# OF CERVICAL CANCER, PRECURSOR LESIONS AND INFECTIONS: A SYSTEMATIC LITERATURE REVIEW



Harper DM<sup>1</sup>, Navarro-Alonso JA<sup>2</sup>, Bosch X<sup>3</sup>, Gilca V<sup>4</sup>, Paavonen J<sup>5</sup>, Stanley M<sup>6</sup>, Sasieni P<sup>7</sup>, Yébenes M<sup>8</sup>, Martínez N<sup>8</sup>, Rodriguez A<sup>9</sup>, García A<sup>9</sup>, Martín-Gomez L<sup>9</sup>, Vallejo-Aparicio LA<sup>9</sup>, Carrión H<sup>9</sup>, Ruiz García Y<sup>9</sup>



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# **Objectives**



Cervical cancer is vaccine preventable but remains the fourth ranked cancer among women worldwide.<sup>1</sup>



Approximately 90% of cervical cancer cases are reported in low- to middle-income countries. This disparity in incidence rates may be due to differences in healthcare policies and risk factors.<sup>2-4</sup>



The WHO has called to eliminate cervical cancer, highlighting the need for early intervention and efficacious vaccines ensuring longlasting protection.<sup>5</sup>

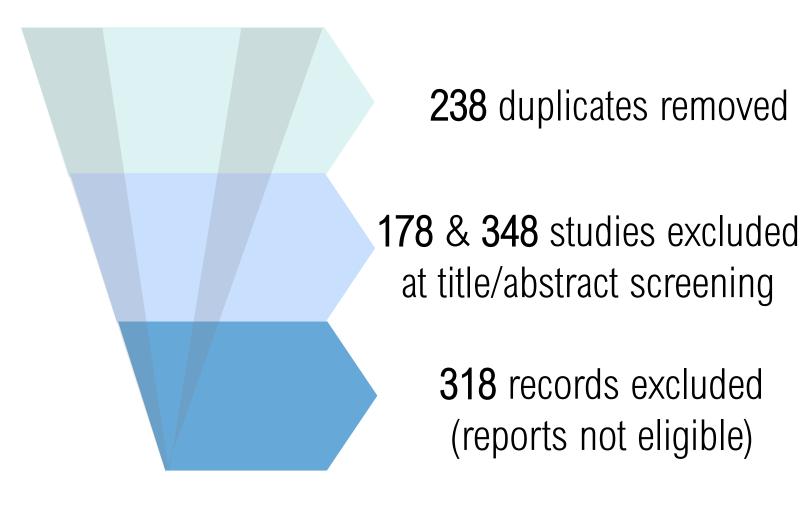


We sum up available evidence on human papillomavirus vaccination for the prevention of cervical cancer in published literature to help discussions on HPV vaccination strategies.

## Methods -

- The systematic literature review analyzed postlicensure studies of all available HPV vaccines against cervical cancer, precursor lesions, and HPV infections published from 2006 to 2022. A pre-defined eligibility criteria was utilized to select relevant studies.
- A search strategy was developed to analyze the clinical impact of HPV vaccines in reducing cervical cancer, precursor lesions, and infections.
- The search was conducted in three electronic databases (Medline [via PubMed], EMBASE and Cochrane) using a comprehensive set of search terms (see QR code for MeSH terms).

#### 1137 identified publications



**55** studies included in the review

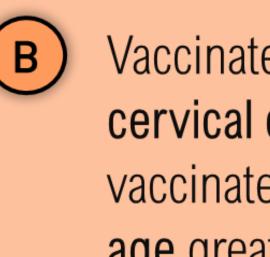




Vaccine efficacy was reported in 19 randomized control trials (RCTs).<sup>6-24</sup> Vaccine effectiveness, impact and safety of HPV vaccination was reported in 15 non-RCTs studies,<sup>25-39</sup> and 7 observational studies. 40-46 Lastly, 14 studies reported results post HPV vaccine implementation in NIPs. 47-60 11 studies assessed safety profiles of HPV vaccines. 25,26,28,31,32,34,39,40,43-45

A substantial decrease in prevalence of HPV types, high-grade cervical lesions and cervical cancer was found in countries with high vaccine coverage and routine vaccination programs.

HPV vaccines may be effective in preventing HPV infection, cervical cancer and lesions among women over the recommended age of vaccination and for at least a decade after administration. Studies found low HPV incidence rates and reduced cervical cancer/CIN lesions in vaccinated women aged over 26 years of age. 33,42,52,55



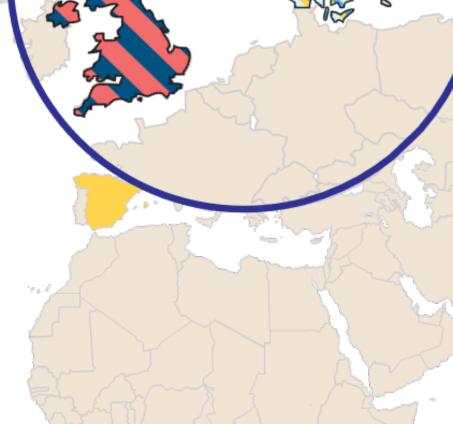
Vaccinated women had a lower risk of cervical cancer compared to those not vaccinated. 56,61 Vaccinating at a younger age greatly reduced incidence of cervical cancer when compared to older ages. 56,61



3 studies reported a significant decline in CIN grades 2 and 3 after HPV vaccination.49-51



Single-dose 2vHPV showed vaccine effectiveness of 97.4% against HPV type 16/18 with antibodies persisting for 11 years after vaccination. 16



Single-dose 4vHPV showed 95.4% protection against HPV type 16/18 and 35% efficacy against any persistent HPV infection 10 years postvaccination.<sup>6</sup>

Cross-protection against HPV 31/33/45 serotypes was observed in two studies.<sup>54,57</sup>



Studies reported that HPV vaccines maintain a positive benefit-risk ratio.

(see QR code for more safety results)

# Conclusions

- Study limitations include the methodological quality of selected studies. About 20% of randomized studies and 83% of non-randomized studies had a high risk of bias. Possible limitations of individual studies could also affect our conclusion.
- The review highlights the importance of early HPV vaccination in preventing cervical cancer and precursor lesions.
- These results can inform policy makers in the implementation of effective vaccination programs to prevent cervical cancer and related lesions.

Abbreviations: CIN cervical intraepithelial neoplasia, HPV human papillomavirus, LIC low-income countries, LMIC lower-middle-income countries, MeSH medical subject headings, NIP national immunization program, RCTs randomized control trials, WHO World Health Organization

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of protection and safety of

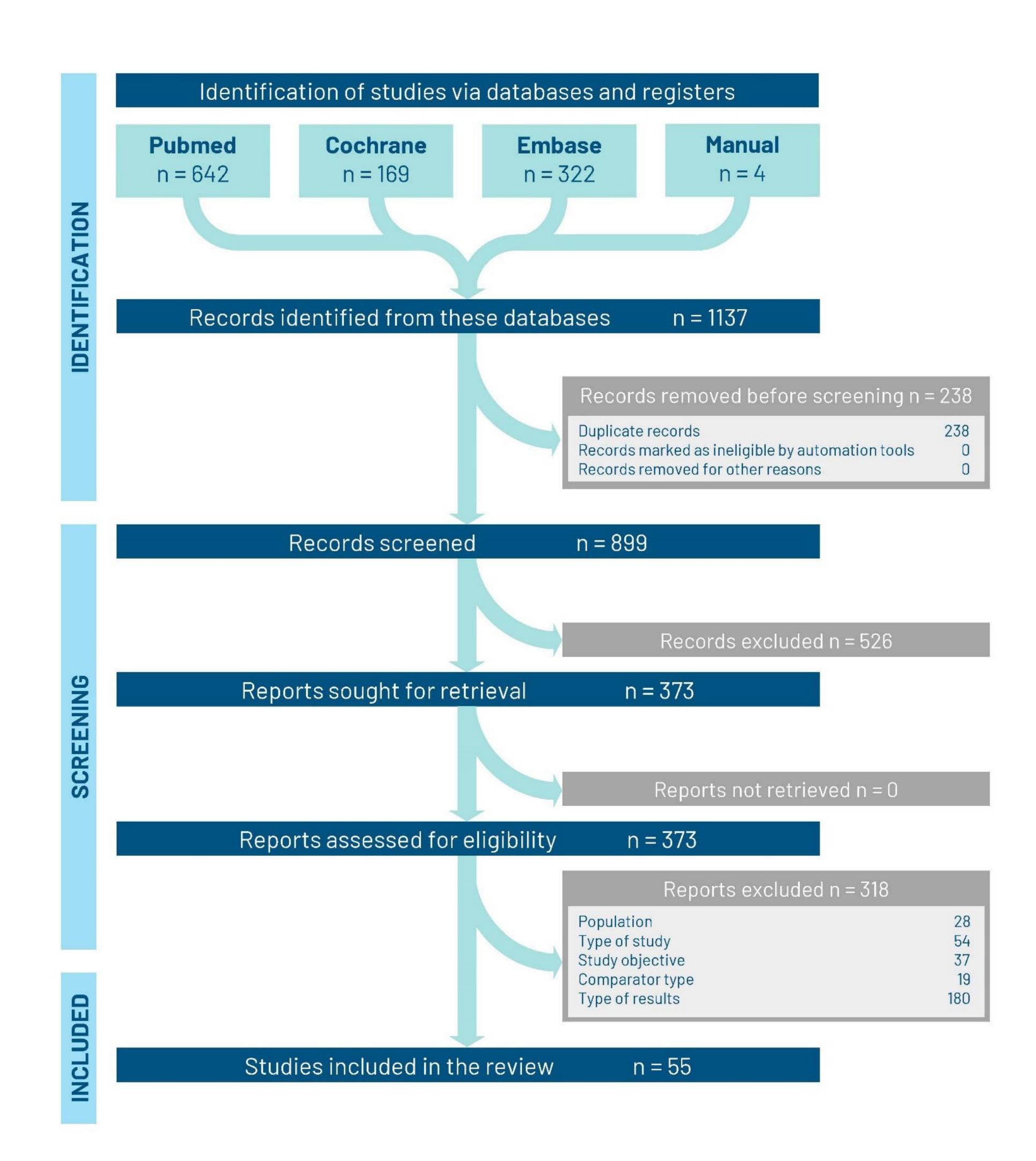
the HPV vaccines

#### Supplementary Information Supplementary Figures -Comparison **Outcomes Population** Intervention Is there a control or alternative What are the patient-relevant What is the management strategy, Who are the relevant patients? diagnostic test, or exposure that you consequences of the intervention? management strategy you would like to compare to the intervention or indicator? are interested in? Efficacy, effectiveness, General population ≥9 years impact (herd effect), duration Non-vaccination, placebo, (humans, female, women)

**HPV vaccines** 

other HPV vaccines, or other

non-HPV vaccines



#### — Authors information and disclosures

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Xavier Bosch declares receiving consulting fees and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events, as well as support for attending meetings and/or travel once a year from MSD. Xavier Bosch also declares receipt of HPV testing kits and reagents from RMS. Peter Sasieni declares receiving grants from Cancer Research UK, NIHR and Yorkshire Cancer Research as well as a contract with GRAIL. He also declares receiving consulting fees from GRAIL for being a Scientific Advisory Board member and from Roche for a Scientific Advisory role. Peter Sasieni also received a supply of Gardasil-9 for the NOVEL trial on which he is the lead statistician from MSD. Margaret Stanley declares having acted as a consultant for GSK and MSD vaccines. Yara Ruiz, Laura A Vallejo-Aparicio and Laura Martin-Gomez are GSK employees and hold stock or stock options from GSK. Andrea Garcia, Angela Rodriguez and Helena Carrion are GSK employees. María Yébenes and Néstor Martínez are Pharmacoeconomics & Outcomes Research Iberia (PORIB) employees. PORIB is a consultant company specialized in economic evaluation of health technologies which has received unrestricted financial support for development of the present study. Diane M Harper declares receiving fees for being a consultant on health economics for Roche and being the president of NAPCRG. Vladimir Gilca, José Antonio Navarro Alonso and Jorma Paavonen declare no financial and non-financial relationships and activities and no conflicts of interest. Xavier Bosch, Peter Sasieni, Margaret Stanley, Yara Ruiz, Laura A Vallejo-Aparicio, Laura Martin-Gomez, Andrea Garcia, Angela Rodriguez, Helena Carrion and Diane M Harper declare no other financial and non-financial relationships and activities.

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## Supplementary Information



Supplementary Table -

#### Characteristics and vaccine safety results of the identified studies

Author, Year	Country	Type of study	Participants (Age group)	Type of vaccine	Results
Verma, 2021 <sup>44</sup>	India	A pilot interventional study	302 cases (9-26 years)	2vHPV	Most common side effect was pain at injection site followed by induration 3.5% and 1.5% respectively. human papillomavirus (HPV) vaccines are quite safe, and safety is not a major concern for non-acceptability of HPV vaccines.
Mauro, 2019 <sup>34</sup>	Brazil	A retrospective, descriptive study	3,390,376 HPV vaccine doses (9-13 years)	4vHPV	The reporting rate was 13.72 per 100,000 vaccine doses administered.  The most frequent adverse events following immunization (AEFI) was syncope, with 5.7 reports per 100,000 doses administered. 39 AEFI cases (8.4%) were classified as severe, with a reporting rate of 1.15 per 100,000 vaccine doses administered. Our data corroborate the safety of HPV vaccines
Ward, 2019 <sup>45</sup>	Denmark	A retrospective observational study	976 women (12-25 years)	2vHPV and 4vHPV	The most common symptoms were fatigue, dizziness and headache but their frequency varied among clusters.  Non-specific symptoms including headache, fatigue and dizziness feature prominently in serious adverse events (AE) reports from females in Denmark
Yaju, 2019 <sup>39</sup>	Japan	A Nagoya City's surveillance data study	30,793 women (15-21 years)	2vHPV and 4vHPV	The odds ratio (OR) between HPV-vaccinated cases and unvaccinated controls was significantly higher for the symptoms of memory impairment (OR: 1.80 [95% confidence interval [CI]: 1.43–2.25]), dyscalculia (OR: 1.80 [95% CI:1.19–2.73]), involuntary movement (OR: 1.82 [95% CI:1.21–2.73]). A consistent causal relationship between HPV vaccination and these symptoms remains uncertain.
Bonaldo, 2019 <sup>25</sup>	USA	A vaccine safety surveillance data study	55,356 Case Safety Reports	2vHPV, 4vHPV and 9vHPV	The highest number of reports was related to $4vHPV$ ® (N = $42,244$ ). The two events more frequently reported and statistically significant for HPV vaccines were: dizziness (N = $6259$ ) relative odds ratio (ROR) = $2.60$ (95% CI $2.53 - 2.66$ ) and syncope (N = $6004$ ) ROR = $6.28$ ( $6.12 - 6.44$ ). The AEFI analysis showed that the events most frequently reported were non-serious and listed in the
Skufca, 2018 <sup>43</sup>	Finland	An observational retrospective nationwide register-based cohort study	240 605 women (11-15 years)	2vHPV	corresponding Summary of Product Characteristics.  The adjusted Hazard Ratios for the entire follow-up ranged from 0.34 (95%CI 0.11–1.05) to 8.37 (95%CI 0.85–82.54) across the 38 outcomes among the vaccinated in relation to the unvaccinated.  However, the 95%CI and the overall Wald test (p > 0.05) showed that HPV2 was not significantly associated with an increased risk for any of the 38 outcomes.
López-Fauqued, 2017 <sup>32</sup>	Several countries	A pregnancy exposure registry study	306 pregnancy exposure reports	2vHPV	There were 18 infants born with a congenital anomaly of which nine were minor structural defects, seven were major structural defects, one was a hereditary disorder, and one was likely the result of a congenital infection. There was no cluster of congenital anomalies suggestive of possible teratogenesis.  These registry data show no evidence that vaccination with ASO4-HPV-16/18 during the defined
Grimaldi- Bensouda, 2017 <sup>28</sup>	France	A systematic prospective case-referent study	Cases:510 Referents: 1953 (11-25 years)	2vHPV and 4vHPV	exposure period increases the risk of teratogenicity  All autoimmune diseases combined were negatively associated to HPV vaccination with an adjusted odds ratio of 0.58 (95% CI: 0.41-0.83).  Similar results were obtained for central demyelination/multiple sclerosis, autoimmune thyroiditis, type-1 diabetes and connective tissue, the last two not reaching statistical significance. Sensitivity analyses showed similar results.
Liu, 2016 <sup>31</sup>	Canada	A population-based study	195,270 women (> 9 years)	2vHPV and 4vHPV	Of the women who received HPV vaccine 958 were hospitalized and 19,351 had an emergency department visit within 42 days of immunization. Four women who had an emergency department visit and hospitalization event were diagnosed with venous thromboembolism. At the end, rates of AEFI after HPV immunization in Alberta are low and consistent with types of events seen elsewhere.
Gasparini, 2011 <sup>26</sup>	Italy	A post-licensure study	4,643 women (12 - 26 years)	2vHPV	No serious adverse events were observed. The most frequent local symptom was pain at the injection site, while fatigue, headache and myalgia were the most common systemic reactions.  Almost all of the local and general reactions proved to be of negligible intensity and duration and required no medical intervention. Our results show better tolerability of the vaccine in comparison with the data from some controlled clinical studies and from other surveillance programs conducted internationally
Donken, 2018 <sup>40</sup>	Netherlands	A prospective cohort study	1635 women (14–16 years)	2vHPV	Among 1635 women, 54% were fully vaccinated. Adjusted vaccine efficacy (VE) against HPV16/18 persistent infections was 97.7% (95% CI, 83.5%–99.7%). Furthermore, VE against HPV31/33/45 persistent infections was 61.8% (95% CI, 16.7%–82.5%). No indications found that the protection against vaccine types or cross-protective types changes up to six years post-vaccination.

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## OF CERVICAL CANCER, PRECURSOR LESIONS AND INFECTIONS: A SYSTEMATIC LITERATURE REVIEW

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# Supplementary Information –



Supplementary Tables –

Population search strategy in PubMed \* Preliminary results without applying limits

#	Term	Search Strategy	# Articles	
Search date: February 2022				
#1	Humans	"human s"[All Fields] OR "humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]	21,081,806	
#2	Female	"femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields]	9,593,231	
#3	Girl	"Girl"[Title/Abstract]	61,976	
#4	Girls	"Girls"[Title/Abstract]	103,032	
<b>#</b> 5	Woman	Woman [Title/Abstract]	246,195	
#6	Women	Women [Title/Abstract]	1,099,051	
<b>#7</b>	#2 OR #3 OR #4 OR #5 OR #6	"femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields] OR "Girls"[Title/Abstract] OR "Girls"[Title/Abstract] OR "Woman"[Title/Abstract] OR "Women"[Title/Abstract]	9,781,254	
#8	#1 AND #7	("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields] OR "Girl"[Title/Abstract] OR "Girls"[Title/Abstract] OR "Woman"[Title/Abstract] OR "Women"[Title/Abstract]) AND ("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "Girls"[Title/Abstract] OR "Girls"[Title/Abstract] OR "Woman"[Title/Abstract] OR "Woman"[Title/Abstract] OR "humans"[All Fields] OR "	8,451,717	

#### Intervention search strategy in PubMed \* Preliminary results without applying limits

#	Term	Search Strategy	# Articles	
Search date: February 2022				
#9	Papillomavirus vaccines	"papillomavirus vaccines"[Title/Abstract]	562	
#10	HPV vaccines	HPV vaccines [Title/Abstract]	2,103	
#11	Human papillomavirus vaccines	"human papillomavirus vaccines"[Title/Abstract]	387	
#12	2vHPV	2vHPV [Title/Abstract]	319	
#13	HPV vaccines VLP	("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("hpv"[All Fields] AND "vaccines"[All Fields]) OR "hpv vaccines"[All Fields]) AND "VLP"[All Fields]	458	
#14	4vHPV	4vHPV [Title/Abstract]	547	
#15	HPV2 OR HPV4 OR HPV9	"HPV2"[Title/Abstract] OR "HPV4"[Title/Abstract] OR "HPV9"[Title/Abstract]	262	
#16	#13 AND #15	("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("hpv"[All Fields] AND "vaccines"[All Fields]) OR "hpv vaccines"[All Fields]) AND "VLP"[All Fields] AND ("HPV2"[Title/Abstract] OR "HPV4"[Title/Abstract] OR "HPV9"[Title/Abstract])	4	
#17	Bivalent OR Quadrivalent OR Nonavalent	Bivalent[tiab] OR quadrivalent[tiab] OR nonavalent[tiab]	11,211	
#18	#13 AND #17	("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("hpv"[All Fields] AND "vaccines"[All Fields]) OR "hpv vaccines"[All Fields]) AND "VLP"[All Fields] AND ("Bivalent"[Title/Abstract] OR "quadrivalent"[Title/Abstract])  "nonavalent"[Title/Abstract])	82	
#19	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #16 OR #18	"papillomavirus vaccines"[Title/Abstract] OR "hpv vaccines"[Title/Abstract] OR "human papillomavirus vaccines"[Title/Abstract] OR "2vHPV"[Title/Abstract] OR (("papillomavirus vaccines"[MeSH Terms] OR ("papillomavirus"[All Fields] AND "vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields] OR ("hpv "[All Fields]) OR "hpv vaccines"[MeSH Terms] OR ("papillomavirus vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields]) OR "hpv vaccines"[All Fields]) OR "papillomavirus vaccines"[All Fields]) OR ("hpv"[All Fields]) OR "hpv vaccines"[All Fields]) OR ("papillomavirus vaccines"[All Fields]) OR ("papillomavirus"[All Fields]) OR "hpv vaccines"[All Fields]) OR "hpv v	3,263	

#### Population and Intervention combined search strategy in PubMed

#	Term	Search Strategy	# articles		
Search date: February 2022					
#20	#8 AND #19	("femal" [All Fields] OR "female" [MeSH Terms] OR "female" [All Fields] OR "females" [All Fields] OR "females" [All Fields] OR "females" [All Fields] OR "Girls" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Girls" [Title/Abstract] OR "Woman" [Title/Abstract] OR "how accines" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Woman" [Title/Abstract] OR "Papillomavirus vaccines" [All Fields] OR ("papillomavirus vaccines" [All Fields]) OR "papillomavirus vaccines" [All Fields] OR ("Papillomavirus vaccines" [All Fields]) OR "papillomavirus vaccines" [All Fields] OR ("HPV" [All Fields] AND "vaccines" [All Fields]) OR "how vaccines" [All Fields] OR ("HPV" [All Fields] AND "vaccines" [All Fields]) OR "how vaccines" [All Fields] OR ("HPV" [All Fields]) OR ("papillomavirus vaccines" [MeSH Terms] OR ("papillomavirus vaccines" [All Fields]) OR "how vaccines" [All Fields]) OR	2,540		

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## Supplementary Information



Supplementary Table ·

#### Outcomes search strategy in PubMed

Gatoon	nes search strategy in Put		
# Search da	Term ate: February 2022	Search Strategy	# Articles
#21 #22	Effectiveness Efficacy	"effect"[All Fields] OR "effecting"[All Fields] OR "effective"[All Fields] OR "effectively"[All Fields] OR "effectiveness"[All Fields] OR "effectives"[All Fields] OR "effectivenesses"[All Fields] OR "effectives"[All Fields] OR "effectivities"[All Fields] OR "effectivity"[All Fields] OR "efficacious"[All F	10,369,912 992,763
#23	Relative Risk Reduction	("risk"[MeSH Terms] OR "risk"[All Fields] OR ("relative"[All Fields] AND "risk"[All Fields]) OR "relative risk"[All Fields]) AND ("reduction"[All Fields] OR "reductions"[All Fields])	191,625
#24	Absolute Risk Reduction	"numbers needed to treat"[MeSH Terms] OR ("numbers"[All Fields] AND "needed"[All Fields] AND "treat"[All Fields]) OR "numbers needed to treat"[All Fields] OR ("absolute"[All Fields] AND "risk"[All Fields] AND "reduction"[All Fields]) OR "absolute risk reduction"[All Fields]	7,125
#25	Reduction incidence	("reduction"[All Fields] OR "reductions"[All Fields]) AND ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms] OR "incidences"[All Fields] OR "incident"[All Fields] OR "incidents"[All Fields])  ("alwestican"[All Fields] OR "divertions"[All Fields]) AND ("prestact"[All Fields] OR "prestacts d"[All Fields] OR "prestactions"[All Fields] OR "prestactions" [All Fields] OR "prestacti	162,429
#26	Duration protection	("duration"[All Fields] OR "durations"[All Fields]) AND ("protect"[All Fields] OR "protected"[All Fields] OR "protecting"[All Fields] OR "protection" [All Fields] OR "protections" [All Fields] OR "protective agents" [Pharmacological Action] OR "protective agents" [MeSH Terms] OR ("protective" [All Fields] AND "agents" [All Fields]) OR "protective agents" [All Fields] OR "protectant" [All Fields] OR "protectively" [All Fields] OR "protectiveness" [All Fields] OR "protectives" [All Fields] OR "protects" [All Fields])	42,793
#27	Duration immunity	("duration"[All Fields] OR "durations"[All Fields]) AND ("immune"[All Fields] OR "immuned"[All Fields] OR "immunes"[All Fields] OR "immunes"[All Fields] OR "immunisation"[All Fields] OR "immunisation"[All Fields] OR "immunisation"[All Fields] OR "immunisations"[All Fields] OR "immunised"[All Fields] OR "immunised"[All Fields] OR "immuniser"[All Fields] OR "immunisers"[All Fields] OR "immunis	23,953
#28	Long-term protection	"Long-term"[All Fields] AND ("protect"[All Fields] OR "protected"[All Fields] OR "protecting"[All Fields] OR "protection"[All Fields] OR "protections"[All Fields] OR "protective agents"[MeSH Terms] OR ("protective"[All Fields] AND "agents"[All Fields]) OR "protective agents"[All Fields] OR "protective"[All Fields] OR "protective"[All Fields]]	63,482
#29	Safety	"safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]	768,145
#30	Adverse events	("adverse"[All Fields] OR "adversely"[All Fields] OR "adverses"[All Fields]) AND ("event"[All Fields] OR "event s"[All Fields] OR "events"[All Fields]) Fields])	297,268
#31	Deaths	"death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields] ("uterine cervical neoplasms"[MeSH Terms] OR ("uterine"[All Fields] AND "cervical"[All Fields] AND "neoplasms"[All Fields]) OR "uterine	1,099,801
#32	Cervical cancer events	cervical neoplasms"[All Fields] OR ("cervical"[All Fields] AND "cancer"[All Fields]) OR "cervical cancer"[All Fields]) AND ("event"[All Fields] OR "events"[All Fields])	2,722
#33	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	"effectives on "effection" [All Fields] OR "effections" [All Fields] OR "effectively" [All Fields] OR "effectivenesses" [All Fields] OR "efficacious" [All Fields] OR "effectivenesses" [All Fields] OR "efficacious" [All Fields] OR "effectivenesses" [All Fields] OR "incidentes" [All Fields] OR "inmunications" [All Fields] OR "immunications" [All Fields] OR "immunicationses" [All Fields] OR "protectiveses" [All Fields] OR "protectiveses" [All	11,739,521

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	Supplementar	y Table ————————————————————————————————————	
Search	limits and result of	the search strategy in PubMed	
# Search date: Febru	Term	Search Strategy	# Articles
#35	Article type (NOT)  Review OR Review Systematic Review OR Case Reports OR Letter OR Guideline OR Techinical Report	"review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields] OR (("review"[Publication Type] OR "review"[All Fields]) AND ("systematic review"[Publication Type] OR "systematic review"[Publication Type] OR "systematic review"[All Fields]) OR ("case reports"[Publication Type] OR "case reports"[All Fields]) OR ("letter"[Publication Type] OR "correspondence as topic"[MeSH Terms] OR "letter"[All Fields]) OR ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guideline"[All Fields]) OR ("Techinical"[All Fields] AND ("reportable"[All Fields]) OR "reports"[All Fields] OR "reports"[All Fields] OR "reports"[All Fields]) OR "research report"[All Fields] OR "reports"[All Fields]) OR ("video s"[All Fields]) OR "videodape recording"[All Fields]) OR "videotape recording"[All Fields]) OR "videotape recording"[All Fields]) OR "videotape recording"[All Fields]) OR "videotape recording"[All Fields]) OR "videosst"[All Fields]) OR "videotape"[All Fields]) OR "videotape"[All Fields]) OR "cost benefit analysis"[All Fields])	7,177,865
#36	#34 NOT #35	((Yennale) (MicSH) Erms) (P. Yennale) (MicSH) Erms) (P. Yennale) (MicSH) (MicSH) (P. Yennale) (MicSH)	863
#37	English	"English"[Language]	29,077,68
#38	#36 AND #37  Article type: Multicenter Study OR	((r/Compl/[All Fields) OR "Grande/[All Fields] OR "Compliant (All Fields) Fields) Fields (All Fields) Fields) OR "Compliant (All Fields) Fields) Fields (All Fields) OR "Compliant (All Fields) OR "Compl	828       
#39	Observational Study OR Randomized OR Controlled Trial OR Clinical Study OR Clinical Trial OR Comparative Study OR Research Support OR Prospective Study OR Retrospective Study OR Cohort Study OR Surveys and	"multicenter study"[Publication Type] OR "multicenter studies as topic"[MeSH Terms] OR "multicenter study"[All Fields] OR "random study"[Publication Type] OR "observational studies as topic"[MeSH Terms] OR ("random"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomisations"[All Fields] OR "randomisations"[All Fields] OR "randomisations"[All Fields] OR "randomising"[All	) 14,320,21
<b>*</b> Published	#38 AND #39 until 31/01/2022	(Referred File File as ) OR Yomes (Theory) OR "Yomes (The Ass) OR "Yomes (A File Conference CNA") Filed Conference (The Associated CON") Filed Conference (The Associated Conference CNA") Filed Conference CNA" Filed Conference	t 642

sectional study"[All Fields])) AND 0001/01/01:2022/01/31[Date - Publication]

Supplementary Information

Fields]) OR "surveys and questionnaires"[All Fields]) OR ("cross sectional studies"[MeSH Terms] OR ("cross sectional studies"[All Fields]) OR "cross sectional studies"[All Fields]) OR ("cross secti