Hauptverband der österreichischen Sozialversicherungsträger

HPV VACCINATION AFTER TREATMENT FOR HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA

HPV-IMPFUNG NACH BEHANDLUNG HOCHGRADIGER INTRAEPITHELIALER ZERVIKALER NEOPLASIEN

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ZUSAMMENFASSUNG

Zielsetzung

Der Bericht hat zum Ziel, die Wirksamkeit und Sicherheit der Impfung gegen Humane Papillomaviren (HPV) bei Frauen bis zum 45. Lebensjahr nach einer chirurgischen Behandlung wegen hochgradigen zervikalen intraepithelialen Dysplasien oder in situ Karzinomen zu untersuchen. Im Besonderen interessiert die Frage, ob eine HPV-Impfung im Vergleich zu keiner Impfung nach Konisation wirksam und sicher ist in der Prävention hinsichtlich des Wiederauftretens von zervikalen Dysplasien.

Einleitung

Indikation und Therapie

Hochgradige zervikale intraepitheliale Dysplasien (HSIL bzw. CIN 2-3) sind als Vorläufer des Zervixkarzinoms anzusehen und sind um ein Vielfaches häufiger als ein Karzinom [1]. Die Behandlung von Präkanzerosen der Zervix erfolgt in Österreich mittels Konisation, einem Exzisionsverfahren. Dafür stehen mehrere Operationstechniken, nämlich die Schlingenexzision, Laserexzision oder Messerexzision zur Verfügung. A0002

In 99,7% aller invasiven Zervixkarzinome können Humane Papillomaviren nachgewiesen werden [2]. Ein kausaler Zusammenhang zwischen einer persistierenden Infektion insbesondere mit onkogenen Hochrisiko (hr)-HPV-Typen und der Entwicklung eines Zervixkarzinoms wurde wissenschaftlich belegt [3]. Wechselnde Sexualpartner oder sexueller Kontakt mit einem Partner, der eine höhere Anzahl von Sexualpartnern hatte bzw. hat erhöht die Wahrscheinlichkeit für eine HPV-Infektion. Rauchen, orale Kontrazeptiva sowie andere Faktoren werden als weitere Risikofaktoren für eine Zervix-Karzinomentstehung bei einer HPV-Infektion diskutiert [4]. A0003

HPV-Infektionen können persistieren und zu präkanzerogenen Vorstufen führen, die sich zu einem invasiven Zervixkarzinom weiterentwickeln. In ca. 80% der Fälle ist eine HPV-Infektion jedoch transient und heilt innerhalb von drei Jahren spontan ohne Symptome wieder ab [5, 6]. Der Spontanverlauf von hochgradigen zervikalen intraepithelialen Dysplasien ist kaum vorherzusagen und durch histopathologische Untersuchungen kann nicht zwischen Läsionen unterschieden werden, die sich zurückbilden oder fortschreiten. Basierend auf Daten aus den 1990er Jahren bilden sich 60% der CIN 1 Läsionen zurück, während 30% persistieren und 10% zu einer CIN 3 Läsion progredieren. CIN 2 Läsionen bilden sich zu jeweils 40% zurück beziehungsweise persistieren, während sich 20% zu einer CIN 3 Läsion weiterentwickeln. Eine CIN 3 Läsion regrediert in 33%, während mehr als 12% zu einem invasiven Zervixkarzinom fortschreiten [7]. A0004

Zielpopulation dieses Berichts sind Frauen bis zum 45. Lebensjahr mit hochgradigen zervikalen intraepithelialen Neoplasien nach chirurgischer Entfernung (Konisation) und dem Risiko des Wiederauftretens von hochgradigen Dysplasien. A0007

Anders als im US-amerikanischen Kontext wird in Österreich wie auch in anderen europäischen Ländern CIN 2 nicht zu den sofort therapiebedürftigen zervikalen Läsionen gezählt [1, 8]. Schlingenexzision und Laserexzision stellen die Methoden der Wahl für die Behandlung der squamösen und glandulären zervikalen intraepithelialen Neoplasie dar [1]. In der Nachbetreuung nach Therapie einer CIN oder eines Adenokarzinoms in situ wird eine kombinierte Untersuchung mit HPV-Test und Zytologie empfohlen [1]. A0025

Beschreibung der Technologie

Die zugelassenen HPV-Impfstoffe basieren auf „virus-like particles“ (VLP), die keine virale DNA enthalten, somit keine Infektion verursachen, jedoch das Immunsystem zur Bildung spezifischer Antikörper stimulieren können. Der Vierfachimpfstoff wurde im September 2006 von der EMA für die Staaten der EU zugelassen [9]. Die Impfung wird angewendet, um Erkrankungen, die durch HPV der Typen 6, 11, 16 und 18 hervorgerufen werden, zu verhindern. Die Impfung ist nicht zur Behandlung von HPV-bedingten Erkrankungen geeignet. Besteht zum Zeitpunkt der Impfung bereits eine Infektion oder Erkrankung, verursacht durch einen oder mehrere HPV-Typen, vor

dem/denen der Impfstoff schützen soll, wirkt der Impfstoff gegen diesen/diese HPV-Typen nicht. Allerdings schützt die Impfung in solchen Fällen vor Infektionen und Erkrankungen, verursacht durch die HPV-Typen, mit denen man noch nicht infiziert ist und gegen die der Impfstoff gerichtet ist [10]. B0002

Die in diesem Bericht untersuchte Indikation ist die Impfung von Frauen mit dem Vierfachimpfstoff nach Konisation wegen hochgradiger zervikaler intraepithelialer Neoplasien im Vergleich zur herkömmlichen Behandlung und Nachsorge ohne Impfung. B0001

Methoden

Die Auswahl der Fragen (Assessment elements) in den einzelnen Kapiteln (Domains) erfolgte auf Basis des EUnetHTA Core Model® für Rapid Relative Effectiveness (REA) Assessments.

Es erfolgte eine systematische Literatursuche im Juli 2017 und Februar 2019 in dem Cochrane Central Register of Controlled Trials, der Database of Abstracts of Reviews of Effects, der Health Technology Assessment Database, NHS Economic Evaluation Database, in MEDLINE und EMBASE sowie eine Suche in Referenzen der inkludierten Publikationen. Das Bias Risiko der inkludierten nicht randomisierten kontrollierten Studie wurde mit dem ROBINS-I assessment Tool ermittelt [11]. Die Literaturauswahl wurde von den beiden Autorinnen unabhängig voneinander durchgeführt.

PICO Frage

Kann die Immunisierung mittels HPV-Impfung im Vergleich zu keiner HPV-Impfung nach Konisation die Rate wiederkehrender zervikaler intraepithelialer Dysplasien reduzieren? Weitere Endpunkte waren die krebsspezifische Mortalität und unerwünschte Ereignisse im Zusammenhang mit der Impfung.

Die Details zur Methodik werden im Appendix 1 ausführlich dargelegt.

Ergebnisse

Verfügbare Evidenz

Eine prospektive nicht-randomisierte kontrollierte Studie [12] und eine randomisierte kontrollierte Studie [13] wurden in die Domäne zur Wirksamkeit und Sicherheit eingeschlossen. Eine retrospektive Analyse [14] wurden zusätzlich in die Domäne zur Sicherheit inkludiert. Drei retrospektive Analysen [15-17] wurden exkludiert, da die HPV-Impfung bereits vor dem Auftreten der hochgradigen intraepithelialen Dysplasien verabreicht wurde und nur junge erwachsene Frauen bis 26 Jahren inkludiert wurden.

Klinische Wirksamkeit

Es liegt keine Evidenz zum Nutzen der Intervention auf die Gesamt-und krankheitsspezifische Mortalität vor. D0001, D0002

In die nicht-randomisierte kontrollierte Studie [12] wurden Frauen zwischen 18 und 45 Jahren eingeschlossen. Es fand sich sechs Monate nach der operativen Entfernung der hochgradigen zervikalen intraepithelialen Dysplasien kein statistisch signifikanter Unterschied in Bezug auf den HPV-Status zwischen der geimpften und nicht geimpften Gruppe. Zu einem Wiederauftreten von hochgradigen zervikalen intraepithelialen Dysplasien kam es innerhalb von 3 Jahren bei 11 Frauen (6,4%) in der nicht geimpften Gruppe, in der geimpften Gruppe waren es 2 Fälle (1,2%). Die Impfung mit dem Vierfachimpfstoff war mit einem statistisch signifikant reduzierten Risiko um 81,2% (95% CI, 34,3-95,7) für wiederauftretende hochgradige zervikale intraepitheliale Dysplasien nach Konisation assoziiert.

In die randomisierte kontrollierte Studie [13] wurden 178 Frauen unter 45 Jahren eingeschlossen, 3 Monate nach Behandlung einer zervikalen intraepithelialen Dysplasie wenn ein negativer HPV-Test, eine negative Zytologie und Kolposkopie vorlag. 30 von 178 Frauen wurden wegen einer niedriggradigen zervikalen intraepithelialen Dysplasie (LSIL) behandelt, 148 erhielten eine Konisation wegen einer hochgradigen zervikalen intraepithelialen Dysplasie. Frauen wurden in 2 Gruppen randomisiert, 1 Gruppe erhielt die HPV-Impfung mit dem Vierfachimpfstoff, die andere

Gruppe wurde nur beobachtet. Nachuntersuchungen erfolgten alle 6 Monate über einen Zeitraum von 3 Jahren. Mittels Kaplan-Meier-Kurven wurde das krankheitsfreie Überleben während des Nachbeobachtungszeitraums gemessen. Bei 12 von 89 (13,5%) Patientinnen in der nicht geimpften Gruppe kam es zu einem Wiederauftreten von 3 vulvovaginalen und 5 zervikalen niedriggradigen intraepithelialen Dysplasien und 4 hochgradigen zervikalen intraepithelialen Dysplasien. In der geimpften Gruppe kam es zu 3 (3,4%) niedriggradigen zervikalen intraepithelialen Dysplasie (LSIL). Die Kaplan-Meier-Kurven zeigten einen statistisch signifikanten Unterschied im krankheitsfreien Überleben während des Nachbeobachtungszeitraums zugunsten der geimpften Gruppe. Die relative Risikoreduktion beträgt 75% (95% KI, 14,4-92,7) für wiederauftretende zervikale, vaginale oder vulväre intraepitheliale Neoplasien. D0006

Sicherheit

Keine der drei inkludierten Studien berichten über Nebenwirkungen der Impfung. Es liegt daher anhand dieser Studien keine Evidenz zur Sicherheit der Impfung bei Frauen nach Konisation wegen hochgradigen zervikalen intraepithelialen Neoplasien vor. C0008

Diskussion

Inkludiert wurden zwei Studien, eine randomisierte klinische Studie [13] und eine prospektive nicht-randomisierte Beobachtungsstudie [12]. In dieser Beobachtungsstudie könnte die Selbstselektion der Frauen in die jeweilige Gruppe ein Fehlerpotential darstellen, ebenso wie die fehlende Verblindung und die hohe lost to follow-up Rate von 33%, die allerdings in beiden Gruppen auftrat. In den RCT wurden 30 von 178 (17%) wegen einer niedriggradigen zervikalen intraepithelialen Dysplasie behandelt und inkludiert, unklar bleibt, ob in diesen Fällen eine Konisation durchgeführt wurde. In der Gruppe der geimpften Frauen trat keine hochgradige intraepitheliale Dysplasie auf, sondern nur LSIL. In der Gruppe ohne Impfung traten 4 hochgradige intraepitheliale Dysplasien auf sowie 8 LSIL. Die teilnehmenden Frauen waren nicht verblindet.

Bei Frauen bis zum 45. Lebensjahr führt die HPV-Impfung mit dem Vierfachimpfstoff nach Konisation wegen hochgradigen zervikalen intraepithelialen Neoplasien in beiden prospektiven Studien zu einer Risikoreduktion von nachfolgenden hochgradigen zervikalen intraepithelialen Dysplasien. Die Ergebnisse sind konsistent mit retrospektiven Studien [14-17], wobei in drei der Analysen [15-17] die HPV-Impfung bereits vor dem Auftreten der hochgradigen intraepithelialen Dysplasien verabreicht wurde und nur junge erwachsene Frauen bis maximal 26 Jahren inkludiert wurden.

Da die Impfung nicht gegen eine bereits bestehende Infektion, verursacht durch einen oder mehreren im Impfstoff enthaltenen HPV-Typen wirkt, sprechen diese Daten für eine hohe Neu- oder Wiederinfektionsrate bei Frauen, die vor der Konisation keine effiziente Immunität generieren konnten und damit von der Impfung profitieren.

Langzeitdaten aus anderen Studien zur Sicherheit der quadrivalenten HPV-Impfung bei erwachsenen Frauen zeigten keine schwerwiegenden unerwünschten Ereignisse [18, 19]. Es traten zwar mehr Todesfälle in der geimpften Gruppe auf, allerdings wurden die Todesfälle von den Studienautoren als nicht kausal mit der Impfung erachtet. Langzeitdaten des bivalenten Impfstoffs bei Frauen älter als 25 Jahre zeigten eine Imbalance von Todesfällen in der geimpften Gruppe. Es konnte jedoch kein Zusammenhang zwischen den Todesfällen und der Impfung identifiziert werden [20, 21]. Schwere unerwünschte Ereignisse, die möglicherweise in Zusammenhang mit der Impfung stehen könnten, traten bei 0,2% der Frauen in der geimpften und bei 0,3% der nicht geimpften Gruppe auf [21].

Conclusio

Die Qualität der Evidenz, dass die HPV-Impfung nach Konisation zu einem signifikant geringeren Wiederauftreten von hochgradigen zervikalen intraepithelialen Dysplasien innerhalb von drei Jahren führt, ist moderat. Basierend auf der Beobachtungsstudie [12] müssen 19 (95% KI, 10-87) Frauen geimpft werden, um eine Frau vor einer wiederkehrenden hochgradigen zervikalen intraepithelialen Dysplasie nach Konisation zu schützen. Basierend auf der randomisierten Studie [13] müssen 10 (95% KI, 5-54) Frauen geimpft um eine Frau vor einer wiederkehrenden zervikalen, vaginalen oder vulvären intraepithelialen Neoplasie zu schützen.

Eine multizentrische, plazebo-kontrollierte, randomisierte doppelblinde Studie [22] „Impact on Disease Relapse of HPV Vaccination in Women Treated With LEEP for Cervical Intraepithelial Neoplasia. HOPE9“ startet im Juni 2019. In der Studie wird die Wirksamkeit der 9-valenten HPV-Impfung nach einer chirurgischen Behandlung wegen hochgradigen zervikalen intraepithelialen Neoplasien zur Prävention des Wiederauftretens von hochgradigen zervikalen intraepithelialen Neoplasien untersucht. Es sollen 1220 Frauen eingeschlossen und in einem 1:1 Verhältnis randomisiert werden, die wegen hochgradigen zervikalen intraepithelialen Neoplasien mit einer Schlingenexzision behandelt werden. Diese Frauen erhalten zum Zeitpunkt des Einschlusses in die Studie und noch vor der Behandlung entweder den 9 valenten Impfstoff oder eine Plazebo-Impfung, nach 2 Monaten zum Zeitpunkt der Operation und nach 6 Monaten zum Zeitpunkt der ersten Nachuntersuchung. Ergebnisse sind 2027 zu erwarten.

SUMMARY

Scope

The objective of this rapid assessment was to evaluate the effectiveness and safety of HPV (Human Papilloma Virus) vaccines in previously not HPV vaccinated women after surgical treatment for high-grade squamous intraepithelial lesion (HSIL) or carcinoma in situ (CIS). Specifically, we addressed the research question whether the quadrivalent HPV vaccine is effective and safe in preventing recurrence of high-grade cervical intraepithelial neoplasia compared to usual care without HPV vaccination.

The scope can be found here: Scope.

Introduction

Health problem

High-grade squamous intraepithelial lesions or high-grade cervical intraepithelial neoplasias (CIN 2-3) are considered the precursors of cervical cancer. CIN 2-3 bears a risk of developing invasive carcinoma if left untreated. Therefore, the recommended therapy for high-grade CIN lesions is surgical excision of parts of the cervix, which is usually done by conization or ablative treatment to eliminate CIN and associated HPV infection. A0002

A persistent infection with oncogenic HPV is the single most important factor in the pathogenesis of cervical cancer and precancerous lesions of the cervix. A0003

The natural history of high-grade CIN is largely unpredictable and current histopathological examination is unable to differentiate between lesions that will regress and those that will not. More than 12% of high-grade cervical intraepithelial neoplasia will progress into invasive cervical cancer and the likelihood of CIN 3 regressing is 33%. A0004

In the scope of this assessment are women with high-grade cervical intraepithelial neoplasia or microinvasive cervical cancer after surgical treatment and at future risk for developing cervical cancer. A0007

Description of technology

The quadrivalent HPV vaccine protects against infections with one or more of four types of the human papillomavirus (types 6, 11, 16 and 18) and thus may prevent from HPV-associated diseases like precancerous lesions in the cervix, vulva or vagina and anus, cervical and anal cancers, and genital warts. Quadrivalent HPV vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. B0002

In this assessment, the intended use of the HPV vaccine is in women with HSIL treated with surgical excision of the cervix. The comparator is usual care of HSIL without vaccination. B0001

Methods

The selection of assessment elements is based on the EUnetHTA Core Model® Application for Rapid Relative Effectiveness (REA) Assessments. For the effectiveness and safety domain, a systematic literature search was performed in July 2017 and in February 2019 according to the Cochrane methodology in standard medical and HTA databases (The Cochrane Central Register of Controlled Trials, The Database of Abstracts of Reviews of Effects, The Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE, and EMBASE).

Two researchers assessed the risk of bias of the included prospective studies independently. The Cochrane risk of bias assessment approach was used on study level and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool (version for cohort-type studies) [11]. Two authors screened the literature independently, inconsistency was solved in discussion. After risk of bias assessment the results were presented according to the proposed endpoints.

Results

Available evidence

One prospective controlled non-randomized study [12] and one RCT [13] were included for the efficacy and safety domain. In addition, one retrospective analysis [14] was included for the safety domain.

Clinical effectiveness

No evidence was found on the expected benefit of the intervention on overall mortality and disease-specific mortality. D0001, D0002

In the observational study six months after surgery and vaccination, HPV positivity status showed no statistically significant difference between the vaccinated and non-vaccinated group. Women with persistent disease defined as histologically confirmed CIN 2+ disease at 6 months after therapy were excluded from the study, because prophylactic vaccines are ineffective at clearing pre-existing infections and associated pre-invasive lesions. High-grade lesions occurred in 11 cases (6.4%) of the unvaccinated women and two cases (1.2%) in the vaccinated group for the median follow-up time of 36 months. Vaccination of women after treatment for high-grade lesions was associated with a statistically significant risk reduction of 81.2% (95% CI, 34.3–95.7) for developing high-grade CIN.

The randomised controlled trial included as well women with low-grade intraepithelial neoplasia (17%) as high-grade lesions. Women with negative HPV test, cytology and colposcopy 3 months after treatment were enrolled. Women were not blinded and therefore aware of being selected for either of the two different groups. The primary endpoint was to evaluate whether the vaccine was effective in reducing recurrent disease by the comparison of the overall disease-free survival. In the V-group 3 out of 89 (3.4%) women developed recurrence during the follow-up period. All recurrences were low-grade cervical squamous intraepithelial lesions. In the NV-group 12 (13.5%) developed recurrence, three vulvovaginal and five cervical low-grade intraepithelial lesions. High-grade lesions occurred in 4 out of 89 (4.5%) women. Vaccination was associated with a relative risk reduction of 75% for developing any CIN. D0006

Safety

No evidence was found regarding safety of the application of HPV vaccines to women treated for high-grade lesions. C0008

Discussion

One study is a prospective non-randomised observational study. The self-selection of women to the intervention group carries a possible risk of bias in favour of the intervention. Neither the patients nor the medical personnel, who performed the colposcopy and Pap test, were blinded to the group assignment. In addition, the high lost to follow-up rate of 33% bears a risk of bias, although the high lost to follow up rate occurred in both groups. The second study is a single blinded RCT. The study including women with low and high-grade lesions gives no information about distribution of study subjects according to selected characteristics and treatment group.

Data of long-term follow-up observation of the safety of quadrivalent HPV vaccine in adult women in a preventive setting revealed no new serious adverse events [18, 19]. More deaths occurred in the vaccine group but the investigators deemed no study deaths as related to vaccination. Data of follow-up observations of women older than 25 years vaccinated with the bivalent HPV vaccine showed an unexpected imbalance in the number of deaths in the vaccine group that was probably caused by chance. However, no causal link to the vaccine could be identified [20, 21]. Serious adverse events possibly related to the vaccine occurred in 0.2% of women in the vaccine group and 0.3% in the control group [21].

Conclusion

There is moderate evidence that HPV vaccination in women treated for high-grade cervical cancer lesions reduces the risk of future HPV related high-grade CIN and is more effective than usual

care. Data on long-term effectiveness are lacking. There is insufficient evidence to determine the safety of the HPV vaccine in women treated for high-grade lesions.

One randomized double-blind, placebo-controlled clinical trial in women treated for CIN 2+ with LEEP technique is ongoing comparing nonavalent HPV vaccine with placebo with regard to recurrence of CIN 2+ after conization. However, study results will be available at the earliest in 2027.

LIST OF ABBREVIATIONS

AIS	Endocervical adenocarcinoma in situ
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical squamous cells - cannot exclude HSIL
CI	Konfidenzintervall
CIN (previous nomenclature)	Cervical intraepithelial neoplasia (zervikale intraepitheliale Dysplasie)
SIL (new nomenclature)	Squamous intraepithelial lesion (plattenepitheliale intraepitheliale Dysplasie)
CIS	Carcinoma in situ
DNA	Desoxyribonukleinsäure
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ICD	International Classification of Diseases
HSIL	High-grade squamous intraepithelial lesion (= CIN 2/3)
HPV	Human papillomavirus
hr-HPV	High risk Human papillomavirus
KI	Konfidenzintervall
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low grade squamous intraepithelial lesion (= CIN 1)
NV-group	Not vaccinated group
TBS	Bethesda system
V-group	Patients submitted to quadrivalent HPV vaccine post-surgery
VLP	Virus-like particles
QoL	Quality of life

1 SCOPE

Description	Project scope
Population	*High-grade cervical intraepithelial neoplasia, CIS MeSH-term C13.351.937* *Adult women, not HPV vaccinated* *Women after loop electrosurgical excision procedure or cervical conization, Mesh-term E04*
Intervention	*Immunization with HPV vaccine after intervention for high-grade cervical intraepithelial dysplasia to prevent recurrence of high-grade cervical intraepithelial neoplasia* *MeSH term N02.421.726; E02.095.465*
Comparison	*No HPV Vaccination, Usual care MeSH-term N02.421.726*
Outcomes	*Recurrence of high-grade cervical intraepithelial neoplasia (CIN 2, CIN 3, CIS, cervical carcinoma), cancer specific mortality* *Severe adverse event after vaccination*
Study design	*Effectiveness: RCT, Cohort study plus control group* *Safety: RCT, Cohort study plus control group, if not available retrospective analysis with more than 100 participants, Register study*

2 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
A0002	What is the disease or health condition in the scope of this assessment?	3
A0003	What are the known risk factors for the condition?	3
A0004	What is the natural course of the condition?	3
A0005	What is the burden of disease for the patient?	2
A0006	What is the burden of disease for society?	2
A0007	What is the target population of this assessment?	3
A0023	How many people belong to the target population?	2
A0024	How the health condition is currently diagnosed according to published guidelines and in practice?	3
A0025	How the health condition is currently managed according to published guidelines and in practice?	3

Sources

- Systematic literature search in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA)
- Hand search for guidelines
- Additional non-systematic search in PubMed, Cochrane Library for guidelines and systematic reviews

2.2 Results

Overview of the disease or health condition

A0002

What is the disease or health condition in the scope of this assessment?

A persistent infection with oncogenic human papillomavirus (HPV) is the most important factor in the pathogenesis of cervical cancer and precancerous lesions of the cervix [2, 23]. The average

time interval between infection with a carcinogenic type of HPV and development of cervical cancer is 25 to 30 years [24]. Invasive squamous cell cervical cancers are preceded by a long phase of preinvasive disease. This is characterized microscopically as a spectrum of events progressing from cellular atypia to various grades of dysplasia or cervical intraepithelial neoplasia (CIN) before progression to invasive carcinoma [25]. CIN may be suspected through cytological examination using the Papanicolaou technique, but final diagnosis of CIN is established by the histopathological examination of a cervical punch biopsy or excision specimen. The original CIN terminology of CIN 1, 2 and 3 has been superseded by the modified CIN terminology of low-grade CIN (CIN 1) and high-grade CIN comprising CIN 2 and 3. According to (TBS) cervical cytology results are reported as a two-grade scheme consisting of low-grade (LSIL) and high-grade (HSIL) lesions. Though designed for cytological reporting, TBS is also used to report histopathology findings. In the Bethesda system (TBS), which is used by WHO, LSIL equates to HPV/mild dysplasia/CIN 1 and HSIL to moderate and severe dysplasia, carcinoma in situ/CIN 2 and CIN 3 [26].

CIN 1 is recognized as a histological diagnosis of benign viral replication that should be managed conservatively, whereas CIN 3 is considered recognized as a true pre-invasive precursor with a potential to progress to cancer. [27] The clinical course and biological behavior of CIN 2 is less well understood. Active surveillance is justified in selected women with untreated, histologically confirmed CIN 2 lesions, particularly if they are young and the likelihood of compliance with follow-up is high [27]. Despite evidence on differences in the clinical course of CIN 2 and CIN 3, the 2014 histopathological classification of the World Health Organization defined these lesions as a single entity as high grade squamous intraepithelial lesion (HSIL) [28].

Precursors bear a risk of developing invasive carcinoma if left untreated [29]. The recommended therapy for high-grade lesions is surgical excision of the cervix, which is usually done by conization [30] or ablative treatment to eliminate CIN and associated HPV infection [31, 32].

In the scope of this assessment are women with high-grade cervical intraepithelial neoplasia (CIN 2-3) or microinvasive cervical cancer after surgical treatment still at risk for HPV infection and cervical cancer development.

A0003

What are the known risk factors for the condition?

Infection with human papillomavirus (HPV) is the single most important factor in the pathogenesis of cervical cancer and precancerous lesions of the cervix [2, 23]. A possible contributing role of Epstein-Barr virus (EBV) as a cofactor in human papillomavirus (HPV)-associated cervical carcinogenesis is not well established so far [33, 34]. Epidemiologic studies have identified some factors associated with increased risk of cervical cancer such as use of oral contraceptive, sexual promiscuity and cigarette smoking [35-39].

However, HPV infection alone is not sufficient to cause cervical cancer; persistent hr-HPV infection is strongly and consistently associated with high-grade CIN acquisition and is considered essential to drive progression of cervical neoplasia to invasive cervical cancer [5, 40, 41]. Several studies have suggested that detection of the same carcinogenic HPV type over time is particularly important for cervical carcinogenesis [42, 43]. While HPV persistence is most commonly defined as two or more HPV-DNA positive time points [40, 44-46], other investigators have evaluated HPV persistence using time to clearance (i.e., duration) [47-49] or proportion of HPV-positive visits [40, 50, 51].

A proportion of CIN 2–3 cases remain infected with hr-HPV even after treatment of lesions [52, 53]. Recurrent CIN may result from inadequate treatment of precancerous cervical lesions (i.e., treatment failure), incomplete removal of HPV infections resulting in hr-HPV infection persistence, re-infection with a new hr-HPV type, or persistence of another HPV type not associated with the primary cervical lesion [31, 54-57].

Given the higher sensitivity of HPV testing for CIN 2+ detection compared to cytology [58, 59] follow-up after CIN 2+ treatment should include cytology and hr-HPV-DNA testing at 6 months, for early detection of any patients at increased risk of recurrence and cancer progression [59-61]. Post-treatment HPV persistence estimates vary widely. Patient age, HPV-type, detection method,

treatment method, and minimum HPV post-treatment testing interval influence the estimates [31]. Persistent positivity of HPV-DNA testing is considered a prognostic index of recurrent disease in patients treated for CIN 2 or higher.

Studies have confirmed the heterogeneity of CIN caused by the influence of infection with multiple HPV types. Some of these HPV infections, such as types 6 or 11, have a negligible risk for cervical cancer development, but may persist. In contrast, HPV16 is more frequently found in lesions classified as CIN 2 or higher and empirically persistent HPV 16 infections are associated with a greater risk for development of invasive carcinoma [29, 62].

A0004

What is the natural course of the condition?

The natural course of CIN is influenced by viral and host factors. Prognosis on progression is very uncertain, as currently established diagnostic methods could not differentiate between lesions that will progress and those that will not [63].

Data from the literature indicate a higher likelihood to regress in women with CIN 1 or CIN 2 as compared to women with CIN 3 [7, 29]. Only a small percentage of women with CIN 3 will eventually progress to invasive cervical cancer [63]. A retrospective cohort study from New Zealand, estimated in women with high-grade lesions that were left untreated a progression to invasive cervical cancer of 13 - 21% within 10-30 years [64].

Östor reported the following data on the likelihood for CIN regression, persistence and progression in 1993 [7, 29] (Table 1).

Table 1: Natural History of Squamous Intraepithelial Lesions

	Regression	Persistence	Progression to CIN 3	Progression to invasive Cancer
LSIL (CIN 1)	57%	32%	11%	1%
HSIL (CIN 2)	43%	35%	22%	5%
HSIL (CIN 3)	32%	56%	-	>12%

LSIL: low-grade squamous lesion, HSIL: high-grade squamous lesion, CIN: cervical intraepithelial neoplasia

Effects of the disease or health condition on the individual and society

A0005

What is the burden of disease for the patient?

Histological diagnosis of CIN 2 or worse on a biopsy sample has been considered the cut-off point to proceed to treatment in the United States [32]. According to the German treatment Guidelines women with CIN 2 should receive cervical smear every 3 months. If the lesion is persistent over 12 months cervical conization is recommended [65].

Local excision of the cervix is the preferred treatment of CIN 2 and CIN 3, which has proved to be effective [27, 30]. Several reports have suggested that successful conization also eradicates HPV infection effectively in most women treated for CIN [24, 66, 67]. However, a proportion of women treated for CIN 2–3 remain hr-HPV positive after treatment [52, 53]. Recurrent CIN may result from inadequate treatment of precancerous cervical lesions (i.e., treatment failure), incomplete removal of persistent HPV infections, re-infection with a new hr-HPV type, or persistence of another HPV type not associated with the primary cervical lesion [31, 54, 56, 57]. The persistence of hr-HPV infection at follow-up is a significant predictor of residual or recurrent CIN after conization. Recurrence of high-grade CIN is related to HPV infection after treatment, and persistent HPV16 infection was the most frequent cause for recurrence [24]. A study with 5 and more years of follow-up investigating the long-term success rate of CIN treatment, reported a rate of invasive cancer in women after CIN treatment of 56 per 100,000 treated women throughout the period of follow-up , which is substantially higher compared to the general population [67].

Between 2010 and 2014, the age standardised 5-year net survival of cervical cancer ranged from 54% to 70% in Europe. The average among EU countries has increased from 61% to 63% over the past decade [68-70]. In Austria, the five-year survival rate was 66% in 2009 to 2013 [71] and 8,482 women with cervical cancer were living in 2015 (end of year prevalence).

Treatment of invasive cervical cancer including surgery, radiotherapy and chemotherapy often causes treatment-related side effects disrupting long-term quality of life (QoL). Given the high 5-year survival rate, the issue of QoL plays an essential role for cervical cancer patients. Cervical cancer patients have reported to have worse quality of life scores than the general population but also when compared with other gynaecological cancer survivors [72-76]. Cervical cancer survivors commonly report late effects including bladder dysfunction, bowel dysfunction, sexual dysfunction, lymphedema and psychosocial problems [72, 77-81].

The mortality rate from invasive cervical cancer varies up to 8-fold between different regions of the world. It is less than 2 in 100,000 people in Western Asia, Western Europe, Australia, and New Zealand, but over 20 per 100,000 people in Melanesia, and Middle and Eastern Africa [82, 83].

A0006

What is the burden of disease for the society?

A woman's risk of developing cervical cancer by the age of 65 ranges from 0.69% in developed countries to 1.38% in developing countries [69, 84]. Worldwide, there are approximately half a million cases of cervical cancer annually and 85% of cases occur in low- and middle- income countries.

The OECD reports for the year 2012 an average invasive cervical cancer incidence of 9.7 per 100.000 for the European countries (highest value for Estonia with 19.9 and lowest value for Switzerland with 3.6). For Austria an incidence of 5.8 per 100,000 is reported, which is below the European average. There is a decreasing trend for cervical cancer incidence in all European countries. In Europe, the average cervical cancer incidence rate decreased from 11.1 per 100,000 in the year 1998 to 9.6 per 100,000 in the year 2008 [85].

The incidence of invasive cervical cancer in Austria was 9 out of 100,000 women in 2015, in absolute numbers 395 women. The age-standardised incidence rate decreased within the last decade by about 19%. The highest rates occurred in Styria on average per year for 2013-2015 and the lowest in Upper Austria, respectively [86]. Approximately, halve of all cases of invasive cervical cancer was diagnosed in an early stage, one quarter (26%) could not assigned to a tumour stage due to insufficient data [87].

Cervical cancer accounts for 10% of all female cancers, making it the fourth leading cause of cancer death in women [88, 89]. In Austria, 139 women died of cervical cancer in the year 2015 resulting in an annual mortality rate of 3 per 100,000, which is 1.5% of all cancer deaths in females in Austria. The age-standardized mortality rate was highest in the region Styria and lowest in Vorarlberg [90]. The one-year survival rate was 84% in 2014 to 2016, the five-year survival rate was 66% in 2009 to 2013 [71].

Approximately 2.7 per 1000 women in developed countries are diagnosed as having CIN (1-3) annually, 1.5 per 1000 women as having CIN 2-3 annually and the incidence is highest among women aged between 25 and 29 years, that is, 8.1 per 1000 women [91]. Approximately 23% of patients develop high-grade CIN after conservative treatment due to either residual or recurrent lesions [24, 92]. Applying these numbers to the Austrian female population about 6.700 women are affected by the diagnosis of high-grade lesions annually corresponding very well to the reported 6.633 conizations performed in Austria in 2017 [93].

After conization 4% to 17% of women develop CIN 2 or greater as a result of residual (persistent CIN confirmed on biopsy within two years of follow-up) or recurrent disease (CIN identified after two years of negative cytology) [56, 94-96]. Previous studies have shown that the risk of residual or recurrent disease is consistently associated with large lesion size before treatment, endocervical extension of the disease and incomplete excision of the lesion [97-99]. However, even women with clear excision margins are at risk for disease recurrence [100]. In addition, the

risk of developing invasive cancer after treatment for high-grade CIN is five times higher than in the general population [67, 69, 101].

Compared with other cancers, cervical cancer is diagnosed in patients at a younger age and consequently is likely to result in a high lifetime burden of disease [102]. The treatment of invasive cervical cancer depends on age, performance status and the stage of the cancer. Surgery, radiation, chemotherapy or a combination of the three may be used.

A number of studies reported significant economic burden of the HPV-related cervical dysplasia and invasive cervical cancer [103-106]. Cost estimates varied considerably between studies depending which costs were included, which cut-offs for referral to immediate treatment were used and which perspective was adopted. The total direct costs of cervical cancer treatment in Austria in 2003 have been estimated at € 10,209,349. The average costs per cervical cancer case amounted to € 21,584 [107]. The lifetime direct costs per incident patient with cervical cancer amounted to € 24,276 in Italy [108]. A Belgium study reports an annual cost per patient with cervical cancer of € 9,716 [106].

Target population

A0007

What is the target population of this assessment?

The target population of this assessment are women under 45 years of age after treatment for high-grade cervical lesions or microinvasive cervical cancer at risk for HPV infection.

A0023

How many people belong to the target population?

The target population can only be estimated, because the frequency with which conization procedures are performed depends on the number of suggested or detected cases of CIN and different screening algorithms in different countries. About 6600 women, in whom conizations were performed in 2017, belong to the target population in Austria, irrespective of age. In Germany, the age-standardized rate of conizations vary between 60 to 290 per 100,000 women across different federal states [109].

Current clinical management of the disease or health condition

A0024

How is the health condition currently diagnosed according to published guidelines and in practice?

Organized or opportunistic cervical cancer screening using Pap cytology or HPV-based testing is the current standard to detect cervical cancer precursors. The fundamental goal of screening is to prevent morbidity and mortality from cervical cancer [110]. Cervical cancer screening should begin at age 21 years. Women aged younger than 21 years should not be screened regardless of the age of sexual initiation or other risk factors [110]. Women aged 21 to 29 years should be screened every 3 years with conventional or liquid-based Pap cytology. Women aged 30 to 65 years should be screened either every 5 years with both HPV test and cytology (Co-testing), or every 3 years with cytology alone [111].

The European guidelines suggest a starting age of 25 years [26]. Among women aged 35 years or older, only one primary test (cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening. Systematic co-testing entails higher costs, higher referral rates to colposcopy, and a lower PPV for CIN 2+ detection [112]. HPV-based primary screening has a higher sensitivity and lower specificity than cytology-based screening in detecting precancerous cervical lesions, and no difference in detecting invasive cancer [112]. In Austria, an opportunistic cervical cancer screening using Pap cytology is in place.

A0025

How is the health condition currently managed according to published guidelines and in practice?

Women with a high-grade cytological lesion, a repeated low-grade lesion or with an equivocal cytology result and a positive HPV test should be referred for colposcopy [26].

While distinction between CIN 2 and CIN 3 is difficult in individual cases, regression rates are lower and progression to cancer more common for women with CIN 3 than for those with CIN 2 [7, 113]. Women with unambiguous CIN 3 have the immediate precursor to invasive cancer and should not be observed, regardless of age or concerns about future fertility. Diagnostic excisional procedure is recommended for women with recurrent CIN 2, CIN 3, or CIN 2/3.

After treatment, co-testing with HPV and cytology at 12 months and 24 months is recommended for women treated for CIN 2, CIN 3, or CIN 2/3. If both co-tests are negative, co-testing in 3 years is recommended. If both tests are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age [32].

After conization, the Austrian guidelines [8] recommend co-testing with HPV and cytology at 6 months. If co-testing is positive, further hr-HPV testing at 12 months is recommended. If both tests are negative, routine screening is recommended.

Follow-up after local treatment for CIN is mandatory, because of the late occurrence of cervical cancer over a period of 20 years [67, 69, 92]. To prevent cervical cancer, early detection of treatment failure is important. It has been suggested that persistence of hr-HPV represents an independent risk factor for recurrent disease and constitutes the basis for introducing hr-HPV testing in patients treated for high-grade CIN [69, 114, 115].

Currently, guidelines do not recommend HPV vaccination after treatment for CIN.

2.3 Discussion

Infection with human papillomavirus (HPV) is the single most important factor in the pathogenesis of cervical cancer and precancerous lesions of the cervix [2, 23]. High-grade squamous intraepithelial lesions (HSIL) or high-grade cervical intraepithelial neoplasias (CIN 2-3) are considered the precursors of invasive cervical cancer. The recommended therapy for high-grade CIN lesions is surgical excision of the cervix, which is usually done by conization to eliminate high-grade CIN and associated HPV infection [30-32].

However, a proportion of treated women remain infected with hr-HPV after treatment or acquire HPV infection in the future [52, 53], bearing the risk of developing invasive cervical cancer in the future. Recurrent CIN may result from inadequate treatment of precancerous cervical lesions (i.e., treatment failure), incomplete removal of HPV infections resulting in hr-HPV infection persistence, re-infection with a new hr-HPV type, or persistence of another HPV type not associated with the primary cervical lesion [31, 54-57].

The risk of developing invasive cancer after treatment for high-grade CIN is five times higher than for women in the general population [67, 69, 101]. After treatment, co-testing at 12 months and 24 months is recommended, but no current evidence from RCTs exists to guide optimal follow-up [69].

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

3.1 Methods

Domain framing

Research questions

Element ID	Research question	Importance 3= critical 2= important 1=optional
B0001	What is the technology and the comparator(s)?	2
B0002	What is the approved indication and claimed benefit of the technology and the comparator(s)?	2
B0003	What is the phase of development and implementation of the technology and the comparator(s)?	2
B0004	Who performs or administers the technology and the comparator(s)?	2
A0020	What is the marketing authorisation status of the technology/the comparator?	1
A0021	What is the reimbursement status of the technology/comparator?	1

Sources

- Systematic literature search in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA)
- Additional search: FDA, EMA

3.2 Results

Features of the technology and comparators

B0001

What is the technology and the comparator(s)?

Three different vaccines, which vary according to the number of HPV types they contain and target, have been developed. Bivalent vaccine targets HPV types 16 and 18 [116]. Quadrivalent HPV vaccine protects against conditions caused by four types of the human papillomavirus (types 6, 11, 16 and 18). The quadrivalent HPV vaccine was originally approved by the Food and Drug Administration (FDA) in 2006 to prevent cancers and diseases associated with four strains of HPV [117]. In 2014, HPV vaccine covering an additional five strains was approved. In 2018 the FDA approved the use of the nonavalent HPV vaccine in individuals between the ages of 27 and 45.

The European Commission granted a marketing authorisation valid throughout the European Union for the nonavalent HPV vaccine in 2015 [118, 119].

The intended use of the HPV vaccine is in women up to 45 years treated for high-grade cervical lesions using surgical excision of the cervix. Both studies included in the review used the quadrivalent HPV vaccine. The comparator is usual care for women after treatment. Usual care includes slightly different surveillance strategies involving co-testing with HPV and cytology.

B0002

What is the approved indication and claimed benefit of the technology and the comparator(s)?

Quadrivalent HPV vaccine is for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types, and genital warts (condyloma acuminata) causally related to specific HPV types. like precancerous lesions in the cervix, vulva or vagina and anus, cervical and anal cancers, and genital warts [9]. Quadrivalent HPV vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine does not prevent lesions due to a vaccine HPV type in individuals infected with that HPV type at the time of vaccination [10].

The optimal time for HPV immunization is prior to the individual's sexual debut. Among women aged 15 to 26 years, HPV vaccines reduce the risk of cervical precancer associated with HPV16/18 from 341 to 157 per 10,000. HPV vaccination reduced also the risk for any precancer lesions from 559 to 391 per 10,000 [120]. None of the studies has followed up participants for long enough to detect an effect on cervical cancer. In women vaccinated at 24 to 45 years of age, there is moderate-certainty evidence that the risks of high-grade cervical intraepithelial neoplasia associated with HPV16/18 and any high-grade cervical intraepithelial neoplasia are similar between vaccinated and unvaccinated women.

B0003

What is the phase of development and implementation of the technology and the comparator(s)?

The use of HPV vaccination to prevent future development of CIN 2+ or microinvasive cervical cancer after surgical treatment is an experimental approach, so far.

B0004

Who performs or administers the technology and the comparator(s)?

Medical personnel administer the HPV vaccination mainly in the outpatient sector.

Regulatory & reimbursement status

A0020

What is the marketing authorisation status of the technology/the comparator?

The HPV vaccine (covering four or nine strains) has a marketing authorisation for women as of age 9 up to age 45 years.

A0021

What is the reimbursement status of the technology/comparator?

The primary target group for routine vaccination is girls at an age before debut of sexual activity, usually 12 to 13 years, in some countries as young as 9 years old. Many countries have catch-up programs for girls at older ages between 14 and 20 years.

In Austria, the HPV vaccine is not reimbursed on a regular base in adults apart from the national vaccination program of children and adolescents.

3.3 Discussion

Although vaccination is not effective in patients with prevalent HPV infection, data suggest that vaccination in women who underwent conization after CIN 2+ diagnosis, could impact on future disease recurrence [15]. The protective role of HPV vaccine in women with a prevalent HPV infection is still not fully understood [12]. Two pathways are hypothesized; first, vaccination may provide protection against new HPV infection for patients not previously exposed to HPV vaccine types, and second, HPV vaccine may prevent loss of the immunological effectiveness, when the immune system is not effective to provide a long-lasting protection, which would lead to the development of HPV-related relapse in women without vaccination.

4 CLINICAL EFFECTIVENESS

4.1 Methods

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
D0001	What is the effect of the intervention on the overall mortality	2
D0002	What is the expected beneficial effect on the disease-specific mortality?	2
D0006	How does the technology affect progression of disease?	3

Sources

A systematic literature search was performed in July 2017 and February 2019 in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA) according to the predefined search strategy. References were included or excluded according to the overall research question, Population-Intervention-Control-Outcome (PICO)-scheme (as described in Scope), and the predefined inclusion/exclusion criteria. Details on search strategy can be found in Appendix 1.

Analysis

We retrieved information from two prospective studies. Quality assessment was performed using ROBINS-I tool risk of bias in non-randomised studies of interventions [11] and risk of bias at study level.

Synthesis

Research questions were answered in plain text format.

4.2 Results

Included studies

Two studies, one non-randomised controlled trial [12] and one randomized controlled trial [13] reported clinical effectiveness data of HPV vaccination in women aged 18–45 years treated with conization for high-grade squamous intraepithelial lesions. The follow-up time varied from 3 to 4 years. Both studies had risks of bias mainly due to lack of blinding. One study [12] included 536 women treated with conization for high-grade squamous intraepithelial lesions, and one study included 178 women of whom 148 received a treatment of conization, 30 were treated for low-grade squamous intraepithelial lesions.

Mortality

D0001

What is the expected beneficial effect of the intervention on overall mortality?

No evidence was found to answer the research question.

D0002

What is the expected beneficial effect on the disease-specific mortality?

No evidence was found to answer the research question.

Morbidity

D0006

How does the technology affect progression of disease?

One study [12] reported no statistically significant difference in relation to the HPV status between the non-vaccinated group (NV-group) and the vaccinated group (V-group) six months after conization. The other study [13] included only HPV negative women 3 months after the treatment, but only 148 women received a treatment of conization, 30 were treated for low-grade squamous intraepithelial lesions but further details are lacking.

Recurrent HSIL was observed in 6.4% of the NV-group and in 1.2% of the V-group within the median follow-up time of 36 months. HPV vaccination after conization was associated with a statistically significant risk reduction of 81.2% (95% CI, 34.3–95.7) for developing HPV related HSIL after cervical surgery [12].

The other study [13] reported recurrent disease in 13.5% in the NV-group, of this 4.5% HSIL and 9% LSIL (5.6% affecting cervix and 3.4% vulva and vagina). 3.4% developed recurrent low-grade cervical squamous intraepithelial lesions in the V-group. The rate of recurrence was higher in the NV-group than in the V-group during the follow-up period of 3 years (13.5% vs 3.4%; $p < 0.05$).

4.3 Discussion

In the study of Ghelardi [12] all women in the V-group received quadrivalent HPV vaccine with the first dose injected 30 days after conization and the remaining two doses 2 and 6 months later. At 6 months after conization all women of the NV-group and V-group were tested for HPV (so called HPV test of cure = TOC) and for cytological abnormalities with liquid based cytology and colposcopy and were followed with HPV test, colposcopy and cervical smear, every six months in the first 2 years and then annually until the fourth year post treatment.

Clinical recurrence was defined as a disease relapse, histologically confirmed CIN 2 or higher during the 4 years follow-up period. Patients with histologically confirmed CIN 2+ disease at 6 months after conization were considered as persistent disease, while CIN 2+ diagnosed on biopsies at ≥12 months follow-up visit were considered as recurrent disease. Persistent disease at 6 months follow-up visit was considered a study exit criteria. Two patients in the V-group and four patients in the NV-group were excluded because of disease persistence at first follow-up visit.

The HPV vaccine has no impact on prevalent infections, as previous known. The HPV test of cure performed 6 months after treatment (TOC) does not show statistically significant differences in the two groups. But the vaccination was associated with a statistically significant reduction in the risk of subsequent HPV related high-grade CIN. However, it is not clear whether the two cases of clinical recurrence in the V-group occurred in HPV-positive or -negative women at the first HPV test 6 months after conization. Therefore, the efficacy in relation to the HPV status after CIN treatment remains unclear.

The study is a prospective non-randomised observational study. The self-selection of women to the V-group carries a possible risk for a selection bias in favour of the intervention. The vaccine had to be paid by the study participants, although at a reduced price, which may also contribute to a selection bias.

Neither the women nor the medical personnel, who performed the colposcopy and cervical smear, were blinded to the group assignment. The outcome could be biased because of a high lost to follow-up rate of 33%, although the high lost to follow up rate occurred in both groups.

HPV vaccination administered post-surgery showed efficacy in reducing the risk for developing subsequent HPV related high-grade CIN. The results are consistent with a previously published

retrospective analysis which showed a significant reduction in the risk of subsequent high grade disease of the cervix of 65% [14]. The number needed to vaccine to prevent one recurrent disease amounts to 19 (95% CI, 87-10) [12], respectively to 10 (95% CI, 54-5) [13].

Prophylactic vaccines are ineffective at clearing pre-existing HPV infections and thus do not prevent associated pre-invasive lesions. Therapeutic vaccines differ from prophylactic vaccines in that they are aimed at generating cell-mediated immunity rather than neutralising antibodies. Therapeutic HPV vaccines that trigger cell-mediated immune responses for the treatment of established infections and malignancies could have a significant impact on the morbidity and mortality associated with HPV [121, 122]. However, there are currently no HPV therapeutic vaccines approved for use in humans. Nevertheless, there have been numerous and extensive studies that have generated promising therapeutic vaccine candidates tested in clinical trials [121, 123-125].

5 SAFETY

5.1 Methods

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
C0001	What kind of harms can use of the technology cause to the patient?	2
C0008	How safe is the technology in comparison to the comparator?	2

Sources

A systematic literature search was performed in July 2017 and February 2019 in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA) according to the predefined search strategy. References were included or excluded according to the overall research question, Population-Intervention-Control-Outcome (PICO)-scheme (as described in Scope), and the predefined inclusion/exclusion criteria. Details on search strategy can be found in Appendix 1.

5.2 Results

Included studies

Three studies were included, two prospective [12, 13] and one retrospective analysis [14], but no study reported safety issues.

Patient safety

C0001

What kind of harms can use of the technology cause to the patient?

No safety issues were reported.

C0008

How safe is the technology in comparison to the comparator?

No evidence was found to answer the research question.

5.3 Discussion

No study reported safety issues in women vaccinated after surgery for CIN 2-3.

End-of-study safety data and long-term follow-up observation of the safety of quadrivalent HPV vaccine in adult women in a preventive setting revealed no new serious adverse events [18, 19]. More deaths occurred in the vaccine group but the investigators deemed no study deaths as related to vaccination.

A 4-year interim follow-up of women older than 25 years vaccinated with the bivalent HPV vaccine showed injection site symptoms in 85% of participants. An unexpected imbalance in the number of deaths occurred in the vaccine group that was probably caused by chance. No clustering in the nature of the cause of death, no consistency with other safety findings from this or any other

study, no temporal relation between vaccination and death, and no medical grounds to support a causal link to the vaccine could be identified [20]. A 7-year follow-up observation of the same study showed serious adverse events possibly related to the vaccine in 0.2% of women in the vaccine group and 0.3% in the control group. An imbalance in the number of deaths in the vaccine group still existed but no deaths were considered by the investigator to be related to study vaccination [21].

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS

Overall description of methods

The selection of assessment elements was based on the EUnetHTA Core Model® Application for Rapid Relative Effectiveness (REA) Assessments [126]. The Checklist for potential ethical, organisational, patient and social, and legal aspects of the HTA Core Model for rapid REA was filled in as well.

For effectiveness and safety domain, a systematic literature search was performed in July 2017 and February 2019 according to the Cochrane methodology [127] in standard medical and HTA databases (The Cochrane Central Register of Controlled Trials, The Database of Abstracts of Reviews of Effects, The Health Technology Assessment Database, NHS Economic Evaluation Database, MEDLINE, EMBASE). Manual searches (from reference lists of relevant studies) were also carried out. The first search in 2017 did not result in a publication according to our predefined requirements for efficacy domain. One abstract reported preliminary results of the Speranza Study [128] which possibly could meet the criteria with an expected full publication in 2018. Therefore, a second search was carried out in February 2019.

Relevant references (after duplicates removed) were screened and assessed for eligibility independently by two researchers. References were included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme and presented according to the PRISMA Statement [129] in Figure 1.

1239 records were identified through database searching and 2 additional records through other sources; 860 results left after deduplication were removed. 41 full-text articles were assessed for eligibility. After the exclusion of 36 full-text articles two prospective controlled studies were included for efficacy and safety domain. In addition, three retrospective analyses were included for the safety domain.

The risk of bias of the included prospective studies, one non-randomized and one randomized, was evaluated independently by two researchers. The Cochrane risk of bias assessment approach was used on study level [127] and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool (version for cohort-type studies) [11].

Table 2: Results of the scoping process regarding the inclusion/ exclusion of Assessment elements

Excluded Assessment elements	Reason for exclusion
D0005 - How does the technology affect symptoms and findings?	Vaccination does not change symptoms
D0011 - What is the effect of the technology on patients' body functions?	Vaccination usually does not affect directly body functions
D0016 - How does the use of technology affect activities of daily living?	Vaccination usually does not affect directly ADLs
D0012 - What is the effect of the technology on generic health-related quality of life?	Vaccination usually does not affect directly QoL
D0013 - What is the effect of the technology on disease-specific quality of life?	Vaccination usually does not affect directly QoL
Patient satisfaction D0017 - Was the use of the technology worthwhile?	Vaccination usually does not affect directly QoL

C0002 - What is the dose relationship of the harms?	We subsume it at C0001 if something is found in literature
C0004 - How does the frequency or severity of harms change over time or in different settings?	We subsume it at C0001 if something is found in literature
C0005 - What are the susceptible patient groups that are more likely to be harmed?	We subsume it at C0001 if something is found in literature
C0007 - What are the user-dependent harms?	We subsume it at C0001 if something is found in literature
Environmental safety C0040 - What kind of harms are there for public and environment?	Not applicable
B0005 - In what context and level of care are the technology and the comparator used?	B0004 and B0005 were put together
B0008 - What kind of special premises are needed to use the technology and the comparator(s)?	Vaccination does not need special premises
B0009 - What supplies are needed to use the technology and the comparator?	Vaccination does not need special supplies
B0010 - What kind of data and records are needed to monitor the use of the technology and the comparator?	Not our aim
B0011 - What kind of registry is needed to monitor the use of the technology and comparator?	Not our aim
D0001 - What is the expected beneficial effect of the intervention on overall mortality?	Disease specific mortality is relevant, studies do not provide data
D0003 - What is the effect of the intervention on the mortality due to causes other than the target disease?	Disease specific mortality is relevant, subsumed in D0002

Documentation of the search strategies

A systematic literature search was performed on 19 – 20 July 2017 and 19 – 20 February 2019

Medline

Database: Ovid MEDLINE(R) <1946 to July Week 1 2017>, Ovid MEDLINE(R) Epub Ahead of Print <July 18, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 18, 2017>, Ovid MEDLINE(R) Daily Update <July 18, 2017>, Ovid MEDLINE(R) Versions

Search Strategy:

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1 exp Cervical Intraepithelial Neoplasia/ (9384)

2 high-grade cervi* intra?epithelial neoplas*.mp. (688)

3 CIN?2*.mp. (1687)

4 CIN?3*.mp. (1117)

5 exp Conization/ (959)

6 coni#ation*.mp. (2478)

7 electro?surgical excision*.mp. (688)

8 LEEP.ti,ab. (594)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (12163)

10 exp Papillomavirus Vaccines/ (6186)

11 (Papilloma* adj10 Vaccin*).mp. (8353)

12 (human?papilloma* adj10 vaccin*).mp. (2)

13 (HPV adj10 vaccin*).mp. (7821)

14 10 or 11 or 12 or 13 (10402)

15 9 and 14 (854)

16 limit 15 to clinical trial, all (125)

17 ((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (3617886)

18 15 and 17 (223)

19 16 or 18 (258)

20 remove duplicates from 19 (221)

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Embase

Session Results

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No.	Query Results	Results	Date
#22.	(('uterine cervix carcinoma in situ'/exp OR 'high-grade cervi* intraepithelial neoplas*':ti,ab OR 'high-grade cervi* intra-epithelial neoplas*':ti,ab OR cin2*:ti,ab OR 'cin 2':ti,ab OR cin3*:ti,ab OR 'cin 3':ti,ab OR 'uterine cervix conization'/exp OR conization*:ti,ab OR conisation*:ti,ab OR 'electrosurgical excision*':ti,ab OR 'electro-surgical excision*':ti,ab OR leep:ti,ab) AND ('wart virus vaccine'/exp OR (papilloma* NEAR/10 vaccin*):ti,ab OR (humanpapilloma*	495	19 Jul 2017

	NEAR/10 vaccin*):ti,ab OR (hpv* NEAR/10 vaccin*):ti,ab)) AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*)		
#21.	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*	1,837,640	19 Jul 2017
#20.	('uterine cervix carcinoma in situ'/exp OR 'high-grade cervi* intraepithelial neoplas*':ti,ab OR 'high-grade cervi* intra-epithelial neoplas*':ti,ab OR cin2*:ti,ab OR 'cin 2':ti,ab OR cin3*:ti,ab OR 'cin 3':ti,ab OR 'uterine cervix conization'/exp OR conization*:ti,ab OR conisation*:ti,ab OR 'electrosurgical excision*':ti,ab OR 'electro-surgical excision*':ti,ab OR leep:ti,ab) AND ('wart virus vaccine'/exp OR (papilloma*	1,556	19 Jul 2017

	NEAR/10 vaccin*):ti,ab OR (humanpapilloma* NEAR/10 vaccin*):ti,ab OR (hpv* NEAR/10 vaccin*):ti,ab)		
#19	'wart virus vaccine'/exp OR (papilloma* NEAR/10 vaccin*):ti,ab OR (humanpapilloma* NEAR/10 vaccin*):ti,ab OR (hpv* NEAR/10 vaccin*):ti,ab	14,886	19 Jul 2017
#18.	(hpv* NEAR/10 vaccin*):ti,ab	9,820	19 Jul 2017
#17.	(humanpapilloma* NEAR/10 vaccin*):ti,ab	3	19 Jul 2017
#16.	(papilloma* NEAR/10 vaccin*):ti,ab	5,867	19 Jul 2017
#15.	'wart virus vaccine'/exp	10,381	19 Jul 2017
#14.	'uterine cervix carcinoma in situ'/exp OR 'high-grade cervi* intraepithelial neoplas*':ti,ab OR 'high-grade cervi* intra-epithelial neoplas*':ti,ab OR cin2*:ti,ab OR 'cin 2':ti,ab OR cin3*:ti,ab OR 'cin 3':ti,ab OR 'uterine cervix conization'/exp OR conization*:ti,ab OR conisation*:ti,ab OR 'electrosurgical excision*':ti,ab OR 'electro-surgical excision*':ti,ab OR leep:ti,ab	17,597	19 Jul 2017
#13.	leep:ti,ab	902	19 Jul 2017
#12.	'electro-surgical excision*':ti,ab	4	19 Jul 2017
#11.	'electrosurgical excision*':ti,ab	809	19 Jul 2017
#10.	conisation*:ti,ab	502	19 Jul 2017
#9.	conization*:ti,ab	2,498	19 Jul 2017
#8.	'uterine cervix conization'/exp	2,438	19 Jul 2017
#7.	'cin 3':ti,ab	1,004	19 Jul 2017
#6.	cin3*:ti,ab	1,528	19 Jul 2017
#5.	'cin 2':ti,ab	1,680	19 Jul 2017
#4.	cin2*:ti,ab	2,416	19 Jul 2017
#3.	'high-grade cervi* intra-epithelial neoplas*':ti,ab	41	19 Jul 2017
#2.	'high-grade cervi* intraepithelial	786	19 Jul 2017

neoplas*':ti,ab

#1. 'uterine cervix carcinoma in situ'/exp 13,454 19 Jul 2017

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CENTRAL via Wiley search strategy

Search Name: HPV-Vaccines to prevent CIN

Last Saved: 19/07/2017 16:56:50.065

ID Search

#1 MeSH descriptor: [Cervical Intraepithelial Neoplasia] explode all trees

#2 high-grade cervi* intraepithelial neoplas*:ti,ab,kw (Word variations have been searched)

#3 CIN2*:ti,ab,kw (Word variations have been searched)

#4 CIN 2*:ti,ab,kw (Word variations have been searched)

#5 CIN3*:ti,ab,kw (Word variations have been searched)

#6 CIN 3*:ti,ab,kw (Word variations have been searched)

#7 MeSH descriptor: [Conization] explode all trees

#8 Conisation*:ti,ab,kw (Word variations have been searched)

#9 Conization*:ti,ab,kw (Word variations have been searched)

#10 electrosurgical excision*:ti,ab,kw (Word variations have been searched)

#11 LEEP:ti,ab,kw (Word variations have been searched)

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor: [Papillomavirus Vaccines] explode all trees

#14 Papilloma* near Vaccin*:ti,ab,kw (Word variations have been searched)

#15 humanpapilloma* near vaccin*:ti,ab,kw (Word variations have been searched)

#16 HPV near vaccin*:ti,ab,kw (Word variations have been searched)

#17 #13 or #14 or #16

#18 #12 and #17 in Trials

85 Hits

****

CENTRAL via CRSO search strategy

Search run on Thu Jul 20 2017

#1 (Cervical Intraepithelial Neoplasia):MH 380

#2 (high-grade cervi* intraepithelial neoplas*):TI,AB,KY 52

#3 CIN2*:TI,AB,KY177

#4 (CIN 2*):TI,AB,KY 110

#5 CIN3*:TI,AB,KY109

#6 (CIN 3*):TI,AB,KY 43

#7 Conization:MH 26

#8 Conisation*:TI,AB,KY 16

#9 Conization*:TI,AB,KY 95

#10 (electrosurgical excision*):TI,AB,KY 51

#11 (electro-surgical excision*):TI,AB,KY 0

#11 LEEP:TI,AB,KY 47

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 634

#13 (Papillomavirus Vaccines):TI,AB,KY 248

#13 (Papillomavirus Vaccines):MH 242

#14 (Papilloma* NEAR Vaccin*):TI,AB,KY 393

#15 (humanpapilloma* NEAR vaccin*):TI,AB,KY 0

#16 (HPV NEAR vaccin*):TI,AB,KY 413

#17 #13 OR #16 451

#18 #13 OR #14 OR #16 476

#19 #12 AND #18 73

****

The systematic literature search was updated on 19 – 20 February 2019

Update search 2019 Cochrane

Last Saved: 20/02/2019 15:18:56

ID Search

#1 MeSH descriptor: [Cervical Intraepithelial Neoplasia] explode all trees

#2 (high-grade cervi* intraepithelial neoplas*) (Word variations have been searched)

#3 CIN2*:ti,ab,kw (Word variations have been searched)

#4 CIN 2*:ti,ab,kw (Word variations have been searched)

#5 CIN3*:ti,ab,kw (Word variations have been searched)

#6 CIN 3*:ti,ab,kw (Word variations have been searched)

#7 MeSH descriptor: [Conization] explode all trees

#8 (Conisation*) (Word variations have been searched)

#9 (Conization*) (Word variations have been searched)

#10 (electrosurgical excision*) (Word variations have been searched)

#11 LEEP:ti,ab,kw (Word variations have been searched)

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 (Word variations have been searched)

#13 MeSH descriptor: [Papillomavirus Vaccines] explode all trees

#14 (Papilloma* near Vaccin*) (Word variations have been searched)

#15 (humanpapilloma* near vaccin*) (Word variations have been searched)

#16 (HPV near vaccin*) (Word variations have been searched)

#17 #13 or #14 or #16 (Word variations have been searched)

#18 #12 and #17 with Cochrane Library publication date Between Jul 2017 and Feb 2019 (Word variations have been searched)

41 Hits

****

Update search 2019 CRD

1 MeSH DESCRIPTOR Cervical Intraepithelial Neoplasia EXPLODE ALL TREES

2 (cervi* intraepithelial neoplas*)

3 (cervi* intra-epithelial neoplas*)

4 (CIN2*)

5 (CIN 2*)

6 (CIN3*)

7 (CIN 3*)

8 MeSH DESCRIPTOR Conization EXPLODE ALL TREES

9 (coni*ation*)

10 (electrosurgical excision*)

11 (LEEP)

12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

13 MeSH DESCRIPTOR Papillomavirus Vaccines EXPLODE ALL TREES

14 (Papilloma* NEAR Vaccin*)

15 (HPV NEAR vaccin*)

16 #13 OR #14 OR #15

17 #12 AND #16

18 (#12 AND #16) WHERE LPD FROM 19/07/2017 TO 20/02/2019

0 Hits

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Embase

Session Results

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No.	Query Results	Results	Date
#21.	#20 AND [19-7-2017]/sd NOT [20-2-2019]/sd	193	20 Feb 2019
#20.	#14 AND #19	1,744	20 Feb 2019
#19	#15 OR #16 OR #17 OR #18	17,676	20 Feb 2019
#18.	(hpv* NEAR/10 vaccin*):ti,ab,de	11,744	20 Feb 2019
#17.	(humanpapilloma* NEAR/10 vaccin*):ti,ab,de	4	20 Feb 2019
#16.	(papilloma* NEAR/10 vaccin*):ti,ab,de	8,267	20 Feb 2019
#15.	'wart virus vaccine'/exp	12,221	20 Feb 2019
#14.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	19,212	20 Feb 2019
#13.	leep:ti,ab	1,045	20 Feb 2019
#12	'electro-surgical excision*':ti,ab,de	8	20 Feb 2019
#11.	'electrosurgical excision*':ti,ab,de	1,005	20 Feb 2019
#10.	conisation*:ti,ab,de	481	20 Feb 2019
#9.	conization*:ti,ab,de	3,589	20 Feb 2019
#8.	'uterine cervix conization'/exp	2,675	20 Feb 2019
#7.	'cin 3':ti,ab	1,098	20 Feb 2019
#6.	cin3*:ti,ab	1,793	20 Feb 2019
#5.	'cin 2':ti,ab	1,844	20 Feb 2019
#4.	cin2*:ti,ab	2,859	20 Feb 2019
#3.	'high-grade cervi* intra-epithelial neoplas*':ti,ab,de	49	20 Feb 2019
#2.	'high-grade cervi* intraepithelial neoplas*':ti,ab,de	877	20 Feb 2019
#1.	'uterine cervix carcinoma in situ'/exp	14,632	20 Feb 2019

Medline

Database: Ovid MEDLINE(R) <1946 to February Week 2 2019>, Ovid MEDLINE(R) Epub Ahead of Print <February 15, 2019>, Ovid MEDLINE(R) Daily Update <February 15, 2019>

Search Strategy:

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1 exp Cervical Intraepithelial Neoplasia/ (9369)

2 high-grade cervi* intra?epithelial neoplas*.mp. (671)

3 CIN?2*.mp. (1645)

4 CIN?3*.mp. (1081)

5 exp Conization/ (968)

6 coni#ation*.mp. (2334)

7 electro?surgical excision*.mp. (614)

8 LEEP.ti,ab. (528)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (11799)

10 exp Papillomavirus Vaccines/ (6887)

11 (Papilloma* adj10 Vaccin*).mp. (8496)

12 (human?papilloma* adj10 vaccin*).mp. (3)

13 (HPV adj10 vaccin*).mp. (7588)

14 10 or 11 or 12 or 13 (10189)

15 9 and 14 (847)

16 limit 15 to ed=20170719-20190219 (94)

17 remove duplicates from 16 (94)

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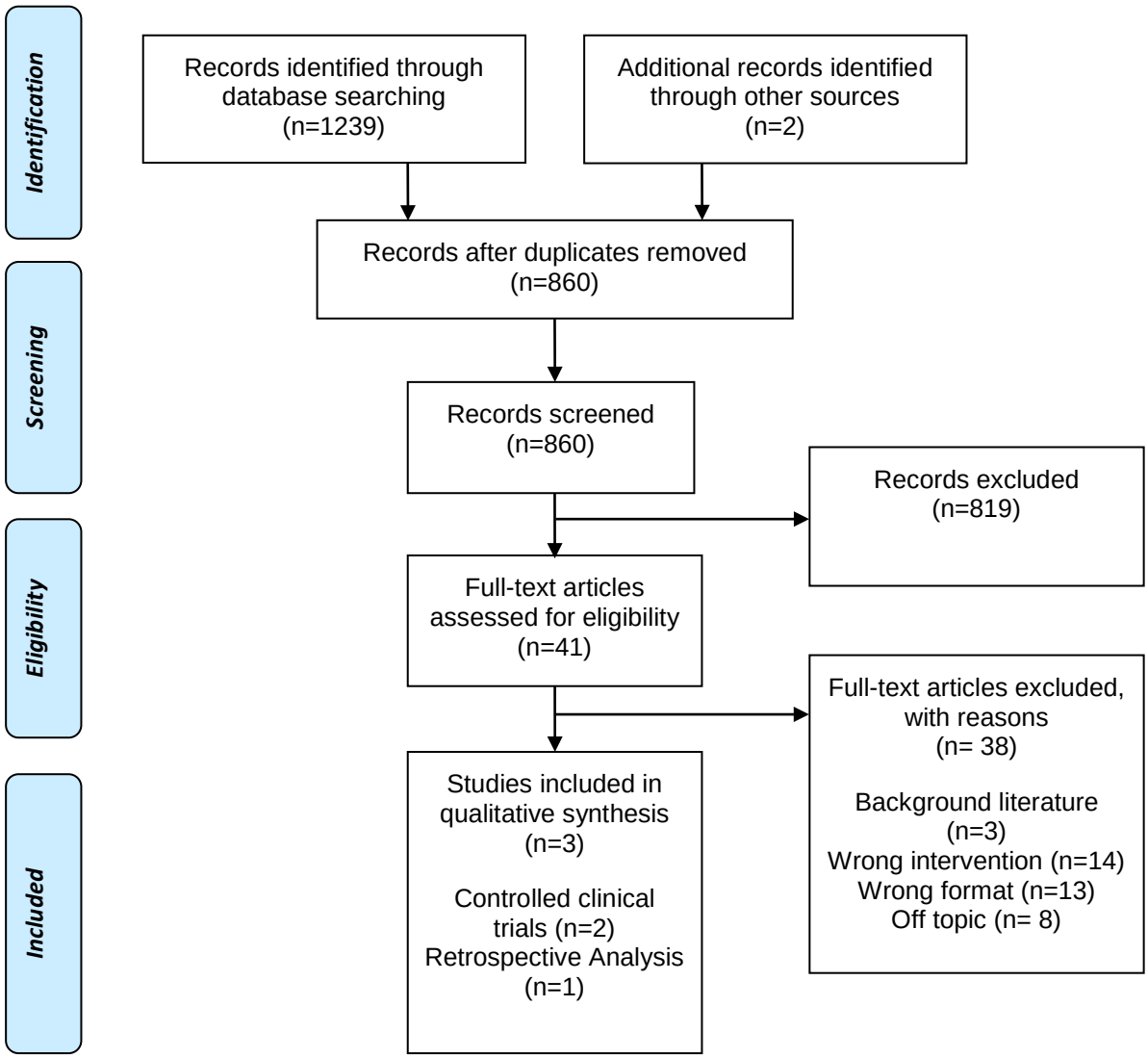
Flow chart of study selection

Figure 1: PRISMA Flow Chart



DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Clinical effectiveness

Table 3: Characteristics of controlled studies

Study	Time	Study type	Number of patients	Intervention (Number of patients)	Comparator (Number of patients)	Patient population	Endpoints
Ghelardi [12]	2018	Prospective non-randomised controlled trial	536	248	276	LEEP surgery for CIN 2+ treatment in women up to 45 years	Clinical disease relapse
Pieralli [13]	2018	Prospective randomized controlled trial	178	89	89	Women up to 45 years, 30 treated for LSIL, 148 conization for HSIL	Recurrent disease by the comparison of the overall disease-free survival.

Safety

Table 4: Characteristics of included retrospective studies

Primary reference source	Study type	Number of patients	Intervention(s)	Comparator (Number of patients) If applicable	Patient population	Endpoints
Kang 2013 [14]	Retrospective analysis	737	360	377	Women aged 20–45 years, LEEP surgery for CIN 2–3	Recurrent disease

Table 5: Characteristics of excluded retrospective studies

Primary reference source	Study type	Number of patients	Intervention(s)	Comparator (Number of patients) If applicable	Patient population	Endpoints
Joura 2012 [15]	Retrospective pooled analysis of trial data	1350	587	763	women aged 15–26 years, previous vaccination with 4-valent HPV vaccine, cervical surgery	Incidence of subsequent HPV related disease, including high grade disease
Garland 2016 [16]	Post-hoc analysis	454	190	264	Women aged 15–25 years, previous vaccination with HPV-16/18 vaccine, surgical therapy for cervical lesions	Incidence of subsequent HPV-related cervical intraepithelial neoplasia grade 2 or greater (CIN 2+) 60 days or more post-surgery

Primary reference source	Study type	Number of patients	Interventio n(s)	Comparator (Number of patients) If applicable	Patient population	Endpoints
Hildesheim [17] 2016	Subgroup Analysis	311	142	169	Women aged 18-25 years, previous vaccination with HPV-16/18 vaccine, surgical therapy for cervical lesions	Squamous intraepithelial lesions, and cervical intraepithelial neoplasia 2+ after excisional treatment

List of ongoing and planned studies

Table 6: List of ongoing studies

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient Population	Endpoints
NCT03848039 [22]	2019-2026	Randomized Double-Blind, Placebo-Controlled Clinical Trial	1220	Gardasil-9 vaccination at 0, 2 and 6 months	Intramuscular Saline 0.9% injection at 0, 2 and 6 months	Participants treated for CIN 2+ with LEEP technique	Recurrence of CIN 2+ after conization
NCT01928225 [130]	2014-2016	Randomized, Placebo-Controlled Trial	180	Quadrivalent Human Papillomavirus vaccine at entry, week 4 and week 26	Saline placebo at entry, week 4 and week 26	LEEP Treatment of Cervical High Grade Squamous Intraepithelial Lesions in HIV-infected Women	Occurrence of cervical HSIL after LEEP/LLETZ up to 52 weeks
JPRN-UMIN000003845 [131]	2010-2018	Open, single arm	600	HPV vaccine (Cervarix) after conization	-	Age below 40 years, conization for CIN 3	Investigation on Post-conization HPV infection rate. Rate of recurrence of CIN

Risk of bias tables

Table 7: Risk of bias – study level

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Ghelardi [12]	No	No	No	No	Yes	Unclear	Moderate
comments: non-randomized, self-selection of patients							
Pieralli [13]	Yes	Unclear	No	Yes	Yes	No	Moderate

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool (version for cohort-type studies), Version 19 September 2016

Table 8: ROBINS-I assessment tool

Ghelardi [12]		
	Signalling questions	**Response options**
Bias due to confounding		
	1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	PN
	Questions relating to baseline confounding only	
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	NA
	Questions relating to baseline and time-varying confounding	
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	NA
	Risk of bias judgement	Low

Bias in selection of participants into the study		
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	PY
	2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA NA
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Y
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA

	Risk of bias judgement	Moderate
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Unpredictable

Bias in classification of interventions		
	3.1 Were intervention groups clearly defined?	Y
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N
	Risk of bias judgement	Low

Bias due to missing data		
	5.1 Were outcome data available for all, or nearly all, participants?	N
	5.2 Were participants excluded due to missing data on intervention status?	N
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y
	5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	Y
	5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	PN
	Risk of bias judgement	Moderate
	Optional: What is the predicted direction of bias due to missing data?	Unpredictable

Bias in measurement of outcomes		
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	PN
	6.2 Were outcome assessors aware of the intervention received by study participants?	PY
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N
	Risk of bias judgement	Low

Bias in selection of the reported result		
	Is the reported effect estimate likely to be selected, on the basis of the results, from...	
	7.1. ... multiple outcome *measurements* within the outcome domain?	N
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	N
	7.3 ... different *subgroups*?	N
	Risk of bias judgement	Low

Overall bias		
	Risk of bias judgement	Moderate
	Optional: What is the overall predicted direction of bias for this outcome?	Unpredictable

APPENDIX 2. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences, which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new technology to the defined, existing comparators point to any differences, which may be organisationally relevant?	No
3. **Social**:	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences, which may be socially relevant?	No
4. **Legal**:	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
4.2. Does comparing the new technology to the defined, existing comparators point to any differences, which may be legally relevant?	No
HVP vaccines are licensed for primary prevention. HPV vaccines in women treated for CIN 2 or CIN 3 or AIS is experimental approach so far.	