination implementation on track (ibid.). For example, as a response to decreasing vaccine take-up numbers in one school, teacher-parent meetings with health care workers were held under the national immunization plan and questions regarding misinformation about the vaccine on social media could be addressed (ibid.). The WHO Uzbekistan team considered these measures very effective (ibid). After receiving information (data/studies/examples) by experts, parents did not only wish for their own child to receive the vaccine, but for as many kids as possible (ibid.). A factor for the great success of the Uzbekistan vaccination program was to bring “all the stakeholders together to speak with one voice” (World Health Organization, 2022), for example teachers were specifically trained (ibid.).

[13] (Spayne and Hesketh, 2021 using data from ; World_Bank, 2020; IARC, 2020; Ferlay *et al.*, 2019; World Bank, 2020, no date; Unicef, 2020, no date, 2019; Huh *et al.*, 2017)

In Austria, vaccine coverage for the years 2014 - 2022 with HPV vaccine Gardasil/Gardasil9 were calculated via an agent-based simulation model (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b). Further details regarding technical aspects of this calculation can be found in the cited report. The Austrian vaccine coverage for children aged 14 in the year 2022 for the first dose is analyzed at 56% and for both doses at 53% (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b, 2023a; World Health Organization, 2023d).

In the Austrian free immunization program, the HPV vaccine is recommended and administered to all genders (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b). At the moment, no data regarding gender distribution among the vaccinated population exists, therefore it is currently impossible to assess the degree to which Austria is approaching the WHO´s target (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b) which leads to the aim of this thesis.

## 1.13 Aim of this Thesis

This study aims to explore if targeted education on the topics of HPV and the HPV vaccine can raise students´ knowledge and awareness and have a positive effect on participants´ willingness to receive the vaccine. The study aims to investigate if targeted education can raise HPV vaccination intention amongst a sample of 12 – 14-year-old unvaccinated students. Furthermore, this study intends to evaluate if targeted education through medical professionals can increase the students´ willingness to recommend the vaccine to others. Additionally, it seeks to obtain a minimal vaccination coverage in a predefined sample group. Lastly, this study shall explore whether knowledge on the topics of HPV and the HPV vaccine is present in the studied sample group and whether this knowledge can be improved by a specific education.

# 2 Material and Methods

## 2.1 Objective and Research Question

When the study was conducted in June 2021, no official statistics of vaccine coverage existed in Austria, it was estimated to be under 50% (Pressestelle des LKH-Univ. Klinikum Graz, 2019; Österreichische Krebshilfe, 2022, 2023b, 2023a). We conducted this study to obtain a minimal vaccine coverage in a predefined sample group. The objective of this study was to explore if targeted education by medical professionals can have a positive effect on HPV vaccination intention in a sample of 12 – 14-year-old students.

## 2.2 Study Population

In June 2021, the Austrian immunization plan included the free-of-charge nonavalent HPV vaccine only for children from 9 – 12 years of age, regardless of gender (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2021). Beyond that age, children up to the age of 15, could receive the vaccine at reduced cost as part of the catch-up-program. During the COVID pandemic the catch-up program was extended until the age of 16 (Österreichische Krebshilfe, 2020; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2021). At that time, children above the age of 15 were given 3 HPV vaccine doses, the costs were not covered by the national children vaccination program and expenses had to be covered by the patients themselves (Österreichische Krebshilfe, 2020).

Hence, the cohort of 12 – 14 (-15, respectively) year old children was the last one to benefit from the cost-reduced HPV catch-up-program (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2021). In June 2021, said program was made accessible until the age of 18 (Simone Traxler Gesundheitsamt Impfstelle Stadt Graz, 2024). At the time we concepted the study, the catch-up-program was for the cohort of 12- to 16-year-olds (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2021; Simone Traxler Gesundheitsamt Impfstelle Stadt Graz, 2024). Therefore, the target group of the study was the last cohort included in the catch-up program. By choosing our target population, we aimed at reaching the last group, that could receive the vaccine at the cost of 69 €/dose (Simone Traxler Gesundheitsamt

Impfstelle Stadt Graz, 2024), before the cost was raised to about 624 € for everyone above the age of 15 years (Waser, Heiss and Borena, 2022).

We picked a cohort with a minimum age of 12 and a maximum age of 14 years old. We conducted the study in the Graz International Bilingual School (GIBS), the intended sample size was 50 students. For that we intended to include two classes. The school´s principal, Edda Berger-Cian, offered us the opportunity to conduct the study in three classes with a total of 82 students. However, the total number of students that handed in the signed parental consent form was below 50. Therefore, we extended the study to five classes in total, with a total of 135 students. The intention-to-treat population consequently was 135.

### 2.2.1 Inclusion Criteria

1.) Age 12-14 years (irrespective of gender)
2.) Parentally signed consent forms

## 2.3 Outcomes

### 2.3.1 Primary Outcome

The primary outcome was the intention of unvaccinated (or vaccination uncertain) students to receive the HPV vaccination intention before and after receiving specific education about HPV.

### 2.3.2 Secondary Outcome

The first part of the survey included demographic data on age and anatomic-medical sex.

Secondary outcomes in all groups, irrespective of HPV vaccination status, were present knowledge about HPV and the HPV vaccine (“Ja”/“Nein”/“Ich habe schon mal was darüber gehört, weiß aber nicht genau darüber Bescheid.”, “Yes”/”No”/”I have heard about it, but I do not know exactly what it is”); willingness to recommend the HPV vaccine to friends (“Ja”/“Nein”, “Yes”/”No”); and opinion on whether the students think it´s good to receive specific HPV education in schools (“Ja”/“Nein”, “Yes”/”No”). The endpoints were evaluated before and after receiving the specific educational class on HPV.

Additionally, in the second questionnaire section ("Fragebogen nach Aufklärung", "Questionnaire after targeted education") we explored whether the student´s opinion on the HPV vaccine changed as a result of the educational class ("Ja"/"Nein", "Yes"/"No") and if yes, for what reasons. Furthermore, we explored possible reasons for the refusal of the HPV vaccine.

Students who were vaccinated were asked at what age they had received the vaccine.

In the cohort with uncertain or negative HPV immunization status, we analyzed whether students were previously informed about the possibility of HPV vaccination.

Moreover, the anamnestic HPV vaccination status at the time of the study was investigated and the percentage of vaccinated students (students who responded with "Ja" ("Yes") to the question "Bist du gegen HPV geimpft?" ("Are you vaccinated against HPV?") and students who ticked off "Ja" ("Yes") and added a written note that they have received only one dose) was investigated separately for each gender.

Lastly, students had the possibility to leave comments at the end of each questionnaire (questionnaires are attached in the annex).

## 2.4 Methods

The principal of the Graz International Bilingual School (GIBS), Edda Berger-Cian, was contacted in March 2021, informed about the planned study and asked about the opportunity of conducting it in two classes of GIBS in June 2021. Due to the COVID-19 pandemic it was unclear at first if the study could be conducted in presence or online. Mrs. Berger-Cian agreed to support the study.

In the meantime, we submitted the protocol to the Ethics Committee of the Medical University of Graz. Approval was obtained in June 2021 (EK-number 33-448 ex 20/21) (annex).

Contact with Mrs. Berger-Cian was resumed in May 2021 to plan whether the study could be held in presence. Further practical details (the number of classes required to reach the targeted number of study participants (50), possible dates, the procedure for obtaining parental consent due to minority of study participants) were discussed. The primarily proposed study dates were the 8, 9 and 11 June 2021. As we received the positive ethics vote on 4 June 2021 and needed time to hand out the parental consent forms to the students before

the start of the study, we started the study on 9 June and postponed the first date (8 June) to the 15 June. At first, we conducted the study in three classes. As the total number of students in the three classes, who handed in signed consent forms and therefore could participate in the study, (n=33) (3a, 3b, 3c) was below our intended sample size of 50 participants, we extended the study to two further classes (4a, 4b) and reached a primary sample size of 55 participants.

As the study participants were minors, written parental consent (patient information and informed consent forms for students and parents are attached in the annex) was obtained in advance. The parental consent forms were handed out to the intention-to-treat population (n=135, 5 classes). Prior to the study start, the author of this study visited the classes, introduced herself and the study and handed out the patient information for the students, as well as the patient information and consent form for the parents to the students themselves. As some of the students were missing when the documents were distributed, the residual patient information and consent forms were given to the class teachers to pass on to the missing students.

At the first intervention day, 9 June 2021, only 10 out of 26 present students (27 students in class in general, 1 missing) handed in signed parental consent forms. Therefore, the author contacted the form teachers of the four classes for which the intervention was still scheduled. She asked them in an email/text message that the student´s parents be reminded to sign the consent forms and have the children return them. Moreover, the patient information and consent forms and the contact information (phone number) of Dr. Taumberger (one of the supervisors of this study) and of the author of this study were attached in the mail again, in case any questions arose. Two form teachers forwarded the documents and the mail, (one teacher added an additional English explanation), one teacher reminded the student´s parents in their WhatsApp group and one teacher did not see the mail in time, however the principal forwarded the reminder in the WhatsApp group of the class in question.

The information sessions were held in June 2021. One double period was made available per class. Dr. Taumberger and the author of this study held the initial day of the study together, the subsequent four study dates were conducted by the author herself.

The children who had submitted a signed parental consent form were allowed to participate in the questionnaire study.

Study participants first completed the first section of the questionnaire (“Fragebogen vor Aufklärung”, “Questionnaire before targeted education”). Next, the author of this study (and

Dr. Taumberger on the first study day) conducted an approximately one-hour specific educational class about HPV and the HPV vaccine (the PowerPoint presentation is attached in the annex). Then, the study participants proceeded to fill in the second part of the questionnaire ("Fragebogen nach Aufklärung", "Questionnaire after targeted education").
The first section of the questionnaire, the educational class and the second section of the questionnaire were conducted on the same day successively. The study participants´ opinion was to be collected independent from other influences, therefore all data were collected on the same day. By that, we wanted to exclude the possibility of the students doing self-research or having a conversation with their parents and but rather solely explore the students´ knowledge and opinion on the relevant topics, without external influence.

The study was conducted as a random sample study. The sample of 55 students that handed in their signed parental consent form is too small for a generalization of the results. It is feasible to repeat this study with a larger sample size, if relevant changes in HPV vaccination intention as a result of the targeted educational class are to be examined more thoroughly. Such an extension (e.g., including further schools) is outside the scope of this thesis.

The abstract of this thesis was submitted for the poster award of the OEGGG (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe) Jahrestagung 2022, at which the author of this study presented the study.

## 2.5 Statistics

### 2.5.1 Data Analysis

Data were analyzed with descriptive statistics in Microsoft Excel. Demographic variables of the study participants were analyzed using data from the first questionnaire.
To analyze the primary outcome measure, study subjects with a history of a positive HPV immunization status were excluded, as were those who reported to have received one dose only (one student, who reported to be vaccinated with one dose in the 1st questionnaire "Ja/Nein, ich hab eine", "Yes/No, I have one") and then responded with "Ja/Nein" ("Yes/No") in the 2nd questionnaire (student ticked off both options), was also excluded). The HPV vaccination intention within the catch-up vaccination program at reduced cost was

analyzed within the cohort with a negative or uncertain HPV immunization status ("Nein" ("No"), "Das weiß ich nicht." ("I do not know that"), before and after receiving the targeted education class. In the same cohort with uncertain or negative immunization status, it was explored, whether students have been informed on the possibility of the HPV vaccination before.

Reasons for HPV vaccine refusal were explored only in students who did not know their HPV immunization status or were not HPV vaccinated at the time the study was conducted and showed no intention to receive the vaccination in a catch-up vaccination program at reduced cost, after receiving the targeted education class. For that all students that were vaccinated fully and vaccinated with one dose were excluded, one student, who reported to be vaccinated with one dose in the 1st questionnaire "Ja/Nein, ich hab eine" ("Yes/No, I have one") and then responded with "Ja/Nein" ("Yes/No") in the 2nd questionnaire (student ticked off both options) was also excluded. Then, to analyze this measure, out of this cohort, only students that responded negatively (with "Nein" ("No")) to the question "Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?" ("If not, would you get vaccinated in a cost reduced catch-up program?") were included.

For the analysis of the other secondary outcome measures, all test subjects meeting age inclusion criteria (12 – 14 years old) and irrespective of immunization status were included.

Relative frequencies, to analyze the share of vaccinated/unvaccinated study subjects in the total sample size, were calculated. The percentage of vaccinated (students who responded with "Ja" ("Yes") to the question "Bist du gegen HPV geimpft?" ("Are you vaccinated against HPV?") and students who ticked off "Ja" ("Yes") and added a written note that they have received only one dose) students were calculated separately for each gender.

All measures, except for reasons for refusal of HPV vaccine, change of opinion regarding HPV vaccine as a result of targeted education and reasons for change of opinion, were analyzed before and after the specific educational intervention. The three exceptions were analyzed only after our targeted educational class.

The primary intention was to calculate whether our results are significant. However, due to the small sample size, it is clear, that statistical significance of our results cannot be reasonably established; therefore, we decided to forego in doing so. Further work using

larger sample sizes is recommended. However, doing so is beyond the scope of and resources available to this study.

## 2.6 Data Protection

Data were collected anonymously with sequential numbering. Study subjects who provided signed parental consent forms received two questionnaires, which were stapled together. The first questionnaire was titled with “Fragebogen vor Aufklärung” (“Questionnaire before targeted education”), the second questionnaire was titled “Fragebogen nach Aufklärung” (“Questionnaire after targeted education”). The questionnaires were marked by sequential numbering, with one number per study subject. After completion of the second questionnaire, each study subject submitted their signed consent form joint to the questionnaires. This enabled us to verify that all participants had signed parental consent forms.

# 3 Results

## 3.1 Demographics

We handed out parental consent forms to 135 students. 55 students (41%) returned parentally signed consent forms and then completed the questionnaires and participated in the educational class. Table 1 shows the number of students participating, present, absent and general number of students in class for the dates the study was conducted.

| | Class | Participating Students | Present Students | General Number of Students in Class | Absent Students |
|---|---|---|---|---|---|
| | 1 | 10 | 26 | 27 | 1 |
| | 2 | 19 | 26 | 27 | 1 |
| | 3 | 4 | 25 | 28 | 3 |
| | 4 | 17 | 19 | 26 | 7 |
| | 5 | 5 | 24 | 27 | 3 |
| **Total** | | 55 | | 135 | |

*Table 1: Number of participating, present, general number of students and absent students per class*

During data analysis we excluded 1 student who was 15 years old. Therefore, 54 students were ultimately included in the study (*Fig 1*).

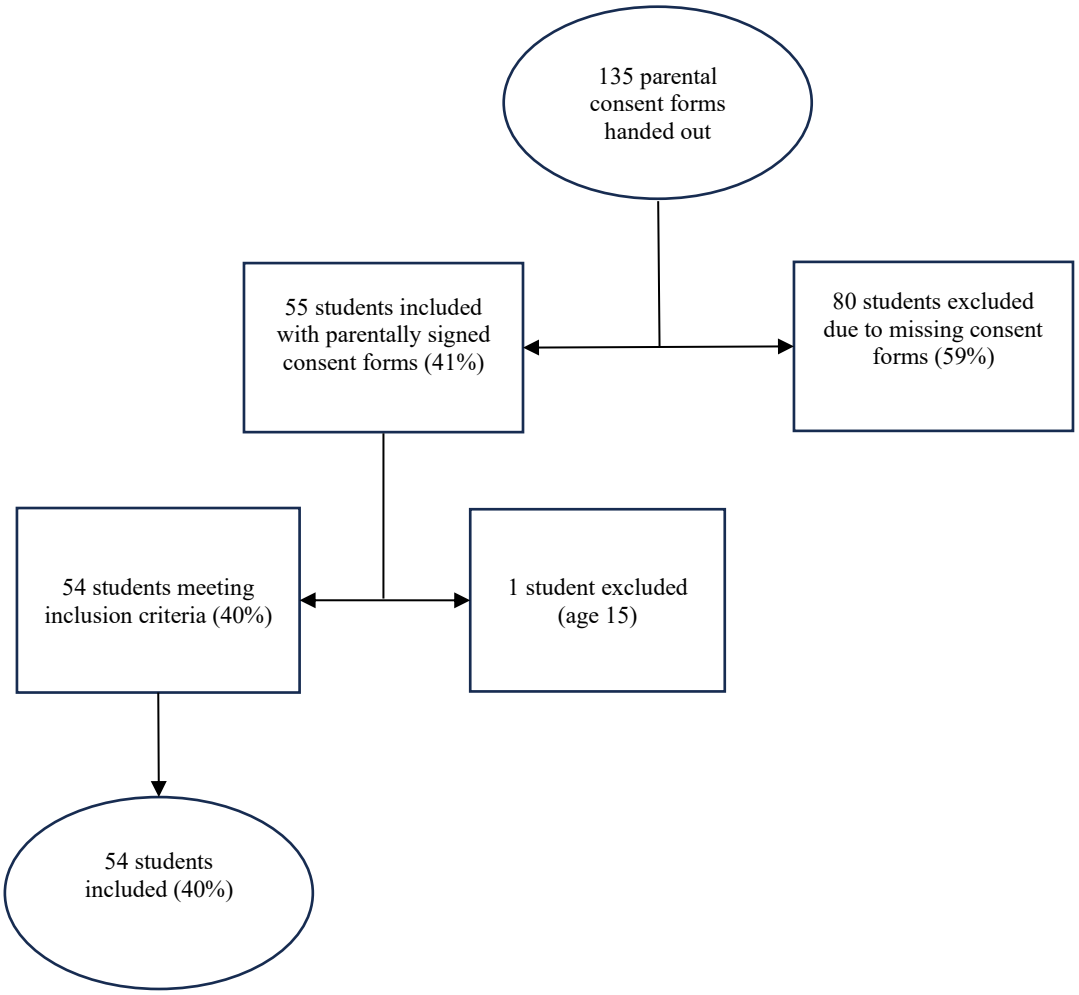


*Figure 7: Flow diagram showing included and excluded subjects*

Demographic variables are described only for the included students. Mean age was 13.2 years, median age was 13 years ("Alter: __ Jahre", "Age: __ years"). 34 out of 54 students were female (63%), 19 were male (35% out of 54) and 1 student did not specify (*Fig. 3*) ("Mein Geschlecht (anatomisch-medizinisch) ist", "My sex (anatomical-medical) is"). The item "sex" in the questionnaires was specified to anatomical-medical sex.

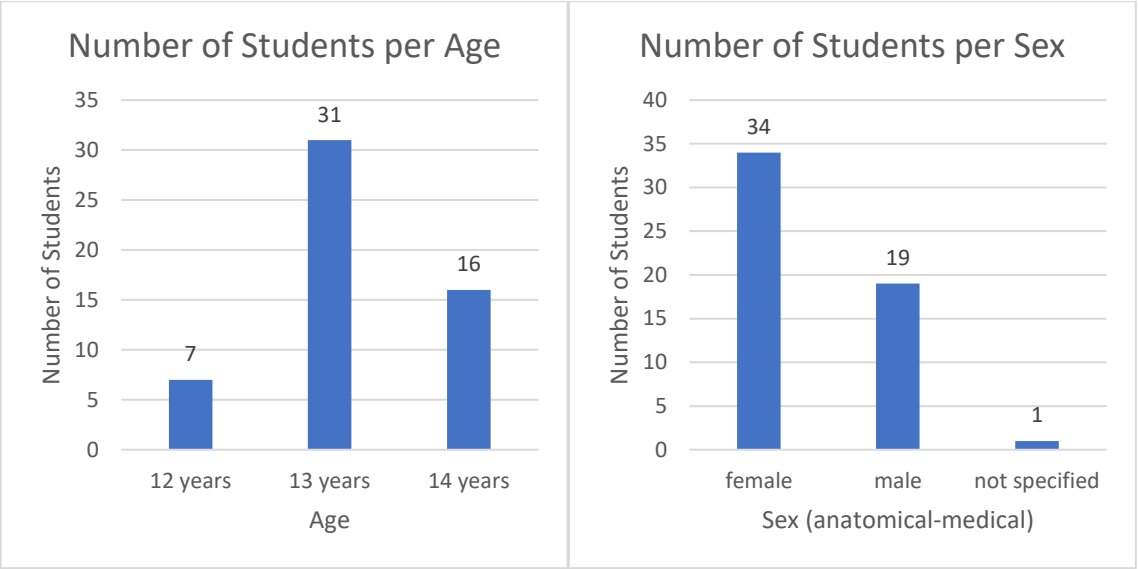


*Figure 8 (left): Number of students by age*

*Figure 9 (right): Number of students by (anatomical-medical) sex*

## 3.2 Knowledge about HPV and HPV vaccine

Before receiving specific education on HPV, 18 of 54 students (33%) reported to know what HPV is, 33 students (61% of 54 students) had heard about it but did not know exactly what it is and 3 students (6%) did not know what HPV is ("Weißt du, was HPV ist?", "Do you know what HPV is?") (*Fig. 4*).

After the targeted education class, all 54 students (100%) reported knowing what HPV was (*Fig. 5*).

Before receiving specific education, 27 of 54 students (50%) stated that they knew what the HPV vaccine is ("Weißt du, was die HPV-Impfung ist?", "Do you know what the HPV vaccine is?"). 21 students (39%) reported to have heard about it, but to not know exactly what it is and 6 students (11%) stated not knowing what the HPV vaccine was ("Weißt du, was die HPV-Impfung ist?", "Do you know what the HPV vaccine is?") (*Fig. 6*).

After receiving targeted education, 53 students (98%) reported knowing what the HPV vaccine was. 1 student (1.85%) stated having heard about it, but not knowing exactly what it is (*Fig. 7*).

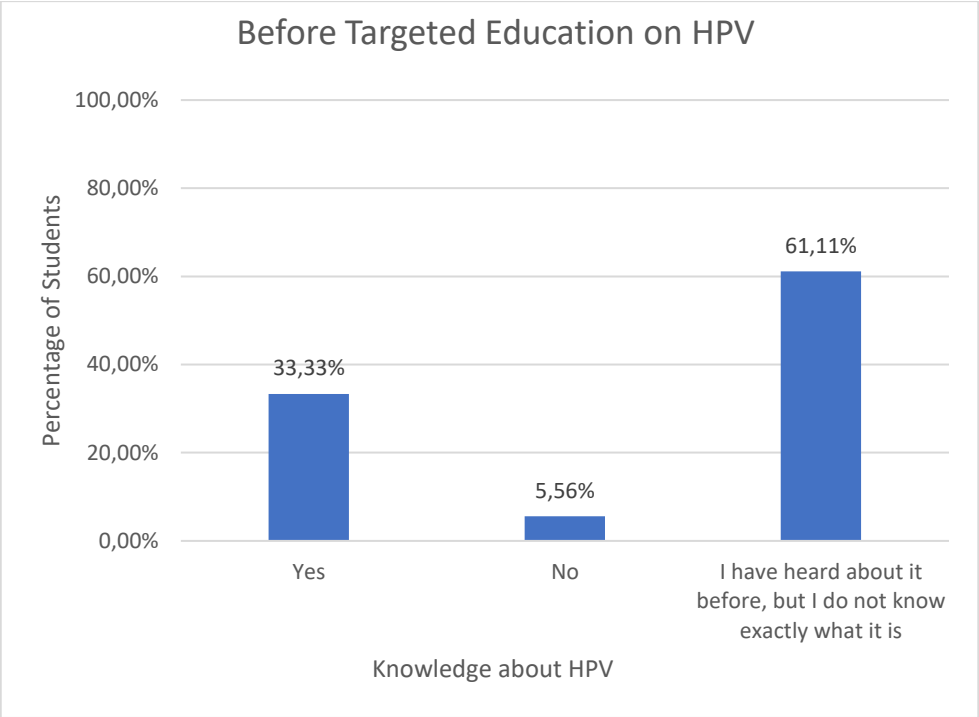


*Figure 10: Percentage of students per response on the question: "Do you know what HPV is?" ("Weißt du, was HPV ist?") of the 1st questionnaire before receiving targeted education on HPV*

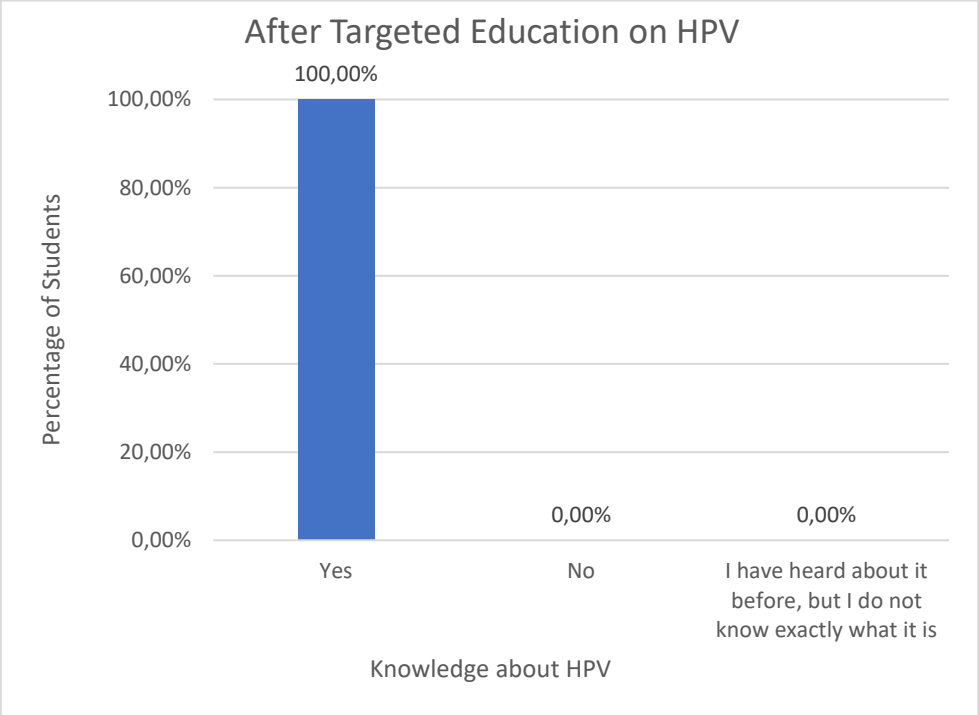


*Figure 11: Percentage of students per response on the question: "Do you know what HPV is?" ("Weißt du, was HPV ist?") of the 2nd questionnaire after receiving targeted education on HPV*

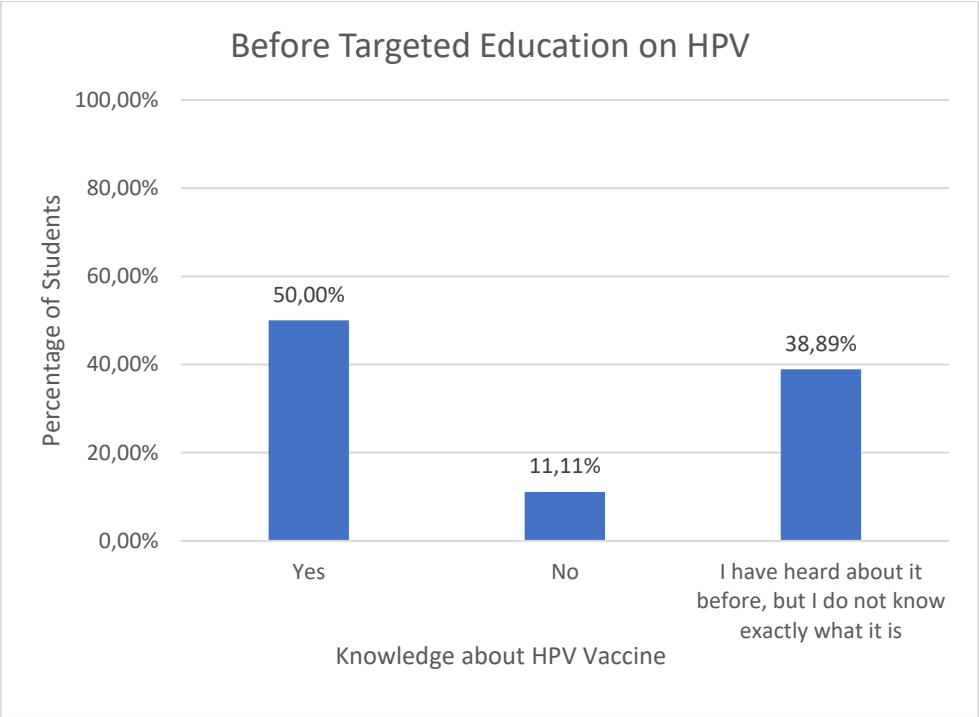


*Figure 12: Percentage of students per response on the question: "Do you know what the HPV vaccine is?" ("Weißt du, was die HPV-Impfung ist?") of the 1st questionnaire before receiving targeted education on HPV*

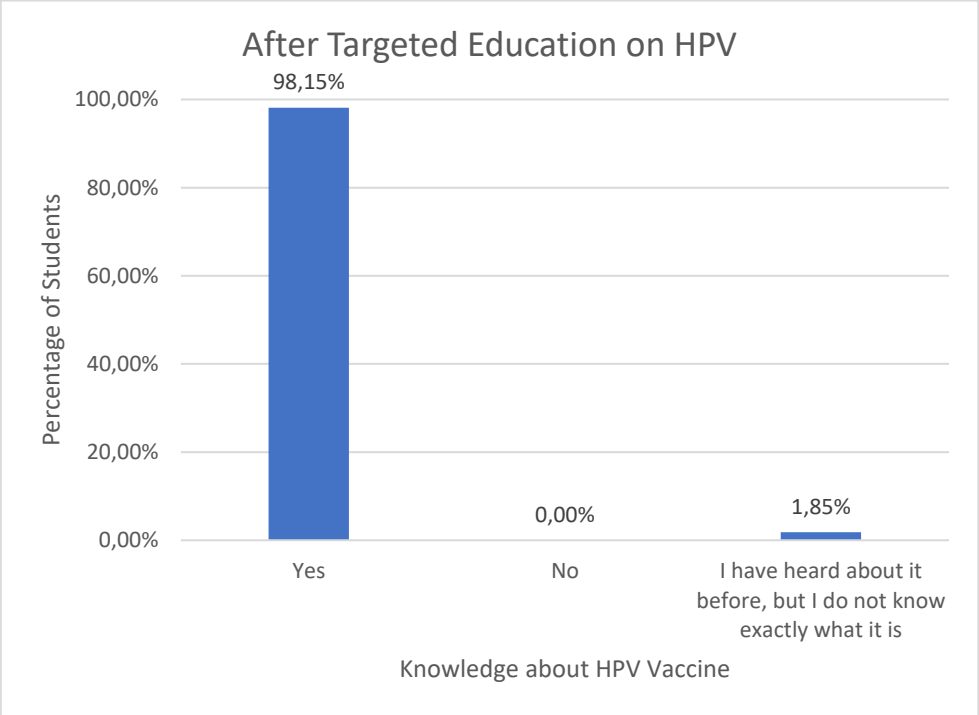


*Figure 13: Percentage of students per response on the question: "Do you know what the HPV vaccine is?" ("Weißt du, was die HPV-Impfung ist?") of the 2nd questionnaire after receiving targeted education on HPV*

## 3.3 Vaccination Coverage in the Cohort

From analysis of the first questionnaire, 38 of 54 students reported to be vaccinated with the HPV vaccine (70%) ("Bist du gegen HPV geimpft?", "Are you vaccinated against HPV?"). 3 students (6%) answered with "Ja" ("Yes") and added a written note that they have received only one dose of the HPV vaccine by the time the study was conducted. Therefore, vaccination coverage with minimum one dose in our cohort was 76% (41/54). Within the overall intention-to-treat population this leads to a minimal anamnestic vaccination coverage of 28% (38/135 students) and 30% (41/135) for minimal one dose.

In the first questionnaire, 8 students (15%) were uncertain of their HPV vaccination status, 4 students (7%) reported to be unvaccinated with the HPV vaccine and 1 student (1.85%) was not vaccinated at the exact time of the study but was to receive the HPV vaccine still on the same day the study was conducted.

After receiving the targeted educational class only 6 students were uncertain of their vaccination status anymore (11%) (first questionnaire: 8 students, 15%), but 2 more students reported to be HPV unvaccinated (6 in total (11%) compared to 4 students (7%) in the 1st questionnaire). 2 students (4%) reported to have received one dose of the HPV vaccine by the time the study was conducted. 1 student (1.85%) ticked off both "Ja" ("Yes") and "Nein" ("No") in response to the question of whether they are HPV vaccinated. The same student initially responded to have received 1 dose of the HPV vaccine in the first questionnaire.
The rest of the parameters were unchanged from the first questionnaire.

In the 1st questionnaire, 76% of female students that participated reported to be HPV vaccinated (26/34). 29/34 (85%) of female students reported to have received at least the first dose of the HPV vaccine.
11/19 (58%) of the male students reported to be HPV vaccinated. The one student who did not specify their sex was vaccinated.

### 3.3.1 (Previous) Information on the Possibility of HPV Vaccination

In the 1st questionnaire, 3/13 (23%) of the unvaccinated/uncertain reported to previously

have been informed about the possibility of HPV vaccination ("Wenn Nein, wurdest du schon mal über die Möglichkeit einer Impfung aufgeklärt?", "If no, have you ever been informed about the possibility to vaccinate?"), 3 (23%) were uncertain about having been informed, 6 (46%) reported not to have been informed and 1 (8%) did not answer to the question. One of the 3 students that stated to have been informed about the possibility of HPV vaccination, added to have received information in primary school.

In the 2nd questionnaire in this group (unvaccinated/uncertain), 8 students (62%) reported to have been informed about the possibility of HPV vaccination. 1 of these 8 students added to have been informed in our educational class. 3 students (23%) stated to not know whether they have been informed about the possibility of HPV vaccination, 1 student (8%) reported not to have been informed about this and 1 (8%) did not answer the question.

## 3.4 HPV Vaccination Intention

Before targeted education, 10/13 (77%) students who were HPV unvaccinated or uncertain whether they were HPV vaccinated, would get vaccinated with the HPV vaccine in a cost-reduced vaccination program („Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?", "If no, would you get vaccinated in a cost-reduced program?").
After the educational class, 11/13 (85%) students from this cohort would get HPV vaccinated in a cost-reduced vaccination program.

The one additional student who did not want to get HPV vaccinated before and did want to get vaccinated in a cost-reduced vaccination program after receiving targeted education, stated in the comments section of the 1st questionnaire "Ich finde es toll dass wir so einen Workshop machen.". In the 2nd questionnaire this student stated that their opinion on the HPV vaccine changed as a result of the targeted education class ("Hat sich deine Meinung zur HPV-Impfung durch die Aufklärung verändert?", "Did your opinion on the HPV vaccine change as a result of targeted education?"). The student´s response to the question on why their opinion on it has changed ("Wenn Ja, warum hat sich deine Meinung zur HPV-Impfung verändert?", "If yes, why did your opinion on the HPV vaccine change?") is: „Ich wurde sehr gut aufgeklärt und weiß jetzt was genau das ist.". In the additional comment section of

the 2nd questionnaire, this student added: “Ich fand den Workshop sehr interessant und ich finde es toll dass wir darüber aufgeklärt wurden”.

To conclude, in the 1st questionnaire 2 out of 13 (15%) students of the same cohort were unwilling to get HPV vaccinated in a cost-reduced program and 1 student (8%) did not answer the question.
In the 2nd questionnaire, 1 student (8%) of this cohort was unwilling to receive the HPV vaccine in a cost-reduced program and 1 (8%) did not respond to the question.

| 5.) Bist du gegen HPV geimpft? | (Mehrere Elemente) | |
|---|---|---|
| vor Aufklärung | | |
| **Zeilenbeschriftungen** | **Anzahl von 8.) Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?** | |
| Ja | 10 | 77% |
| Nein | 2 | 15% |
| x | 1 | 8% |
| **Gesamtergebnis** | **13** | **~100%** |

| 16.) Bist du gegen HPV geimpft? | (Mehrere Elemente) | |
|---|---|---|
| nach Aufklärung | | |
| **Zeilenbeschriftungen** | **Anzahl von 19.) Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?** | |
| Ja | 11 | 85% |
| Nein | 1 | 8% |
| x | 1 | 8% |
| **Gesamtergebnis** | **13** | **~100%** |

### 3.4.1 Reasons for Refusion of HPV Vaccine

The one student (male) who remained unwilling to receive the HPV vaccine after education on the topic provided as a reason for his HPV vaccine refusal:

- “Ich bin der Meinung das es keinen richtigen Schutz gegen Impfungen gibt und unser Vorfahren haben auch überlebt”.

## 3.5 Willingness to Recommend HPV Vaccine to Friends

Before targeted education, 45/54 (83%) of students would recommend the HPV vaccine to their friends. After education 50/54 (93%) would recommend the vaccine.

Before receiving targeted education, 3 (6%) students were uncertain (ticked off both “Ja” (“Yes”) and “Nein” “No”) whether they would recommend the vaccine, 3 (6%) would not recommend the vaccine, and 3 (6%) did not answer the question.

After the educational class, only 1 student (2%) was uncertain (ticked off both “Ja” (“Yes”) and “Nein” (“No”)) on recommending the vaccine and 3 (6%) did not answer the question. No student would not recommend the vaccine to friends after receiving targeted education about it.

## 3.6 Opinion on Targeted Education about HPV Vaccine in School

In the 1st questionnaire, 52/54 students (96%) considered it to be good that targeted education about the HPV vaccine is provided in school. One of these 52 students even added an exclamation mark next to the “Yes” option.
One student (2%) answered with “~“ and one student (2%) ticked off both options “Ja” (“Yes”) and “Nein” (“No”).

In the 2nd questionnaire, 53/54 students (98%) considered it good that targeted education is provided in school. One of these 53 students added an exclamation mark next to the “Yes” option (“Ja!” (“Yes!”)). One student (1.85%) ticked off both options “Ja” (“Yes”) and “Nein” (“No”).

## 3.7 Change of Opinion Regarding HPV Vaccine as a Result of Targeted Education

19/54 students (35%) stated that their opinion on the HPV vaccine changed as a result of

targeted education about HPV. For their reasons for this change of opinion, refer to Chapter 3.7.1.

35/54 students (65%) did not change opinion on the HPV vaccine. 3 out of the 35 students added extra information to their response: 1 student answered: “Nein, ich finde sie trotzdem noch gut.”, 1 student replied: “Nein, ich hatte davor keine wirkliche Meinung” and 1 student responded with: “Nein, ich wollte mich vorher auch impfen lassen.”.

### 3.7.1 Reasons for Change of Opinion

15/19 students (79%) provided reasons for their change of opinion as a result of the targeted educational class (“Wenn Ja, warum hat sich deine Meinung zur HPV-Impfung verändert?”, “If yes, why did your opinion on the HPV vaccine change?”). The students´ responses were not corrected with regards to grammar and/or spelling. Reasons (in German, original language of the study) are listed here:

- „Weil man jetzt genau darüber Bescheid weiß und man Freunden diese Impfung empfehlen kann. Und für so einen kleinen Stich sollte sich jeder Impfen lassen weil man dann geschützt ist.“
- „Weil ich jetzt besser + genauer weiß, was es ist, und wie gefährlich es sein kann.“
- „Weil ich davor nicht wusste wie wichtig es ist und dass man davon sterben kann.“
- „Weil Bewusstsein geschaffen wurde, dass das wirklich gefährlich ausgehen kann und man deshalb sogar keine Kinder bekommen könnte, oder sterben könnte“
- „Weil ich nicht wusste das es so gefährlich ist“
- „Weil ich nicht wusste das es so ernst ist.“
- „Ich hab halt gesehen, dass HPV gefährlicher ist, als gedacht“
- „Ich wurde sehr gut aufgeklärt und weiß jetzt was genau das ist.“
- „Weil mir die Wichtigkeit noch deutlicher gemacht wurde.“
- „Weil es sehr detailliert erklärt wurde.“
- „Ich habe vorher gedacht, "ja, gut und schön, es kann ja nicht schaden", aber jetzt denke ich, dass es extrem wichtig ist, sich impfen zu lassen.“
- „Ich sehe wie wichtig es ist“
- „Nicht wirklich geändert aber ich fühle mich jetzt noch sicherer“
- „Ich bin jetzt informier und finde es gut jedoch weiß ich nicht ob ich geimpft bin“
- „Ich meine es macht mir Angst“

4 students who indicated a change of opinion did not answer the question.

1/35 students who did not indicate a change of opinion stated: “Sie hat sich nicht wirklich geändert, sie hat meine Meinung nur bestärkt.”. The same student responded before, that they would recommend the vaccine to friends and considered it to be good that targeted education about the HPV vaccine is provided in school.

## 3.8 Selected Comments from the Commentary Section

### 3.8.1 1st Questionnaire

A selection of comments (in German, original language of the study) concerning the topic, from the 1st questionnaire, before students received targeted education, are listed here:

- „Ich finde es toll dass wir so einen Workshop machen.“
- „Ich finde es sehr schade, dass Schüler, vor einer möglichen Impfung nicht informiert werden, was das ist, warum mann das macht…“
- „Ich finde Impfungen zwar nicht immer gut, manchmal ist weniger mehr, ich kann mich aber auch nicht mehr genau erinnern, ob ich gegen HPV geimpft wurde. Impfen würde ich mich aber mit genügend Informationen schon.“
- „Ich finde diesen Kurs sehr toll :)“
- „Ich finde es wichtig, aufgeklärt zu werden und ich bin froh, heute geimpft zu werden.“
- „Ich finde, Aufklärung über HPV ist sehr wichtig für Jugendliche, da viele sich der Gefahren nicht bewusst sind.“
- „Ich finde es gut wenn Leute sich gegen HPV impfen lassen. Weil ein kleiner Stich in den Körper ist nicht so schlimm wie Krebs oder andere Krankheiten zu haben.“
- „Ich weiß nicht viel darüber“
- „Ich weiß nur, dass es eine Impfung ist.“
- „Ich habe die erste Impfung gekriegt, aber bald kriege ich die zweite.“
- „Ist Gelbfieber eine Art von einer HPV Impfung“

### 3.8.2 Commentary Section: 2nd Questionnaire

A selection of comments (in German, original language of the study) concerning the topic from the 2nd questionnaire, after students received targeted education, are listed here:

- „Ich finde das diese Presentation sehr wichtig war und noch dazu war sie sehr interessant. Ich würde die Presentation auch für andere Klassen weiterempfehlen."
- „Ich finde es interessant, dass uns genauer erklärt wurde, was das eigentlich ist. Obwohl meine Mama mich in der 4. Klasse Volksschule impfen hat lassen und ich damals nichts darüber wusste, würde ich mich auch jetzt impfen lassen, wenn ich noch nicht geimpft wäre. Der Arzt hat uns damals empfohlen, dass ich mich impfen lasse."
- „Ich denke, dass die Idee Schüler in diesem Alter über den Virus näher zu informieren recht gut ist. Informationen über ein Thema zu erhalten kann auch oft die Einstellung dem gegenüber ändern."
- „Ich fand den Workshop sehr interessant und ich finde es toll dass wir darüber aufgeklärt wurden"
- „Das Thema HPV ist wichtig und man sollte darüber bescheid wissen."
- „Ich finde es gut, dass man über die Impfung aufgeklärt wird und man erfährt gegen was die Impfung eigentlich ist. Es ist auch gut zu wissen, wann man sich impfen lassen sollte."
- „Ich finde es gut dass sie uns aufgeklärt haben."
- „Ich finde es gut, das man aufgeklärt wird"
- „Ich finde es toll, nähere Information zu bekommen. Danke!"
- „Ich finde, dass die PP super interessant und spannend war."
- „Mega gut xD"
- „Danke für die tolle Aufklärung! Viel Glück beim Studium noch!"
- „Danke für die Informationen und den Vortrag."

# 4 Discussion

This study analyzes the impact of targeted education about HPV on 12 to 14-year-old high school students. To the best of our knowledge this is the first study in Austria assessing the effect of targeted education about HPV on (pre-)adolescents.

## 4.1 General Knowledge

Before the targeted education, 61% of students had heard about HPV but did not know exactly what it was, 6% did not know what HPV is at all, 39% of students had heard about the HPV vaccine but did not know exactly what it is and 11% did not know what the HPV vaccine is. Therefore, 33% and 50% of all students knew what HPV and the HPV vaccine is, respectively. This finding shows that pre-educational knowledge on HPV and HPV vaccine was rather low in our cohort of 12 – 14-year-old students, even in a relatively exclusive, international school.

Studies from China have found similar results with even lower baseline knowledge on HPV and the HPV vaccine in large samples of (pre-)adolescent students (Zhang: 12.6% and 15.7% for HPV and HPV vaccine; Liu: 15.1% and 17.5% for HPV and HPV vaccine, respectively) (Liu *et al.*, 2019; Zhang *et al.*, 2020). A South African study investigated a large sample of adolescents and found dramatically low levels of HPV and HPV vaccine knowledge, stating it to be 4.08% and 3.31%, respectively. (Mbulawa *et al.*, 2023). Nevertheless, this cohort might not be best to compare to our students because of the different socioeconomical background between South Africa and Austria (ibid.).

In contrast, an Italian study in a large group of pre-adolescents, 70% reported having heard about HPV, information was mostly received from their doctor and parents (Icardi *et al.*, 2020). Moreover, this study also investigated pre-adolescents´ parents´ (86% were mothers) knowledge about HPV and the HPV vaccine and found that, 88% and 87% have heard about HPV infection and the HPV vaccine before, respectively (ibid.). However, although awareness about HPV and knowledge about HPV vaccine age (97%) and gender (87%) recommendations were high in pre-adolescents, knowledge about its spread and its potential to cause condylomata was lacking (40% and 17% responded correctly). (Icardi *et al.*, 2020). This study is better comparable to our cohort due to the geographical and socioeconomic background of two neighboring middle-European countries (ibid.).

As part of a study on adolescents´ consent to vaccines in Tyrol, Austria, Kreidl et al. also investigated on their knowledge on HPV, although it was framed differently than in our study (Kreidl *et al.*, 2020a). They studied 367 adolescents and found that 55% disagreed that HPV is a childhood illness, 62% were aware of its sexual transmission mode and 67.2% knew that the HPV vaccine is recommended gender-neutrally (Kreidl *et al.*, 2020a).
Knowledge levels differed in the mentioned studies, nevertheless, authors of most of these studies (Liu *et al.*, 2019; Icardi *et al.*, 2020; Zhang *et al.*, 2020; Mbulawa *et al.*, 2023) conclude that their participants´ knowledge on HPV/ HPV vaccine is deficient and targeted education of students is required, Liu and Zhang proposed integrating HPV education in already existing sexual-health school curricula (Liu *et al.*, 2019; Zhang *et al.*, 2020).

## 4.2 Effect of Targeted Education on HPV and HPV Vaccine Knowledge

Therefore, our study investigated whether targeted education increases students´ knowledge on HPV and the HPV vaccine. The results show that targeted education clearly raises the number of students who stated to know what HPV and the HPV vaccine are. After receiving the educational intervention, 100% and 98.15% knew what HPV and the HPV vaccine are, respectively. Hence, in this study, targeted education led to an increase of knowledge regarding primary prevention of HPV associated cancers. However, due to the small study sample size, the significance of the results is unclear.
Previous studies that analyzed large samples of female and male (pre-) adolescents found similar effects of targeted education (Liu *et al.*, 2019; Zhang *et al.*, 2020; Thanasas *et al.*, 2022; Mbulawa *et al.*, 2023). For example, a large Greek study of 11 – 12 year-old students found that at pre-intervention 44% of students did not know what HPV is and 52% knew that it is a virus, whereas directly post-intervention only 1.6% of students did not know what HPV is and the percentage of students who knew it is a virus rose to 96% (Thanasas *et al.*, 2022). Additionally, percentage of students who knew that sex is the most common transmission route rose from 38% pre-intervention to 95.6% directly post-intervention (Thanasas *et al.*, 2022). Moreover, this study also analyzed knowledge three months post-intervention and saw that 8% did not know what HPV is, 88% knew it is a virus (ibid.). 86.3% knew about its transmission via sex (ibid.). The percentage of study participants in the third questionnaire (88.3%) who knew that HPV is a virus notably differs from the 52.4%

in the first questionnaire, but lightly less than in the second questionnaire (95.6%) (ibid.). Similarly, a South African study with a sample of over 2000 high school learners (median age: 18), found that educational intervention raised students´ HPV knowledge significantly (Mbulawa *et al.*, 2023). In this study, before intervention only 1% of learners showed "good" HPV knowledge, compared to 73% with "good" knowledge post-intervention (ibid.).

In line with these results, a Chinese study of 13 - 14 year-olds found that after receiving an educational intervention, HPV-associated knowledge rose significantly (Zhang *et al.*, 2020). A different Chinese study found that at 1-year post-intervention students (median age: 12.31 years) who received the educational intervention had significantly higher awareness of HPV and HPV vaccines compared to a control group (Liu *et al.*, 2019).

Molokwu et al. investigated the impact of educational intervention on HPV and the vaccine on immunization rates in 2380 adults (18 - 26 years) and parents of children that were aged 9-17 and have not received the full HPV immunization in a mostly Hispanic community (Molokwu *et al.*, 2019). They found a significant change of HPV awareness from 62% to 88% in adults and 85% to 96% in the parents(ibid.).

In conclusion, our results suggest that education can raise knowledge on HPV among students. As described above, other studies with greater participant samples, showed statistical significance in knowledge level increase pre- and post-educative intervention (Thanasas *et al.*, 2022; Mbulawa *et al.*, 2023). Therefore, our results are in line with those of previous studies.

## 4.3 Effect of Targeted Education on HPV Vaccination Intention

Our primary outcome was whether targeted education has an impact on vaccination intention in students with negative or uncertain HPV immunization status. We found that the number of students who, after receiving targeted education, were willing to receive the vaccine in a cost-reduced vaccination program, increased by 1 (pre-intervention: 10/13 and post-intervention: 11/13). These small numbers preclude a clear and unambiguous answer to the primary research question. Several reasons explain the lack of an unambiguous result: First, the study was conducted in a small sample. Secondly, within the intended-to-treat population only 41% of students (55/135) returned parentally signed consent forms. Third, vaccination coverage in our per-protocol cohort (n=54) was surprisingly high with 76% (41/54) having received minimum one dose of the HPV vaccine. Therefore, there was only a small group of

students with negative or uncertain immunization status (n=13). Out of this group, 10 students already showed willingness to get HPV vaccinated in a cost-reduced catch-up vaccination program before receiving education.

These results were unexpected. Probably the fact that the study was conducted at a single school contributes to the results. It is also necessary to emphasize the distinctive character of the high school the study was conducted in. GIBS is a bilingual school with language focus (*Admission*, no date; *Admission Years 2-6/Grades 6-10*, no date). It is an "Austrian state-funded school" (*Admission*, no date), but the admission process includes interviews of the applying students (*Admission Year 1/Grade 5*, no date). Although GIBS Graz is a state school and tuition fees are not charged, student families pay a membership fee (400€/child/school year in 2023/24) to the GIBS Foundation to "cover non-government funded operating costs" (*Parents*, no date), families in financial distress are however supported by the school´s guidelines (ibid.). In a call with GIBS´ principal Edda Berger-Cian, she added that the membership fee is voluntary and should cover the cost for language assistants and school-related events (Edda Berger-Cian, 2024). Unfortunately, we had no data on parents´ educational level or socioeconomic status. On request, Berger-Cian speculated, that by observation there is a high academic level amongst their students´ parents, however there is no official data on the matter (Edda Berger-Cian, 2024). These factors distinguish GIBS from other Austrian high schools.

In general, as we saw only one additional student who, after receiving education, would have wanted to receive the HPV vaccine in a cost–reduced program, our results do not allow recommendations on whether targeted education can raise HPV vaccination intention. However, previous studies of larger samples and in multiple educational institutions did find that educative interventions improve HPV vaccination intention (Liu *et al.*, 2019; Zhang *et al.*, 2020; Thanasas *et al.*, 2022). Liu et al. explored a large sample of adolescent students from one urban and one rural school (both school groups were split in control and intervention groups) and found that at baseline, 55% of students from both intervention (503/890, (57%)) and control (338/634, (53%)) groups were willing to receive the HPV vaccine, if available (Liu *et al.*, 2019). In the intervention group, readiness to receive HPV vaccination rose significantly after receiving education: from 57% pre- to 88% post-education (ibid.).

Zhang et al. investigated a large sample of adolescents from seven geographical areas (one city chosen per area) in China (Zhang *et al.*, 2020). Per city, one rural and one urban middle

school were selected and one control (ibid.). At baseline 67% (2937/4367) adolescents from both, intervention (1515 adolescents/2216, (68%)) and control group (1422/2151, (66%)), stated they were willing to receive prophylactic vaccination (ibid.). After receiving education, 92% of the intervention class (2262/2472) showed willingness to receive the HPV vaccine, if available (ibid.). Students who were willing to receive the HPV vaccine showed significantly higher knowledge regarding HPV transmission modes, the link between cervical cancer and HPV, the most effective HPV infection prevention methods and the best timing for immunization, compared to students that were unwilling to vaccinate after receiving education (ibid.).

Thanasas et al. studied 434 preadolescent students from various rural schools, urban schools and one private school in Greece (Thanasas *et al.*, 2022). Their results are in line with the above-mentioned findings: willingness for HPV vaccination increased from 71% at baseline to 89% directly after receiving education (ibid.). Three months post-education this rate decreased to 84% (ibid.) Despite this slightly lower willingness rate compared to directly after intervention, results are still significantly higher in comparison to baseline willingness rates (ibid.). It is noteworthy, that in the intervention group, after receiving education, a statistically significant difference was found in HPV vaccination willingness rates based on yearly income per family, sex and whether they live in rural or urban areas (ibid). Females, adolescents from high-income families and those living in urban regions were more willing to receive HPV vaccination (ibid.).

Feemster et al. explored the potential effect of sociodemographic characteristics on the efficacy of tailored educational video messages on HPV vaccination intent within 12 months among mothers of 11 – 14 year old children in the U.S. (Feemster *et al.*, 2021). Effect modification was analyzed between two trial arms: 1.) a general informational video and 2.) a general informational video supplemented by video(s) tackling all vaccine concerns (ibid.). In stratified analysis HPV vaccination willingness was significantly higher in the second arm in comparison to the first arm among mothers aged 36 or younger, mothers with vocational or college education, among household earnings higher than US$100,000, households with one or two kids, among younger kids (11 – 12 years old), White and Black kids and non-Hispanic children (ibid.). (Feemster *et al.*, 2021)

In conclusion, future studies on this topic should have adequate sample sizes and include multiple schools, both private and public, from rural and urban areas. Moreover, it would be important to have data on parents´ educational levels and socio-demographic data.

## 4.4 Strategies to Raise HPV Vaccination Coverage in Austria

In the present study, several students were absent on the study days. During the first two interventions only one student was absent per class, whereas during the third intervention three were absent. At the fourth intervention, seven students were absent and at the fifth intervention three were absent. Furthermore, we observed participation hesitancy among a few parents. One parent emailed us asking about whether the study is anonymous and was approved by an Ethics committee. A different parent called Dr. Taumberger, asked for information and then the parent was willing to let its child participate. Lastly, one parent refused participation for their child. Overall, only 41% of students returned parentally signed consent forms.

We hypothesize that this nonparticipation may partly have mundane reasons, such as children simply forgetting to show parents the consent forms, parents not checking their email in time, and teachers not sending reminder emails to parents in time. Another possible explanation could be general uncertainty regarding vaccination, vaccine hesitancy up to and including anti-vaccination movement beliefs. However, it may also be due to the possibly sensitive topic of discussing HPV, a predominantly sexually transmitted virus, with a (pre-)adolescent child. Discussing HPV with a child may pose a challenge to parents who might additionally perhaps be underinformed on the topic themselves as well.

HPV vaccine coverage in Austria is insufficient and measures to raise coverage are necessary. As in Austria, children before the age of 14 require their legal guardians´ consent for vaccination (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2023a) and the HPV vaccine is best administered before the age of 14, (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024) it is essential to establish strategies on how the decision-making parents/ legal guardians can be reached. Additionally, children above the age of 14 need to be informed about their possibilities. Strategies should include:

1.) Outreach to parents of children under the age of 14 and provision of education on HPV and the HPV vaccine.
2.) Awareness campaigns aimed at parents of children under the age of 14 and adolescents below and above the age of 14.

3.) Adressing vaccine hesitancy among parents of children under the age of 14.
4.) Substitution of the Austrian opt-in system by an opt-out system
5.) Education of children above the age of 14 about their right to decide for themselves on vaccination (Kreidl *et al.*, 2020b; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2023a; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024).
6.) Lowering practical barriers to vaccination by measures such as making vaccinations available in all schools (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2024)

### 4.4.1 Outreach to Parents of Children under the Age of 14 and Provision of Education on HPV and the HPV Vaccine

In Styria HPV vaccines are provided to children/adolescents in primary schools (4$^{th}$ grade) and secondary schools (amongst other possibilities) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2024). The city of Graz directly provides free HPV vaccination to schools as part of an HPV vaccination campaign for students (Stadt Graz, 2024). In 2024 in Graz, students´ parents receive information about the possibility of the HPV vaccine via the schools´ communication app "schoolfox" (Stadt Graz, 2024). Unfortunately, we do not know how the information about the HPV vaccine program is distributed to parents in the rest of Austria. We do not know whether information had been delivered to our intention-to-treat population´s parents at the time their children reached the age of 9. However, we saw several uncertainties and doubts among parents as well as a low participation rate (41%) in our study. Therefore, we figure that it is necessary to enhance outreach to parents and include the (pre)adolescents' parents in educational campaigns.
This is supported by findings of an Austrian study with 334 parents (93% were mothers/maternal guardians), that, although demonstrating a high overall parental HPV vaccine acceptance rate of 82% for their children, showed that the leading reasons for HPV vaccine rejection were "fear of permanent side effects, children's being too young to be vaccinated, and not being adequately informed about the vaccine" (Waser, Heiss and Borena, 2022, p. 4). The study also found that the odds of HPV vaccine acceptance for children were lower when parents used the Internet to inform themselves about HPV, and that the likelihood for vaccinating children, especially female, against HPV augmented when parents

had received HPV education flyers (ibid.). Lastly, parents that showed higher HPV knowledge also demonstrated higher HPV vaccine acceptance regarding their female children (ibid.). The authors of that study conclude that education about the HPV vaccine is required to tackle parental knowledge gaps and counteract existing misinformation about the HPV vaccine that potentially leads to vaccine rejection (ibid.).

An Indonesian study showed efficacy in educating parents of (pre-)adolescent females on HPV: in a cohort of 506 parents who received a presentation led by a trained pediatrics resident and a subsequent discussion, parents willingness for their children to be vaccinated against HPV for free (=parental acceptability) rose from 74% pre-intervention to 87% post-intervention (Sitaresmi *et al.*, 2020). After being educated, parental awareness, knowledge about cervical cancer, infection with HPV and HPV vaccine and perception of the latter were significantly enhanced (ibid.). Increase of vaccine acceptability was significantly associated with improvement of all of the latter items (Sitaresmi *et al.*, 2020).

A study from the U.S. assessed the impact of an educational video on parental HPV vaccine acceptability and found that out of 186 female adults who watched the video and completed the questionnaires, before watching the video 67% "would vaccinate their child if the vaccine were free" (Chapman *et al.*, 2010, p. 105) versus 87% post-video (ibid.). Before watching the educational video, 55% indicated the vaccine should be mandatory for all kids versus 73% that indicated so after the video (ibid.). The percentage of participants who "would agree to vaccination of their children at school (Chapman *et al.*, 2010, p. 105), increased from 51% pre-video to 65% post-video (ibid.). Additionally, before the intervention only 13% showed willingness to vaccinate their children at 9 years old against HPV, after watching the video this percentage rose to 43% (ibid.).

In the case of our study, we propose that targeted education on HPV and the HPV vaccine could for example be provided at parents´ evenings in schools. Education could either be given by teachers who were educated on the subject or by medical professionals.

### 4.4.2 Awareness Campaigns aimed at Parents of Children under the Age of 14 and Adolescents below and above the Age of 14

Social media education campaigns could be another efficient option for reaching parents as well as adolescents. Teoh explored the potential of social media for HPV immunization

(Teoh, 2019). The study cites an ecologic study by Dunn et al. (Dunn *et al.*, 2017; Teoh, 2019). Dunn et al. investigated more than 273 million exposures to more than 258 400 HPV vaccine associated tweets and the results suggest "that in states where negative opinions about HPV vaccines are popular-ized [sic] by mainstream media, the coverage is often lower than would be expected by socioeconomic differences alone" (Dunn *et al.*, 2017, p. 3040) (Ortiz, Smith and Coyne-Beasley, 2019; Teoh, 2019). The authors concluded that the media have a potential to either mirror, enhance or impact how the HPV vaccine is accepted (Dunn *et al.*, 2017).

Teoh suggests that "Health care providers and health care organi-zations [sic] need to maximize pro–HPV vaccine messaging and appeal to both logic and emo-tion [sic] to overcome the anti–HPV vaccine mes-saging [sic] that exists on social media" (Teoh, 2019). In order to raise vaccine coverage in Austria, the Österreichische Krebshilfe demands Austrian health politics to drastically scale up the outreach of targeted education on the HPV vaccine (Österreichische Krebshilfe, 2024). Austrian HPV campaigns include "From ten to teen", "Das beste Alter" and "Gemeinsam gegen HPV" (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2023b; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), no date; Gitti Grobbauer Communications im Auftrag von: Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG), no date; Merck Sharp & Dohme Ges.m.b.H., no date). The campaigns "From ten to teen" and "Gemeinsam Gegen HPV" amongst others use(d) social media for outreach. (Gitti Grobbauer Communications im Auftrag von: Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG), no date; Merck Sharp & Dohme Ges.m.b.H., no date). To my best knowledge, the only campaign that was active on social media in 2024 is "Gemeinsam Gegen HPV", that additionally involves popular Austrians, amongst others, Christl Clear, Nina Radman, Michael Buchinger, Valerie Huber and Martina Reuter (Merck Sharp & Dohme Ges.m.b.H., no date; *gemeinsam.gegen.hpv*, no date; *Gemeinsam gegen HPV*, no date a; *Gemeinsam gegen HPV*, no date b).

It is essential to pursue the demand from the Österreichische Krebshilfe (Österreichische Krebshilfe, 2024) and establish outreach to the Austrian target population and their parents. Outreach, whether via social media, or in persona educational campaigns needs to be increased until sufficient vaccination coverage is reached.

### 4.4.3 Addressing Vaccine Hesitancy among Parents of Children under the Age of 14

The European Commission measured the state of vaccine confidence in Europe and found that Austria ranked 19 among the 27 EU member states regarding the percentage of adults (44%) from the general public that believe vaccines to be "important, safe, effective, and compatible with their beliefs" (European Commission. Directorate General for Health and Food Safety., 2022; European Commission. Directorate General for Health and Food Safety. *et al.*, 2022). Austria ranked 26 regarding the percentage of health care professionals that believe vaccines to be the same items as listed above (74%) (compared to for example Luxembourg with 100%) (ibid).

The Austrian public's confidence regarding general vaccine safety was 78% (6 percentage points less than in 2020) and confidence in vaccine importance was 76% (12.2 percentage points less than in 2020) (European Commission. Directorate General for Health and Food Safety., 2022).

Public confidence in Austria in the HPV vaccine´s importance was 68% in 2022 (7.4 percentage points less than in 2020) (European Commission. Directorate General for Health and Food Safety., 2022). The public confidence in the HPV vaccine´s safety was 71% in 2022 (no change from 2020), in effectiveness was 69% and in its compatibility with beliefs was 74%, all below general EU percentage rates (ibid.).

An Austrian study found that despite parental HPV vaccine acceptance being high (82%), the leading reasons for vaccine rejection were "fear of permanent side effects, children's being too young to be vaccinated, and not being adequately informed about the vaccine" (Waser, Heiss and Borena, 2022, p. 4).

Taumberger et al. reviewed, discussed and debunked the most common myths regarding the HPV vaccine (Taumberger *et al.*, 2022). Amongst others, the addressed myths included whether the recommended age for HPV vaccination is too early, since the child is not sexually active at this point, and whether the vaccine encourages unsafe sexual behavior and "sexual disinhibition in adolescents" (Taumberger *et al.*, 2022, p. 1318). Taumberger et al. tackle the first concern in stating the fact that a better immune response is given, provided the vaccine is administered under 15 years old (Taumberger *et al.*, 2022). A clinical trial showed that adolescents aged 9 to 14 who received a 2-dose series (0-6 months and 0-12 months) had consistently higher geometric antibody titers against all HPV types included in

the nonavalent vaccine than females between the ages 16 and 26 who were administered a 3-dose series (0-2-6 months) (Iversen *et al.*, 2016b; Meites, Kempe and Markowitz, 2016b; Taumberger *et al.*, 2022). Moreover, when addressing this myth, Taumberger et al. point out the fact, that despite the most common HPV infection mode being sexual, non-sexual transmission routes of HPV have also been proposed (Tay, Ho and Lim-Tan, 1990; Casalegno *et al.*, 2012b; Gallay *et al.*, 2015b; Liu, Rashid and Nyitray, 2016b; Petca, Borislavschi, M. E. Zvanca, *et al.*, 2020; Taumberger *et al.*, 2022). Taumberger et al. conclude their discussion of this myth: "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." (Taumberger *et al.*, 2022, p. 1318).

Taumberger et al. cite various studies dispelling the misconception that HPV vaccination leads to sexual disinhibition in teenagers (Taumberger *et al.*, 2022; Kasting *et al.*, 2016; Forster *et al.*, 2012; Smith *et al.*, 2015; Rysavy *et al.*, 2014; Bednarczyk *et al.*, 2012). A systematic review of 20 studies with female populations found that "the consistent and replicated evidence indicates that HPV vaccination does not lead to risk compensation/sexual disinhibition" (Kasting *et al.*, 2016, p. 1446). One study found no significant difference in the change of proportion of sexually active females and the change in the number of sex partners (both baseline to follow-up) between the vaccinated and unvaccinated cohort (Forster *et al.*, 2012; Kasting *et al.*, 2016; Taumberger *et al.*, 2022). Moreover, "Change in condom use between baseline and follow-up did not differ by vaccination group" (Forster *et al.*, 2012, p. 4942). Smith et al. used pregnancy and sexually transmitted infection (STI) as clinical indicators for sexual behavior and did not observe HPV vaccination to have a significant effect on the composite measures of pregnancies and STI (other than HPV) in in a large cohort of female teenagers (Smith *et al.*, 2015; Kasting *et al.*, 2016; Taumberger *et al.*, 2022). The same applies to the examination of pregnancy and non-HPV-associated STI individually (ibid.). Lastly, Rysavy et al. found that HPV vaccinated and unvaccinated females aged 13 – 23 years showed similar (high-risk) sexual behaviors, which underlines the assumption that HPV vaccination is not linked to higher sexual activity (Rysavy *et al.*, 2014; Kasting *et al.*, 2016; Taumberger *et al.*, 2022). However, early sexual debut was observed in this cohort, highlighting the necessity of early HPV vaccination (ibid.).

### 4.4.4 Substitution of the Austrian Opt-in System by an Opt-out System

One possibility to raise vaccine coverage in Austria is to change the current "opt-in" system to an "opt-out" approach. In Austria, students´ parents need to "opt-in" for their children to receive the vaccine (Österreichische Krebshilfe, 2024). The Österreichische Krebshilfe demands the implementation of an "opt-out" option regarding the HPV vaccine (Österreichische Krebshilfe, 2024). This means, that after being educated on the matter, parents who explicitly do not wish to have their child(ren) vaccinated, should be able to give written dissent/contradict the vaccine in written form (ibid.).

The matter is handled differently around the globe. In Chile the HPV vaccine is obligatory (Ministerio de Salud, 2023). In the United States in Virginia, Rhode Island, Washington D.C., Hawaii and Puerto Rico HPV immunization is required for school entry (Hawai'i Department of Health Immunization Branch, 2020; Department of Health, 2024; *School Health Requirements*, no date; *Human Papillomavirus (HPV) Vaccine*, no date; *School Requirements*, no date; Vázquez-Otero *et al.*, 2021) although in many areas exemptions can be made for medical or religious reasons (Oficina de Gerencia y Presupuesto del Gobierno de Puerto Rico, 1983; Hawai'i Department of Health Immunization Branch, 2020; Vázquez-Otero *et al.*, 2021; DC Health Government of the District of Columbia, 2024; Department of Health, 2024; *12VAC5-110-80. Exemptions from immunization requirements.*, no date; *School Requirements*, no date; *School Health Requirements*, no date).

In the United States, 80% and 68% of females turning 15 in 2023 have initiated and completed the vaccine series at some point between the 9$^{th}$ and 14$^{th}$ birthday, respectively (World Health Organization, 2024b).

In Chile, 91% and 82% of females turning 15 in 2023 have initiated and completed the vaccine series at some point between the 9$^{th}$ and 14$^{th}$ birthday, respectively (World Health Organization, 2024c).

The mentioned countries are far closer to the HPV vaccine coverage goal (90% of 15-year old females fully immunized) set by the WHO (World Health Organization, 2020a) than Austria (53% of 14-year old children with both vaccines in 2022) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2023b, 2023a; World Health Organization, 2023d). Considering the Österreichische Krebshilfe´s claim (Österreichische Krebshilfe, 2024), an adaptation of the current opt-in to an opt-out system, could be one possible approach to raise HPV vaccine coverage in Austria. Waser et al. have

also previously hypothesized about this tactic to reach a possible vaccine coverage increase in Austria (Waser, Heiss and Borena, 2022).

### 4.4.5 Education of Children above the Age of 14 about their Right to Decide for Themselves on Vaccination

The HPV vaccine is most effective when given between the ages 9 – 11/ before sexual debut (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). The option that parents do not agree with the vaccine before the age of 14 and therefore the child is not vaccinated, exists. In Austria, adolescents, starting from the age of 14 can opt for HPV vaccination themselves (if decision-making ability is given) (Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz, 2023a; Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK), 2024). However, an Austrian study from Tyrol found that only 35% of 14-year-old adolescents knew that they could get vaccinated without parental consent (Kreidl *et al.*, 2020b). 67% of the same cohort were aware of the HPV vaccine´s recommendations regarding sex and 28% were aware that schools offered the free HPV vaccine for everyone between the 9$^{th}$ and 12$^{th}$ birthday (ibid.). At the same time, however 65% of the 367 adolescents were unwilling to share their HPV immunization status or were uncertain of it, leaving only an estimated share of 39% of respondents being HPV vaccinated (ibid.). This is a low vaccine coverage for a cohort that is targeted by the HPV program (Kreidl *et al.*, 2020b). The authors discussed that:

> "This lack of awareness that schoolchildren do not need their parents' consent to vaccinate was neither associated with vaccine hesitancy nor the intention to vaccinate against measles or HPV, but this may change if more schoolchildren are aware about their rights in the future." (Kreidl *et al.*, 2020b, p. 9,10)

These results and the currently insufficient vaccine coverage in Austria demand action. Educational campaigns that aim to increase knowledge about HPV and the HPV vaccine (and other vaccine-preventable diseases) in adolescents need to raise awareness about their right to decide for vaccination without parental consent when turning 14. Moreover, medical personal (especially general physicians, school physicians, gynecologists and pediatricians) that is in touch with this defined age group should inform them about their possibilities and encourage pro-vaccination decisions. Furthermore, in the era of social media platforms,

informational campaigns about their vaccine-related rights and the vaccines that 14-year-olds can now opt for could have promising outreach in this age group. Lastly, teachers, especially biology and ethics teachers, should integrate this information in their curriculum.

### 4.4.6 General Strategies Suggested by the Österreichische Krebshilfe

Strategies to increase vaccine coverage in Austria were suggested in a 6-point program in 2020 by the Österreichische Krebshilfe and AGO-Austria (Arbeitsgemeinschaft Gynäkologische Onkologie) (Österreichische Krebshilfe, 2020, 2022, 2023a, 2024). In addition to some of the previously discussed strategies (substitution of the opt-in system with an opt-out system, scale up of HPV vaccine education and information dissemination), demands included the extension of the HPV vaccine catch-up program, the implementation of an electronic vaccination card, facilitated access to the HPV vaccine (all physicians authorized to administer the vaccine) and the intensive cooperation of school doctors to make sure all students targeted by the vaccination program receive the vaccine (Österreichische Krebshilfe, 2020, 2022, 2023a, 2024).

Some of the demands have (partially) succeeded in the meantime, while others still require implementation (Österreichische Krebshilfe, 2020, 2022, 2023a, 2024). Firstly, the catch-up program has been extended until the 21$^{st}$ birthday, with a limited additional extension until the 30th birthday until 2025 (ibid.). Secondly, the electronic vaccination card was implemented with a mandatory documentation of the HPV vaccine, among others (ibid.). As the documentation remains uncontrolled, the Österreichische Krebshilfe argues it remains "voluntary" (Österreichische Krebshilfe, 2024, p. 35). Thirdly, as a consequence of the COVID-19 pandemics, physicians of all specialties are authorized to administer vaccines (Österreichische Krebshilfe, 2024). However, scale up of immunization centers and doctors is still necessary (ibid.). Fourth, a legal amendment enabled facilitated information regarding school vaccinations (ibid.). Fifth, an awareness campaign was installed by the Austrian Health Ministry in 2023, further campaigns are necessary (ibid.). The introduction of an opt-out system is still pending (Österreichische Krebshilfe, 2020, 2022, 2023a, 2024).

## 4.5 Limitations

Our study has several limitations. Firstly, our sample size was small and precluded statistical analyses. Secondly, our questionnaire asked students whether they knew what HPV and the HPV vaccine were, offering three possible answers (Yes/ No/ I have heard about it before, but I do not know exactly what it is) in lieu of an HPV/ HPV vaccine knowledge scale (Waller *et al.*, 2013; Perez *et al.*, 2016) or questionnaire (Harrison *et al.*, 2021). Our study was conducted in a single bilingual school and selection bias is possible. We had no data on students´ sociodemographic background.
Furthermore, similar to the study by Waser, Heiss and Borena (Waser, Heiss and Borena, 2022) the participation in this study was voluntary and no incentives, other than the students´ receiving education, were used. This is not a limitation per se, but similar to the limitation found in the study by Waser, Heiss and Borena (ibid.) it might have attracted parents/students, that were generally informed and/or interested in the topic, to a further extent than others (ibid.). Similar to their study, it is possible, that in our study too, parents that were not aware of the topic were not as susceptible to the parental information sheet previously handed out and that parents affected by vaccine hesitancy or anti-vaccine movement beliefs might have not let their children participate (Waser, Heiss and Borena, 2022). Due to the discussed limitations, our results do not allow generalization.

### 4.6 Strengths

To our knowledge, no comparable study has been conducted in Austria. It is therefore the first study, that evaluated the immediate effect of a targeted educational intervention on HPV and HPV knowledge and on HPV vaccination intention in a sample of 12–14-year-old students in Austria. Furthermore, although not generalizable, this study measured vaccine coverage per sex in the analyzed cohort. An additional strength of this study is that it was conducted prospectively.

## 5 Conclusion

In our small cohort, one additional student was willing to get vaccinated after receiving targeted education on HPV/ the HPV vaccine. The results of this limited study do not allow

conclusive and unequivocal recommendations on whether targeted education can raise HPV vaccination intention in Austria. But we did find that after targeted education nearly all students stated to know what HPV and the HPV vaccine are. Targeted education led to an increase in the number of students with knowledge regarding primary prevention of HPV associated cancers. Therefore, education may lead to increased knowledge and awareness regarding HPV and the HPV vaccine. This is important because increased knowledge might have an indirect effect and lead to increased HPV vaccination intention. Furthermore, as we only know the rate of vaccination of the study participants (n=54), we cannot state the actual vaccination rate within the group that was intended to be investigated (n=135).

These topics require further study. Future studies should have an adequate sample size; include students from multiple schools in diverse settings (urban and rural, public and private schools, vocational schools, junior high schools, high schools); use a valid HPV-knowledge scale; obtain detailed demographic and socioeconomic information; and, possibly, include randomization into interventional and control groups.

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- **DeepL/DeepL Pro**
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# Annex

## Ethics Approval

Medizinische Universität Graz
Ethikkommission

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

**VOTUM**
**gültig bis 04.06.2022**

| | |
|---|---|
| **EK-Nummer:** | 33-448 ex 20/21 |
| **Studientitel:** | Does education about HPV have a positive effect on vaccination intention amongst a sample of 12 to 14 year old students?<br><br>Report from a high school in Graz |
| **Prüfer:** | Univ.-Prof. Dr. Karl Tamussino<br>Medizinische Universität Graz |
| **Sponsor:** | Medizinische Universtität Graz, Universitätsklinik für Frauenheilkunde und Geburtshilfe |
| Ansprechpartner: | Dr.med.univ. Nadja Taumberger, 8036 Graz, Auenbruggerplatz 14 |
| **CRO:** | - |
| **Antragsteller:** | Medizinische Universität Graz |
| Ansprechpartner: | Maria Rissner |

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 26.04.2021 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

**Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.**

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

**Zur Beurteilung vorliegende Dokumente:**

| | |
|---|---|
| **Dokumente eingegangen am 19.04.2021, begutachtet im 'expedited Review' am 26.04.2021** | |
| ✓ Cover Letter Anschreiben Diplomarbeit_MR 1.0 | 13.04.2021 |
| ✓ Antragsformular ECS | 19.04.2021 |
| Originalprotokoll Studienprotokoll_V1_MR 1.0 | 13.04.2021 |
| Informed Consent Form Patient_inneninfo und Einverständniserklärung_V1_MR 1.0 | 13.04.2021 |
| ✓ Conflict of Interest Erklärung Erklaerung Interessenskonflikt_MR 1.0 | 13.04.2021 |
| Case Report Form Fragebogen HPV und HPV-Impfung bei 12-14-jährigen Schueler_innen_V1_MR 1.0 | 13.04.2021 |
| ✓ CV CV Karl Tamussino 0120 1.0 | 19.04.2021 |
| ✓ Sonstiges: Mailverkehr Direktorin GIBS 1.0 | 26.03.2021 |
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| **Dokumente eingegangen am 17.05.2021 (in der nächsten Begutachtung mitbegutachtet)** | |
| ✓ Originalprotokoll 2.0 | 16.05.2021 |
| ✓ Informed Consent Form Eltern 2.0 | 16.05.2021 |
| ✓ Informed Consent Form (12-14 Jahre) 1.0 | 16.05.2021 |
| ✓ Fragebögen (12-14 Jahre) 2.0 | 16.05.2021 |
| ✓ Sonstiges: E-Mail: Stellungnahme zur Bearbeitungsmitteilung | 17.05.2021 |
| **Dokumente eingegangen am 26.05.2021, begutachtet im 'expedited Review' am 04.06.2021** | |
| ✓ Letter of Authorization | 26.05.2021 |

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

**zusätzliche Auflagen:** Die behördlich vorgeschriebenen Maßnahmen hinsichtlich der COVID-19 Pandemie müssen beachtet werden. Der Prüfer und der Sponsor müssen in ihrem jeweiligen Wirkungskreis unter allfälliger Beachtung von Leitlinien gewährleisten, dass keine zur Bekämpfung der Pandemie benötigten Ressourcen gebunden werden bzw. ausreichend Personal vorhanden ist und die TeilnehmerInnen durch ihre Studienteilnahme keiner zusätzlichen Infektionsgefahr ausgesetzt werden.

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 04. Juni 2021

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Peter Dimai
Stv. Vorsitzender

**Achtung:** Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!



**Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at**
Rechtsform: Juristische Person öffentlichen Rechts gem. UG 2002. Information: Mitteilungsblatt der Universität. UID: ATU 575 111 79. Bankverbindung: Raiffeisen Landesbank Steiermark IBAN: AT443800000000049510, BIC: RZSTAT2G

# Information und Einwilligungserklärung zur Studie: Erhöht gezielte Aufklärung die HPV-Impfbereitschaft bei 12-14-jährigen Schüler*innen?

Liebe Eltern!

Wir möchten Ihr Kind gerne einladen, an obengenannter Studie teilzunehmen. Die Studie ist Teil einer Diplomarbeit, die im Zuge des Humanmedizinstudiums an der Medizinischen Universität Graz verfasst wird. Die Teilnahme an der Studie erfolgt freiwillig und kann jederzeit, ohne Angabe von Gründen und ohne entstehende Nachteile abgebrochen werden.

## Worum geht es bei dieser Studie?

Humane Papillomaviren (HPV) kommen weltweit vor. Von den über 200 Typen gelten circa 14 als potenziell krebserregend, zwei davon (6 und 11) sind unter anderem für Genitalwarzen (Kondylome) verantwortlich. Vor allem zwei dieser HPV-Typen, 16 und 18, werden stark in Zusammenhang mit der Krebsentstehung am Gebärmutterhals gebracht; sie sind für ca. 70 % der bösartigen Neubildungen am Gebärmutterhals verantwortlich. Die HPV-Typen 31, 33, 45, 52, 58 sind ursächlich für weitere 20 % der Gebärmutterhalskrebse (1). HPV-Infektionen werden außerdem in starken Zusammenhang mit anderen Krebsarten (Mund-Rachen-Raum, Anus, Penis, Vagina und Vulva) gebracht. Humane Papillomaviren werden überwiegend bei sexueller Aktivität übertragen (1,2)

Durch die Impfung namens „Gardasil-9$^{R}$“ werden Personen vor den HPV-Typen 6, 11, 16, 18, 31, 33, 45, 52 und 58 geschützt. Die Impfung wirkt vorbeugend gegenüber HPV-Infektionen. Um optimalen Impfschutz zu erhalten, sollte die Impfung laut der Empfehlung des österreichischen Impfplanes Kinder ab dem 9. Lebensjahr und noch vor dem Eintritt in das sexuell aktive Alter erfolgen. Da man unabhängig vom Geschlecht von HPV assoziierten Erkrankungen betroffen sein kann, ist es wichtig, dass so viele Kinder wie möglich geimpft werden, um so die Infektionskette zu stoppen und einen Herdenschutz erreichen zu können (1).
In Österreich wird derzeit, trotz kostenfreiem Impfprogramm für Jugendliche zwischen 9 und 12 (1), von einer Durchimpfungsrate von 30 % ausgegangen (4).

Die Weltgesundheitsorganisation (WHO) hat sich 2020 das Ziel gesetzt, Gebärmutterhals zu eliminieren. Dazu sollen weltweit definierte Maßnahmen bis 2030 getroffen werden, u.a. soll auch eine 90 % HPV-Durchimpfungsrate von weiblichen Jugendlichen erreicht werden (3). Da es keine Statistik zur Durchimpfungsrate in Österreich gibt, möchten wir anhand dieser Studie innerhalb einer Stichprobe von 50 Schüler*innen eine Bestandsaufnahme durchführen.

Des Weiteren möchten wir neben den Angaben zur Person (Alter, Geschlecht) herausfinden, wie der Wissenstand zu den Themen HPV und HPV-Impfung bei Ihrem Kind ist, ob es geimpft ist, wenn Ja in welchem Alter es geimpft wurde, ob es die Impfung Freund*innen weiterempfehlen würde, ob es schon mal über die Möglichkeit einer Impfung aufgeklärt wurde, ob es sich bei negativem Impfstatus im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen würde und ob es Aufklärung in der Schule zum HPV gut findet.

Was ist der Zweck dieser Studie (Diplomarbeit)?

Der Zweck dieser Studie ist, herauszufinden, ob durch gezielte medizinische Aufklärung die HPV-Impfbereitschaft gesteigert werden kann und wie hoch der Prozentsatz der geimpften Kinder ist. Zudem soll erforscht werden, ob die Bereitschaft zur Weiterempfehlung der Impfung durch zielgerichtete Edukation durch (angehende) Medizinerinnen erhöht werden kann. Weiters soll aufgezeigt werden, inwieweit Wissen zu HPV und zur HPV-Impfung vorhanden ist.

Wie läuft die Studie ab?

Wenn es aus Sicht der COVID19-Pandemie im Juni dieses Jahres schon möglich ist, wird die Studie in Präsenz stattfinden. In diesem Fall erhält ihr Kind zwei zusammengeheftete Fragebögen. Einer ist vor der Aufklärungseinheit zu HPV und einer danach auszufüllen. In der Aufklärungseinheit werden Dr. Taumberger und Cand.med. Rissner über die Natur der HPV, damit verbundene Erkrankungen, den HPV-Impfstoff und den idealen Zeitpunkt für die Impfung sprechen. Die Dauer der Studie beträgt einen Tag.

Worin liegt der persönliche Nutzen einer Teilnahme bei ihrem Kind und gibt es Risiken?

Ein unmittelbarer Nutzen für ihr Kind ist durch die Teilnahme nicht zu erwarten. Die medizinische Aufklärungseinheit zu den Themen HPV und HPV-Impfung könnte aber das Wissen ihres Kindes dazu steigern und das Bewusstsein im Umgang mit HPV erhöhen. Die Erkenntnis, ob gezielte Aufklärung zu einer erhöhten Impfbereitschaft in dieser Stichprobe führen kann, könnte aber neue Anhaltspunkte liefern, die bei der Erreichung des WHO-Ziels Gebärmutterhalskrebs zu eliminieren, von Bedeutung sein könnten.

Ihr Kind erhält eine gezielte Aufklärung über HPV und HPV-Impfung. Somit kann das Wissen zu diesen Themen erweitert werden. Sie könnten nach der Aufklärung eher dazu bereit sein, die Impfung im Rahmen des Catch Up Programms wahrzunehmen. Das hat finanzielle Vorteile, verglichen mit der Impfung zum vollen Selbstkostenpreis ab dem 16. Lebensjahr sowie medizinische Vorteile, da durch die Impfung Krankheiten und Krebserkrankungen verhindert werden können. Es sind keine Risiken zu erwarten.

Die Studie wird unabhängig von der pharmazeutischen Industrie durchgeführt.

Kosten und Vergütung

Es entstehen weder Kosten, noch ist eine Vergütung für die ProbandInnen vorgesehen.

Datenschutz

Bei den Daten, die über Ihr Kind im Rahmen dieser Studie (Diplomarbeit) erhoben und verarbeitet werden, kommt es zur Verwendung von anonymisierten Daten, bei denen eine Rückführung auf Ihre Person nicht mehr möglich ist.
Eine Weitergabe der Daten erfolgt nur in anonymisierter Form. Auch für etwaige Publikationen werden nur die anonymisierten Daten verwendet.

Sämtliche Personen, die Zugang zu Ihren verschlüsselten und nicht verschlüsselten Daten erhalten, unterliegen im Umgang mit den Daten der Datenschutz-Grundverordnung (DSGVO) sowie den österreichischen Anpassungsvorschriften in der jeweils gültigen Fassung.

Im Rahmen dieser Studie (Diplomarbeit) ist keine Weitergabe von Daten in Länder außerhalb der EU vorgesehen.

Sie können Ihre Einwilligung zur Erhebung und Verarbeitung Ihrer Daten jederzeit widerrufen. Nach Ihrem Widerruf werden keine weiteren Daten mehr über Sie erhoben. Die bis zum Widerruf erhobenen Daten können allerdings weiter im Rahmen dieser klinischen Studie verwendet werden.

Aufgrund der gesetzlichen Vorgaben haben Sie außerdem, sofern dies nicht die Durchführung der Diplomarbeit voraussichtlich unmöglich macht oder ernsthaft beeinträchtigt, das Recht auf Einsicht in die Ihre Person betreffenden Daten und die Möglichkeit der Berichtigung, falls Sie Fehler feststellen.

Sie haben auch das Recht, bei der österreichischen Datenschutzbehörde eine Beschwerde über den Umgang mit Ihren Daten einzubringen (www.dsb.gv.at).

Die voraussichtliche Dauer der Studie ist ein Tag. Die Dauer der Speicherung Ihrer Daten über das Ende der klinischen Studie hinaus ist durch Rechtsvorschriften geregelt

Falls Sie Fragen zum Umgang mit Ihren Daten in dieser Studie (Diplomarbeit) haben, wenden Sie sich zunächst an Ihre/n Studienleiter*in. Diese/r kann Ihr Anliegen ggf. an die Personen, die am Studienzentrum für den Datenschutz verantwortlich sind, weiterleiten.

Die Kontaktstelle zum Datenschutz am LKH-Univ.Klinikum Graz ist datenschutz@medunigraz.at. Die Kontaktstelle zum Datenschutz in den Krankenanstalten der KAGes ist datenschutz@kages.at.

## Hier finden Sie weiterführende Literatur:

1. Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK). Impfplan Österreich 2021. Wien; 2021. 184 S.

2. HPV and Cancer - National Cancer Institute [Internet]. NATIONAL CANCER INSTITUTE. 2021 [zitiert 17. April 2021]. Verfügbar unter: https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer

3. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem [Internet]. Geneva: World Health Organization; 2020. 56 S. Verfügbar unter: https://apps.who.int/iris/handle/10665/336583

4. HPV-Impfung ist äußerst sicher und schützt vor fünf Krebsarten [Internet]. Comprehensive Cancer Center Vienna. [zitiert 16. April 2021]. Verfügbar unter: https://www.ccc.ac.at/news/singleview/hpv-impfung-ist-aeusserst-sicher-und-schuetzt-vor-fuenf-krebsarten/d4c3f62313d80926cf3ae1773977820f/?tx_ttnews%5Bpointer%5D=18

Österreichische Krebshilfe: HPV Info: https://www.krebshilfe.net/information/krebs-krebs-risiko/infektionen-/-hpv-/-impfung

**Einwilligungserklärung (Eltern)**

Name des Kindes:
Geb.Datum:

Ich stimme zu, dass mein Kind an der Studie „Erhöht gezielte Aufklärung die HPV-Impfbereitschaft bei 12-14- jährigen Schüler*innen?“ teilnimmt.

Ich bin von Herrn/Frau ..... ausführlich und verständlich über die Studie, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der Studie, für mein Kind daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patient*innenaufklärung und Einwilligungserklärung, die insgesamt 5 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir von der Studienleiter*in verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.
Ich stimme ausdrücklich zu, dass die Daten meines Kindes, welche im Rahmen dieser klinischen Studie erhoben werden, wie im Abschnitt „Datenschutz“ dieses Dokuments beschrieben verwendet werden.

Eine Kopie dieser Patient*inneninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt bei der Studienleiter*in.

Bei Rückfragen stehen wir Ihnen gerne telefonisch zur Verfügung.

Cand. med. Maria Rissner

Dr. med Nadja Taumberger

.....
(Datum und Unterschrift der erziehungsberechtigten Person)

.....
(Datum, Name und Unterschrift der verantwortlichen Studienleiter*in)



Note: Adaption of the original document: phone numbers have been deleted to secure privacy.

## Information für Schüler*innen: Erhöht gezielte Aufklärung die HPV-Impfbereitschaft bei 12-14-jährigen Schüler*innen?

**Hallo!**

Hast du schon mal von HPV gehört? Hast du eine Vorstellung davon, was das sein könnte? Deine Antworten auf diese und noch ein paar weitere Fragen interessieren uns sehr. Im Rahmen meiner Diplomarbeit, die im Zuge des Medizinstudiums geschrieben werden muss, möchte ich nämlich erforschen, ob gezielte Aufklärung einen Einfluss auf die HPV-Impfbereitschaft junger Menschen in deiner Altersklasse hat.

**Warum machen wir das?**

Humane Papillomaviren (HPV) sind Viren, die weltweit vorkommen. Sie sind für viele Erkrankungen, unter anderem für einige Krebsarten, verantwortlich. Es gibt eine Impfung, die diese Erkrankungen weitgehend verhindern kann. Heute wissen wir schon viel darüber – zum Beispiel, dass wenn genügend Menschen dagegen geimpft sind, ganze Krebsarten möglicherweise verschwinden könnten. In Österreich jedoch, sind nur sehr wenige Menschen dagegen geimpft. In meiner Diplomarbeit möchte ich herausfinden, ob durch medizinische Informationen und Gesprächen mit Menschen in deiner Altersklasse die Bereitschaft zur Impfung gegen HPV gesteigert werden kann.

**Was machen wir bei dieser Studie?**

Zuerst möchten wir dir gerne einige Fragen zu Humanen Papillomaviren (HPV) und zur HPV-Impfung stellen. Im Anschluss an das Ausfüllen des Fragebogens würden wir dir gerne circa eine Stunde lang etwas darüber erzählen, was HPV genau ist, welche Erkrankungen es auslösen kann und wie man sich davor schützen kann. Nach der Aufklärung bitten wir dich, den mit „Fragebogen nach Aufklärung“ gekennzeichneten Teil auszufüllen. Das wird jeweils nur einige Minuten in Anspruch nehmen.

Das war es dann schon. Wenn du dich an irgendeiner Stelle nicht wohl fühlst damit, dann kannst du natürlich jederzeit Bescheid geben, wenn du nicht weitermachen möchtest.

Vielen Dank für deine großartige Mithilfe!



Alter Jahre

**Schriftliche Einwilligung**

Ich habe diese Information gelesen und verstanden, habe die Möglichkeit gehabt mit meinen Eltern darüber zu sprechen und alles erfragt, was mir unklar war.

Ich möchte freiwillig an dieser Studie zu HPV und zur HPV-Impfung teilnehmen und weiß, dass ich jederzeit, ohne zu sagen warum, die Teilnahme abbrechen kann.

Schüler*in:

Mein Alter: Jahre

Vorname: Nachname:

Unterschrift: Datum:

Eltern/gesetzliche*r Vertreter*in:

Vorname: Nachname:

Unterschrift: Datum:



Alter Jahre

# Questionnaire

Fragebogen HPV und HPV-Impfung bei 12-14-jährigen Schüler*innen 16.05.2021 Version 2.0

## Fragebogen vor Aufklärung

Liebe/r Schüler*in!

Im folgenden Fragebogen möchten wir dir gerne einige Fragen zu Humanen Papillomaviren (HPV) und zur HPV Impfung stellen. Im Anschluss an das Ausfüllen des Fragebogens würden wir dir gerne etwas darüber erzählen, was HPV genau ist, welche Erkrankungen es auslösen kann und wie man sich davor schützen kann. Nach der Aufklärung bitten wir dich, den mit „Fragebogen nach Aufklärung" gekennzeichneten Teil auszufüllen. Das wird jeweils nur einige Minuten in Anspruch nehmen.

Wir benötigen deine Mithilfe und Antworten für eine Diplomarbeit, die im Zuge des Medizinstudiums geschrieben werden muss und ein wissenschaftliches Thema behandeln soll. Darin möchten wir genauer betrachten, ob gezielte Aufklärung einen Einfluss auf die HPV-Impfbereitschaft junger Menschen in deiner Altersklasse hat.

Vielen Dank für deine großartige Mithilfe!

Nummer: _____

**1.)** Alter:____Jahre

**2.)** Mein Geschlecht (anatomisch-medizinisch) ist:

- ☐ weiblich
- ☐ männlich
- ☐ keine Angabe

**3.)** Weißt du, was HPV ist?

- ☐ Ja
- ☐ Nein
- ☐ Ich habe schon mal was darüber gehört, weiß aber nicht genau darüber Bescheid.

**4.)** Weißt du, was die HPV-Impfung ist?

- ☐ Ja
- ☐ Nein
- ☐ Ich habe schon mal was darüber gehört, weiß aber nicht genau darüber Bescheid.

**5.)** Bist du gegen HPV geimpft?

- ☐ Ja
- ☐ Nein
- ☐ Das weiß ich nicht.

**6.)** Wenn Ja, in welchem Alter wurdest du geimpft?

_____Jahre

**7.)** Wenn Nein, wurdest du schon mal über die Möglichkeit einer Impfung aufgeklärt?

☐ Ja
☐ Nein
☐ Das weiß ich nicht.

**8.)** Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?

☐ Ja
☐ Nein

**9.)** Wenn Ja oder Nein, würdest du deinen Freund*innen die Impfung weiterempfehlen?

☐ Ja
☐ Nein

**10.)** Findest du es gut, wenn in der Schule über HPV Impfung aufgeklärt wird?

☐ Ja
☐ Nein

**11.)** Falls du uns noch etwas zu dem Thema sagen möchtest, würden wir uns über deine Anmerkungen sehr freuen:

## Fragebogen nach Aufklärung

Nummer: _____

**12.)** Alter:____Jahre

**13.)** Mein Geschlecht (anatomisch-medizinisch) ist:

☐ weiblich
☐ männlich
☐ keine Angabe

**14.)** Weißt du, was HPV ist?

☐ Ja
☐ Nein
☐ Ich habe schon mal was darüber gehört, weiß aber nicht genau darüber Bescheid.

**15.)** Weißt du, was die HPV-Impfung ist?

☐ Ja
☐ Nein
☐ Ich habe schon mal was darüber gehört, weiß aber nicht genau darüber Bescheid.

**16.)** Bist du gegen HPV geimpft?

☐ Ja
☐ Nein
☐ Das weiß ich nicht.

**17.)** Wenn Ja, in welchem Alter wurdest du geimpft?

_____Jahre

**18.)** Wenn Nein, wurdest du schon mal über die Möglichkeit einer Impfung aufgeklärt?

☐ Ja
☐ Nein
☐ Das weiß ich nicht.

**19.)** Wenn Nein, würdest du dich im Rahmen eines kostenvergünstigten Impfprogrammes impfen lassen?

☐ Ja
☐ Nein

**20.)** Wenn Nein bei Frage 19.), was sind deine Gründe für die Ablehnung der Impfung?

**21.)** Wenn Ja oder Nein, würdest du deinen Freund*innen die Impfung weiterempfehlen?

☐ Ja
☐ Nein

**22.)** Findest du es gut, wenn in der Schule über HPV Impfung aufgeklärt wird?

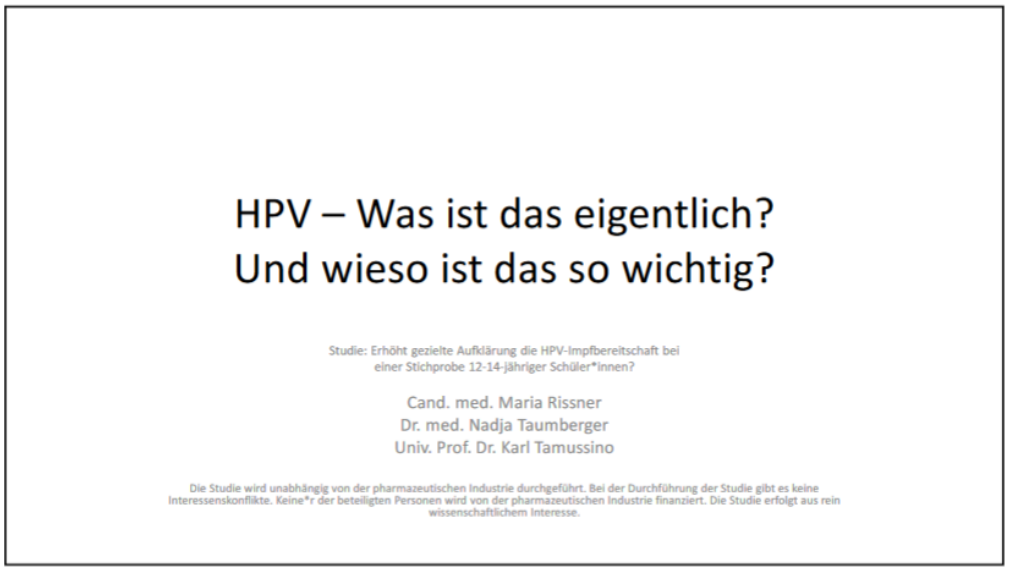
☐ Ja
☐ Nein

**23.)** Hat sich deine Meinung zur HPV-Impfung durch die Aufklärung verändert?

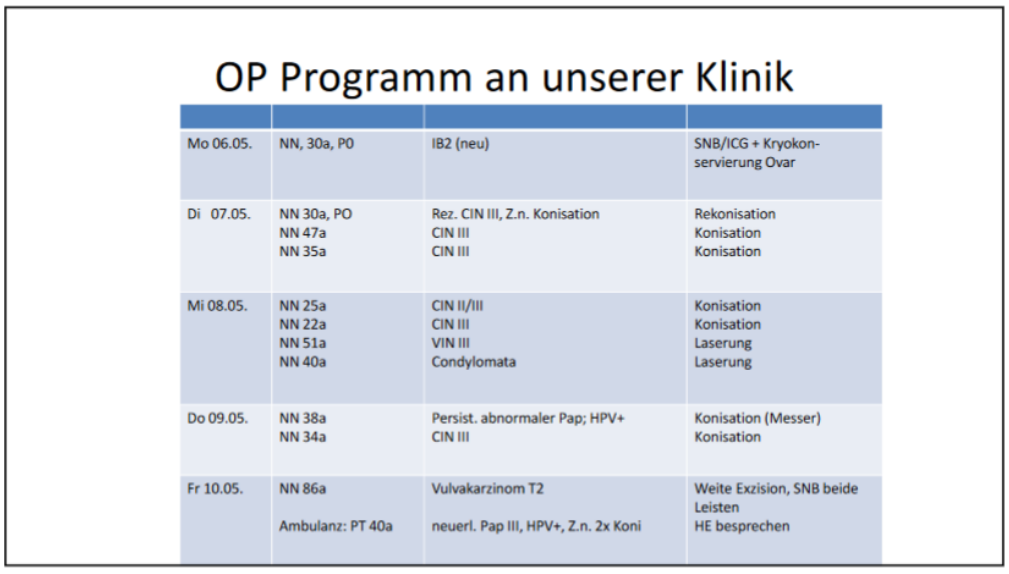
☐ Ja
☐ Nein

**24.)** Wenn Ja, warum hat sich deine Meinung zur HPV-Impfung verändert?

**25.)** Falls du uns noch etwas zu dem Thema sagen möchtest, würden wir uns über deine Anmerkungen sehr freuen:


HPV – Was ist das eigentlich?
Und wieso ist das so wichtig?
Studie: Erhöht gezielte Aufklärung die HPV-Impfbereitschaft bei einer Stichprobe 12-14-jähriger Schüler*innen?
Cand. med. Maria Rissner
Dr. med. Nadja Taumberger
Univ. Prof. Dr. Karl Tamussino
Die Studie wird unabhängig von der pharmazeutischen Industrie durchgeführt. Bei der Durchführung der Studie gibt es keine Interessenskonflikte. Keine*r der beteiligten Personen wird von der pharmazeutischen Industrie finanziert. Die Studie erfolgt aus rein wissenschaftlichem Interesse.

1

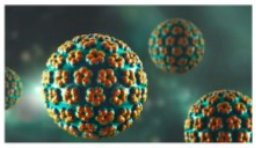

OP Programm an unserer Klinik
Mo 06.05. | NN, 30a, P0 | IB2 (neu) | SNB/ICG + Kryokon-servierung Ovar
Di 07.05. | NN 30a, PO<br>NN 47a<br>NN 35a | Rez. CIN III, Z.n. Konisation<br>CIN III<br>CIN III | Rekonisation<br>Konisation<br>Konisation
Mi 08.05. | NN 25a<br>NN 22a<br>NN 51a<br>NN 40a | CIN II/III<br>CIN III<br>VIN III<br>Condylomata | Konisation<br>Konisation<br>Laserung<br>Laserung
Do 09.05. | NN 38a<br>NN 34a | Persist. abnormaler Pap; HPV+<br>CIN III | Konisation (Messer)<br>Konisation
Fr 10.05. | NN 86a<br><br>Ambulanz: PT 40a | Vulvakarzinom T2<br><br>neuerl. Pap III, HPV+, Z.n. 2x Koni | Weite Exzision, SNB beide Leisten<br>HE besprechen

2

1

# Humane Papillomaviren (HPV)

- Unbehüllte DNA Viren
- Mehr als 200 Subtypen
- Haut und Schleimhäute
- Low Risk: 6, 11, 42 …. → Haut- und Anogenitalwarzen
- High Risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59→ sicher krebserregend



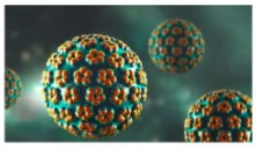
3


Papillomavirus Infections and Human Genital Cancer

Nobelpreisgewinner 2008:
<u>für seine Entdeckung der Auslösung von Gebärmutterhalskrebs durch humane Papillomviren</u>

4

## Wer ist gefährdet?



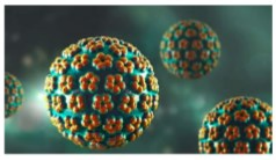
- ♂ > ♀
- ♂: High Risk Typen ca. 30 %, Low Risk Typen ca. 40 %
- ♀ : High Risk Typen ca: 15 %, Low Risk Typen ca. 20 %
- ♀ < 25 Jahre: Prävalenz: 27 – 38%
- Krankheitshäufigkeit Feigwarzen: 5 – 10 %
  - Inzidenz: 170 / 100.000 Einwohner*innen in DE pro Jahr

5

## Wie wird es übertragen?

- Sehr ansteckend

- Sexuelle Übertragung
- Schmierinfektion
  - Handtücher
  - Bei der Geburt von der Mutter auf das Kind



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## Welche Symptome macht die Infektion?

- Oft keine (asymptomatisch)
  - Übertragung trotzdem möglich
- Symptomatisch (Juckreiz):
  - Feigwarzen (Condyloma accuminata) v.a. anogenital und an SH/Haut
  - Gutartige Kehlkopftumore (Larynxpapillome)
  - Krebsvorstufen an Vulva, Anus, Penis, Gebärmutterhals, Rachen, Kehlkopf, Mund
  - Invasiver Krebs derselben Stellen

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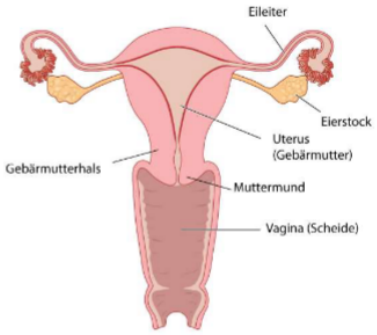
## Um welche Krebsarten geht es im speziellen?

- **Gebärmutterhals**
- Vulva
- Vagina
- Penis
- Anus
- Mund
- Rachen
- Kehlkopf

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## Welche Therapien gibt es?

- Abwartendes Vorgehen, Beobachten
  - Spontanremission in 90% der Fälle
- Medikamentöse Therapien
- Chirurgische Therapien

- Nachsorgekontrolle in engmaschigen Intervallen

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## Gibt es eine Möglichkeit der HPV Infektion vorzubeugen?

Ja, gibt es!

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# Vorbeugung

- HPV-Impfung
- 2-fach, 4-fach und 9-fach zugelassen


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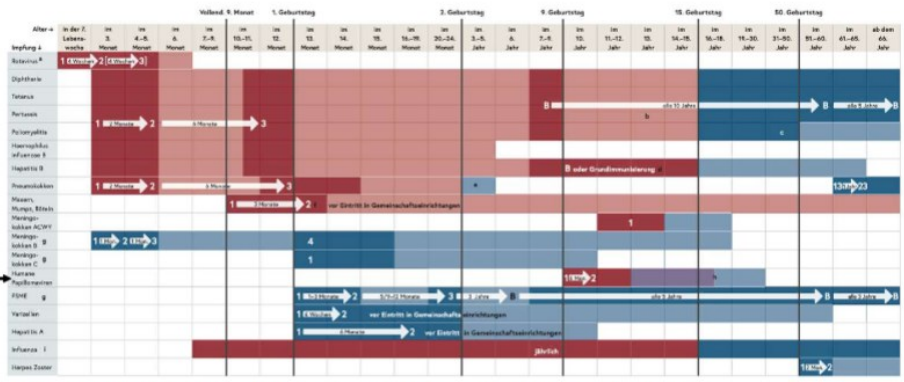
## Impfplan Österreich 2021

Bundesministerium
Soziales, Gesundheit, Pflege
und Konsumentenschutz



https://www.sozialministerium.at/Themen/Gesundheit/Impfen/Impfplan-%C3%96sterreich.html

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## HPV-Impfung

- Vorzugsweise zwischen 9 und 14 Jahren
- Idealerweise **VOR** dem ersten Geschlechtsverkehr
- Grundimmunisierung
  - Alter 9–14 Jahre: 2 Impfdosen im Abstand von 5–12 Monaten
  - Alter ≥15 Jahre: Immer 3 Impfdosen
    - 1. Impfdosis Tag 0
    - 2. Impfdosis im Mindestabstand von 1 Monat zur 1. Impfdosis
    - 3. Impfdosis 4–12 Monate nach der 1. Impfdosis
  - Nach 15. Lebensjahr: empfohlen nachzuholen
- Derzeit keine Auffrischung empfohlen

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## HPV Impfung

- "Gardasil 9" deckt 90 % der HPV-Typen ab, die Krebs am Gebärmutterhals verursachen
- Außerdem teilweiser Schutz vor anderen Krebsarten der Vulva, Vagina, Anus, Penis, Mund, Rachen, Kehlkopf
- 90 % Schutz vor Feigwarzen

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## Impfung in Österreich

- Im kostenfreien Impfprogramm enthalten und empfohlen[1]
  - 9.-12. Lebensjahr: 2 x kostenlos
  - 12.-15. Lebensjahr: Catch-up Impfungen: 2 x 55 €
- Älter als 15: 3 x 205 €
- Durchimpfungsrate in Österreich:
  - Keine offizielle Statistik
  - Geschätzt bei ca. 30 %[2]

1. https://www.sozialministerium.at/Themen/Gesundheit/Impfen/Impfplan-%C3%96sterreich.html
2. https://www.springermedizin.at/innere-medizin/onkologie-und-haematologie/optimierungsbedarf-bei-hpv-impfrate-in-oesterreich/18416958

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## WHO: Eliminierung von Gebärmutterhalskrebs

- November 2020
- Weltgesundheitsorganisation beschließt das erste weltweite Ziel, einen Krebs zu eliminieren, 3 Ziele:
  - 70% aller Frauen erhalten ein Screening mit 35 und 45 Jahren
  - 90% aller Frauen mit Vorstufen und Krebs erhalten eine Therapie
  - 90 % Durchimpfungsrate aller Mädchen bis zum 15. LBJ
- **Beispiel Australien**

1. https://www.who.int/health-topics/cervical-cancer#tab=tab_2
2. https://www.who.int/publications/i/item/9789240014107

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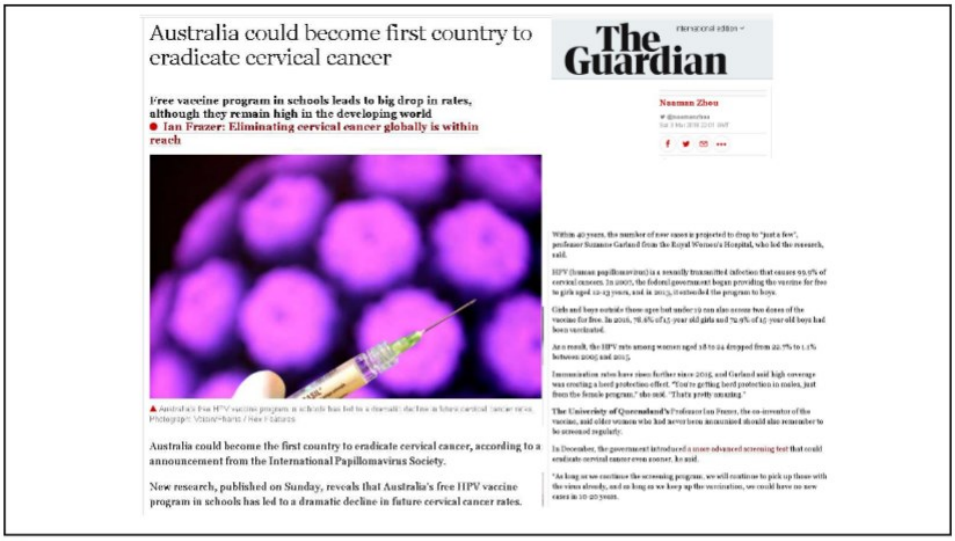

Australia could become first country to eradicate cervical cancer

The Guardian

**Free vaccine program in schools leads to big drop in rates, although they remain high in the developing world**

**Ian Frazer: Eliminating cervical cancer globally is within reach**

Australia could become the first country to eradicate cervical cancer, according to a announcement from the International Papillomavirus Society.

New research, published on Sunday, reveals that Australia's free HPV vaccine program in schools has led to a dramatic decline in future cervical cancer rates.

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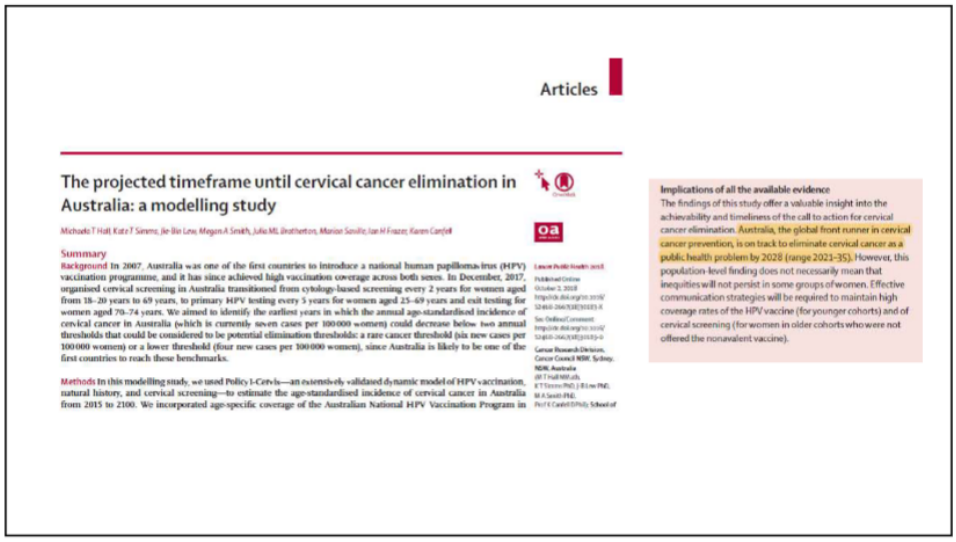

Articles

The projected timeframe until cervical cancer elimination in Australia: a modelling study

Michaela T Hall, Kate T Simms, Jie-Bin Lew, Megan A Smith, Julia ML Brotherton, Marion Saville, Ian H Frazer, Karen Canfell

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Summary

Background In 2007, Australia was one of the first countries to introduce a national human papillomavirus (HPV) vaccination programme, and it has since achieved high vaccination coverage across both sexes. In December, 2017, organised cervical screening in Australia transitioned from cytology-based screening every 2 years for women aged from 18–20 years to 69 years, to primary HPV testing every 5 years for women aged 25–69 years and exit testing for women aged 70–74 years. We aimed to identify the earliest years in which the annual age-standardised incidence of cervical cancer in Australia (which is currently seven cases per 100 000 women) could decrease below two annual thresholds that could be considered to be potential elimination thresholds: a rare cancer threshold (six new cases per 100 000 women) or a lower threshold (four new cases per 100 000 women), since Australia is likely to be one of the first countries to reach these benchmarks.

Methods In this modelling study, we used Policy1-Cervix—an extensively validated dynamic model of HPV vaccination, natural history, and cervical screening—to estimate the age-standardised incidence of cervical cancer in Australia from 2015 to 2100. We incorporated age-specific coverage of the Australian National HPV Vaccination Program in

Lancet Public Health 2018

Published Online October 2, 2018 https://doi.org/10.1016/S2468-2667(18)30183-X

See Online/Comment https://doi.org/10.1016/S2468-2667(18)30189-0

Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia (M T Hall MM, K T Simms PhD, J-B Lew PhD, M A Smith PhD, Prof K Canfell DPhil); School of

**Implications of all the available evidence**

The findings of this study offer a valuable insight into the achievability and timeliness of the call to action for cervical cancer elimination. Australia, the global front runner in cervical cancer prevention, is on track to eliminate cervical cancer as a public health problem by 2028 (range 2021–35). However, this population-level finding does not necessarily mean that inequities will not persist in some groups of women. Effective communication strategies will be required to maintain high coverage rates of the HPV vaccine (for younger cohorts) and of cervical screening (for women in older cohorts who were not offered the nonavalent vaccine).

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# Zukunftsziele

- Der Gebärmutterhalskrebs (und andere HPV-assoziierte Krebsvorstufen und -arten) können/werden/sollen **verschwinden**.
- **Primärprävention: Impfung, Impfung, Impfung**
  - Aufklärung, Aufklärung, Aufklärung
- Austria ≠ Australia
- Sekundäre Prävention
  - HPV-basiertes Screening besser als Pap
  - HPV-Test bei Frauen* >30a
- Hoffentlich schaut unser OP-Programm 2028 anders aus!

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**Take Home Message:**
**Man kann sich gegen bestimmte Krebsarten impfen!**

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## Quellen


- Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK). Impfplan Österreich 2021. Wien; 2021. 184 S.
- HPV-Impfung ist äußerst sicher und schützt vor fünf Krebsarten [Internet]. Comprehensive Cancer Center Vienna. [zitiert 16. April 2021]. Verfügbar unter: https://www.ccc.ac.at/news/singleview/hpv-impfung-ist-aeusserst-sicher-und-schuetzt-vor-fuenfkrebsarten/d4c3f62313d80926cf3ae1773977820f/?tx_ttnews%5Bpointer%5D=18
- https://next.amboss.com/de/article/ZO0ZIT#Zf1c75a14f0d2006dde0085448974961a


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