

Review Article

Efficacy and long-term impact of HPV vaccination strategies: A Scoping review of clinical trials and follow-up studies

Sozan M. Abdelkhalig 

Received (first version): 11-March-2025,

Accepted: 01-May-2025,

Published online: 29-Oct-2025

Abstract

Background: Human papillomavirus (HPV) is a leading cause of cervical cancer and other HPV-related cancers globally. Vaccination against HPV has proven to be a pivotal intervention in reducing the burden of these diseases. However, questions remain regarding long-term efficacy, dosing strategies, and real-world outcomes of HPV vaccines. **Objective:** We aim to synthesise evidence from randomised controlled trials and long-term follow-up studies on the efficacy, immunogenicity, safety, and real-world impact of HPV vaccines. **Methodology:** A comprehensive search was conducted in PubMed, Cochrane Library, Embase, Scopus, and Web of Science for studies published in English from 2019 to 2024. Eligible studies included randomised controlled trials and long-term follow-up analyses focusing on HPV vaccine efficacy, dosing regimens, and population-specific outcomes. Data were extracted and synthesised narratively, with findings organised into five thematic areas. **Results:** Seventeen studies met the inclusion criteria. Findings confirm the high efficacy of HPV vaccines in preventing HPV-related cancers and precancers, with durable immunogenicity observed up to 12 years post-vaccination. Evidence supports the potential of single-dose regimens, which could improve accessibility in resource-limited settings. Real-world data demonstrated significant reductions in HPV-related diseases across diverse populations, reinforcing the global impact of HPV vaccination programs. **Conclusion:** This review highlights the critical role of HPV vaccines in reducing the burden of HPV-related cancers, with robust efficacy, long-term protection, and favourable safety profiles. The findings underscore the need for continued research into optimised vaccination strategies and the expansion of global vaccination efforts.

Keywords: Human Papillomavirus; HPV- vaccine; Cervical Cancer; Efficacy; Safety; Clinical Trial.

INTRODUCTION

Human papillomavirus (HPV) is a leading cause of cervical cancer and other anogenital and oropharyngeal cancers worldwide. In 2022, cervical cancer was the fourth leading cause of cancer and cancer deaths in women, with approximately 660,000 new cases and around 350,000 deaths globally. The highest rates of cervical cancer incidence and mortality are observed in low- and middle-income countries, reflecting significant inequities in access to HPV vaccination, cervical screening, and treatment services (WHO, 2024). HPV vaccines, including bivalent, quadrivalent, and 9-valent formulations, have demonstrated high efficacy in preventing infections caused by high-risk HPV types such as HPV 16 and 18. Large pre-licensure trials have shown vaccine efficacy exceeding 90% against HPV 16 and 18 persistent infections and associated cervical intraepithelial neoplasia grade 2 or worse in women without infection at vaccination¹.

Recent studies have indicated that single-dose HPV vaccination may be highly effective in preventing persistent oncogenic HPV infection, offering a potential strategy to simplify vaccination schedules and improve coverage, particularly in resource-limited settings². This scoping review aims to

synthesise evidence from randomised controlled trials and long-term follow-up studies to evaluate the efficacy, safety, and immunogenicity of HPV vaccines. By examining diverse populations, dosing strategies, and real-world outcomes, this review seeks to inform vaccination policies and contribute to the global effort to reduce the burden of HPV-related diseases.

METHODOLOGY

Study Design and Eligibility Criteria

This scoping review followed a structured protocol to ensure methodological rigour and transparency. The review included studies published in English between 2019 and 2024. Eligible studies focused on randomised controlled trials and long-term follow-up analyses assessing HPV vaccine efficacy, immunogenicity, and safety.

Literature search strategy

A comprehensive search was conducted across five databases: PubMed, Cochrane Library, Embase, Scopus, and Web of Science. Search terms included combinations of "HPV vaccine," "efficacy," "long-term immunogenicity," "clinical trials," and "follow-up studies." Filters were applied to limit results to English-language studies published within the specified timeframe. The search strategy was designed to identify all relevant studies on HPV vaccination.

Screening and selection process

The author conducted the screening and selection of studies in two stages. First is title and abstract screening, where the author assesses the relevance of studies based on titles

Sozan Mohamed Abdelkhalig*. 1Assistant Professor of Microbiology, Department of Basic Medical Sciences, College of Medicine, AlMaarefa University. P.O.Box 71666, Riyadh, 11597 Saudi Arabia, sfadl@um.edu.sa. 2Research center, Deanship of Scientific Research and Post-Graduate Studies, AlMaarefa University, Diriyah, 13713, Riyadh, Saudi Arabia.



and abstracts. Second, Full-text articles were evaluated to confirm their eligibility. Discrepancies in the selection process were managed by revisiting the eligibility criteria to ensure consistency.

Data extraction

The author extracted data using a pretested form designed to capture key study details, including Author(s), year, country, Type of HPV vaccine, Study design, population, Intervention, comparator, and outcomes. The author manually reviewed each study to ensure the accuracy of the extracted data.

Quality assessment

The quality and validity of the included studies were assessed through critical appraisal. The Mixed Methods Appraisal Tool (MMAT) was employed to evaluate the evidence [Appendix 1].

RESULTS

Out of 820 articles initially identified, 500 were excluded during title and abstract screening for irrelevance or not meeting inclusion criteria, such as focusing on HPV vaccination or long-term efficacy. After a full-text review of 320 articles, 303 were excluded for lacking primary clinical data or long-term follow-up analyses. Ultimately, 17 studies, including randomised controlled trials and long-term follow-up studies, were included in this review [Figure 1]. These studies were categorised into four main themes (Efficacy of HPV vaccines in preventing HPV-related cancers and precancers, Long-term immunogenicity and protection, Comparative efficacy of dosing regimens, Safety and efficacy of novel vaccines). The included studies provide comprehensive evidence on the effectiveness, durability, and safety of HPV vaccines, alongside strategies to optimise vaccination practices globally [Table 1]. See the PRISMA chart for the selection process [Appendix 2].

Efficacy of HPV Vaccines in Preventing HPV-Related Cancers and Precancers

Clinical trials demonstrated the high efficacy of HPV vaccines in preventing precancers and invasive cancers. In a Finnish population-based trial, the bivalent and quadrivalent vaccines reduced the incidence of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) by 87% (95% CI: 82–92%) over a 4-year follow-up³. Similarly, the Costa Rica Vaccine Trial reported a 94% (95% CI: 90–97%) efficacy of the bivalent vaccine in preventing HPV 16/18-related precancers over 7 years¹. The vaccine significantly reduced invasive HPV-positive cancers in a randomised Finnish trial, with a population-level efficacy of 89%⁴.

Long-Term Immunogenicity and Protection

Long-term follow-up studies underline the durability of vaccine-induced immunity and protection. An eight-year follow-up in Chinese women vaccinated with the quadrivalent HPV vaccine showed 92% efficacy in preventing high-risk HPV infections⁵. The CVT highlighted the sustained antibody responses of a single dose of the bivalent vaccine, maintaining 95% seropositivity for HPV 16/18 antibodies over six years⁶. In a multi-country study, the 9-valent HPV vaccine maintained high antibody levels and durable protection for up to 10 years. A longitudinal analysis in Nordic countries also reported stable antibody levels for up to 12 years, remaining above those associated with natural infections⁷.

Comparative Efficacy of Dosing Regimens

Studies examining dosing regimens emphasise the potential for simplifying HPV vaccination strategies. The Doris trial in Tanzania found that a single dose of the bivalent vaccine achieved seroconversion rates of 97% for HPV 16 and 98%

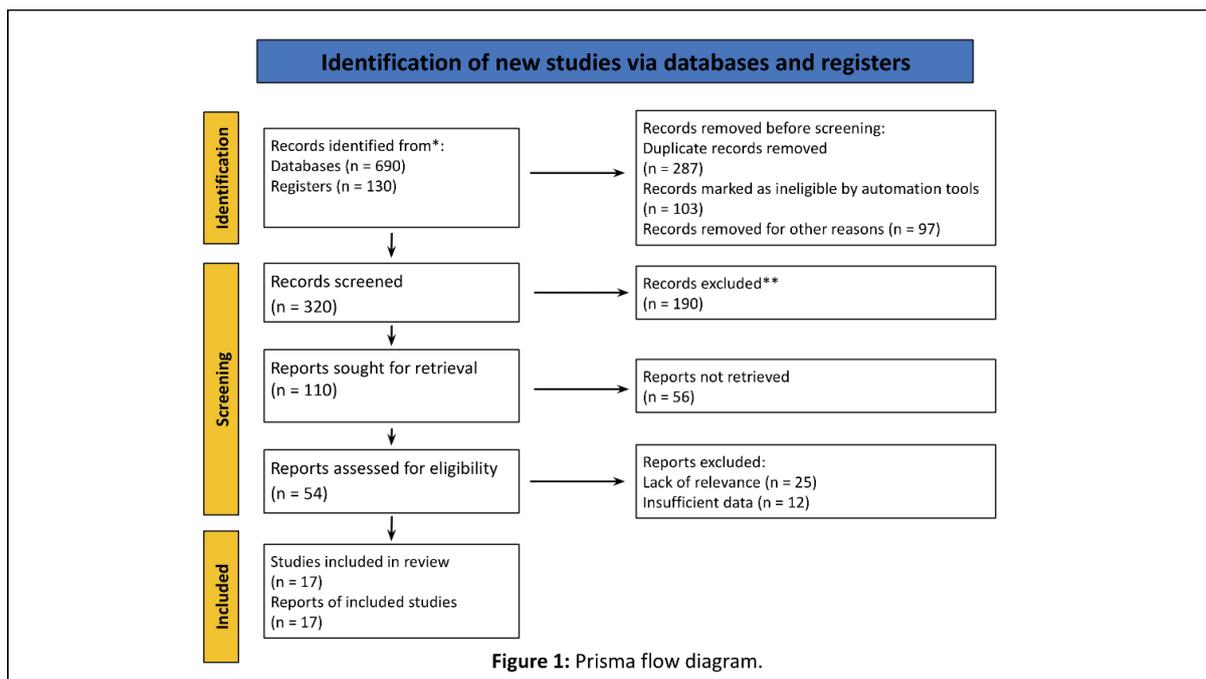


Figure 1: Prisma flow diagram.

Table 1 Characteristics of the studies of Efficacy and Long-Term Impact of HPV Vaccination Strategies with PICO

Study	Title	Country	Study Design	Population (P)	Intervention (I)	Comparator (C)	Outcome (O)
Ayatollahi et al., (2022)(1)	Efficacy of oral zinc sulfate supplementation on clearance of cervical HPV	Iran	Randomized Controlled Trial (RCT)	Women with HPV infection	Zinc supplementation	None	HPV clearance
Watson-Jones et al., (2022)(2)	Immunogenicity and safety of one-dose HPV vaccine compared with two or three doses in Tanzanian girls	Tanzania	Open-Label Non-Inferiority Trial	Tanzanian girls	One-dose HPV vaccine	Two or three doses	Immunogenicity, safety
Lehtinen et al., (2021)(3)	Effectiveness of various HPV vaccination strategies: A community randomized trial in Finland	Finland	Community Randomized Trial	Finnish population	Various vaccination strategies	None	HPV-related cancer reduction
Barnabas et al., (2022)(4)	Efficacy of single-dose HPV vaccination among young African women	Africa (multiple countries)	Randomized Controlled Trial (RCT)	African women	Single-dose HPV vaccine	None	HPV infection prevention
Lehtinen et al., (2024)(5)	Head-to-head comparison of two HPV vaccines for efficacy against CIN3 and AIS	Finland	Population-Based Cluster Randomized Trial	Finnish population	Bivalent and quadrivalent vaccines	None	Efficacy against CIN3 and AIS
Shing et al., (2022)(6)	Precancerous cervical lesions caused by non-vaccine-preventable HPV types after bivalent HPV vaccine	Costa Rica	Long-Term Follow-Up Analysis	Vaccinated women	Bivalent vaccine	None	Lesions caused by non-vaccine HPV types
Zhao et al., (2022)(7)	The eight-year long-term follow-up on the effectiveness of the quadrivalent HPV vaccine in Chinese women	China	Long-Term Follow-Up Study	Chinese women	Quadrivalent vaccine	None	Long-term efficacy
Shu et al., (2022) (8)	Immunogenicity and safety of HPV 4- and 9-valent vaccines in Chinese women	China	Randomized Blinded Controlled Trial	Chinese women	HPV 4- and 9-valent vaccines	Gardasil	Safety, immunogenicity
Qiao et al., (2019)(9)	Efficacy, safety, and immunogenicity of an Escherichia coli-produced bivalent HPV vaccine	China	Interim Analysis of Randomized Clinical Trial	Chinese population	E. coli-produced bivalent vaccine	None	Efficacy, safety
Kreimer et al., (2020)(10)	Evaluation of durability of a single dose of the bivalent HPV vaccine	Costa Rica	Long-Term Follow-Up of RCT	Vaccinated women	Single-dose bivalent vaccine	None	Durability of immunity



Porras et al., (2020)(11)	Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer	Costa Rica	Long-Term Follow-Up Analysis	Women	Bivalent vaccine	None	Efficacy against HPV 16/18 precancers
Lehtinen et al., (2021)(12)	HPV vaccine efficacy against invasive, HPV-positive cancers	Finland	Cluster Randomized Trial	Finnish population	HPV vaccine	None	Invasive HPV-positive cancers prevention
Donken et al., (2019)(13)	Immunogenicity of 2 and 3 doses of the quadrivalent HPV vaccine up to 120 months postvaccination	Canada	Follow-Up of Randomized Controlled Trial	Vaccinated women	2 or 3 doses of quadrivalent vaccine	None	Long-term immunogenicity
Porras et al., (2022)(14)	Design of a trial to evaluate one or two doses of HPV vaccine	Costa Rica	Design of Randomized Non-Inferiority Trial	Women	One or two doses of HPV vaccine	None	Efficacy and cost-effectiveness
Garland, S. M., et al., (2023)(15)	Ten-year follow-up of 9-valent human papillomavirus vaccine	Multi-country study	Long-term Follow-Up Study	9-valent HPV vaccine	None	Long-term immunogenicity, effectiveness, and safety	Individuals vaccinated with 9-valent HPV vaccine
Luxembourg, A., et al., (2020)(16)	Long-term immunogenicity, effectiveness, and safety of nine-valent HPV vaccine	Multi-country study	Extended Follow-Up of Clinical Trial	9-valent HPV vaccine	Quadrivalent HPV vaccine	Immunogenicity, effectiveness, and safety up to 8 years	Adolescents and young adults vaccinated with 9-valent HPV vaccine
Artemchuk, H., et al., (2018)(17)	Long-term antibody response to HPV vaccines: Up to 12 years of follow-up in the Nordic cohort	Nordic countries	Long-term Follow-Up Study	Females aged 10–14 years at vaccination	HPV-16/18 AS04-adjuvanted vaccine	Placebo	Antibody levels up to 12 years post-vaccination

for HPV 18, comparable to multi-dose regimens⁸. An African trial confirmed that single-dose vaccination achieved 96% efficacy in preventing HPV infections, aligning with multi-dose outcomes². Similarly, trial designs in Costa Rica suggest that one- or two-dose schedules offer cost-effective solutions without compromising efficacy⁹.

Safety and Efficacy of Novel Vaccines

Novel vaccines continue to expand HPV prevention strategies. In China, 4- and 9-valent vaccines demonstrated efficacy rates exceeding 95% against high-risk HPV types, with safety profiles comparable to Gardasil¹⁰. The Escherichia coli-produced bivalent vaccine demonstrated an 89% efficacy against HPV 16/18-associated conditions, providing an affordable alternative for low-resource settings¹¹.

Real-world studies reinforce the impact of HPV vaccines in diverse populations. High vaccine coverage (94%) in Finland reduced HPV-related cancers by 75% over five years¹². The CVT further demonstrated the vaccine's effectiveness in a community setting, with evidence of cross-protection against non-vaccine HPV types⁶. Adjunct strategies like zinc

supplementation improved HPV clearance rates by 21%, supporting vaccine efficacy¹³.

DISCUSSION

The current review underscores the substantial efficacy of HPV vaccines in preventing HPV-related cancers and precancers. Notably, the 9-valent HPV vaccine (9vHPV) has demonstrated sustained immunogenicity and durable effectiveness through approximately 7 to 8 years post-vaccination in both girls and boys aged 9–15¹⁴. Additionally, long-term follow-up data indicate that antibody responses remain robust up to 10 years after the third dose, reinforcing the vaccine's long-term protective benefits¹⁵. Our findings align with previous studies highlighting the long-term effectiveness of HPV vaccines. Real-world studies have demonstrated decreases in the prevalence of vaccine-covered HPV types and reduced rates of high-grade cervical lesions and invasive cervical cancer in vaccinated populations¹⁶. Furthermore, evidence suggests that reduced-dose schedules, including single-dose regimens, may offer comparable protection against HPV infection, significantly enhancing vaccine accessibility and compliance¹⁷.



The demonstrated long-term efficacy and safety of HPV vaccines support their continued use in preventing HPV-related diseases. The potential effectiveness of single-dose regimens could simplify vaccination schedules, reduce costs, and improve coverage, particularly in resource-limited settings (CDC, 2024). Policymakers should consider these findings to optimise vaccination strategies and achieve broader public health benefits.

Future research should focus on evaluating the long-term effectiveness of single-dose regimens, assessing the impact of HPV vaccination in diverse and underrepresented populations, and exploring the development of next-generation vaccines that provide broader protection against additional HPV types. Continuous monitoring of vaccine safety and effectiveness in real-world settings remains essential to inform evidence-based policy decisions.

Strengths and limitations

The current review's strength lies in its comprehensive inclusion of randomized controlled trials and long-term follow-up studies, which provide a holistic view of HPV vaccine efficacy, immunogenicity, and safety. The focus on diverse populations and various vaccine types enhances the generalizability of the findings, offering valuable insights into global vaccination strategies. Certain limitations must be acknowledged. The reliance on published data may introduce publication bias, and variations in reporting could affect the comparability of results. Additionally, the review period (2019–2024) may exclude

earlier pivotal studies that have significantly contributed to understanding HPV vaccine efficacy and safety.

CONCLUSION

In conclusion, the review reaffirms the significant role of HPV vaccines in preventing HPV-related diseases, with sustained efficacy and immunogenicity observed over extended periods. The potential for reduced-dose vaccination schedules offers a promising avenue to enhance vaccine uptake and accessibility and contribute to the global effort to reduce the burden of HPV-related cancers.

AUTHORS' CONTRIBUTIONS

The author declares sole responsibility for the conception and design of the work, data acquisition, analysis, and interpretation. The author drafted the manuscript, revised the results and tables, critically evaluated the content for intellectual rigour, approved the final version to be published, and is fully accountable for all aspects of the work, ensuring that any questions related to accuracy or integrity are appropriately addressed and resolved.

CONFLICTS OF INTEREST

No conflicts of interest or competing interests

References

1. Porras C, Tsang SH, Herrero R, Guillén D, Darragh TM, Stoler MH, Hildesheim A, Wagner S, Boland J, Lowy DR, Schiller JT. Efficacy of the bivalent HPV vaccine against HPV 16/18-associated precancer: long-term follow-up results from the Costa Rica Vaccine Trial. *The Lancet Oncology*. 2020 Dec 1;21(12):1643-52.
2. Barnabas RV, Brown ER, Onono MA, Bukusi EA, Njoroge B, Winer RL, Galloway DA, Pinder LF, Donnell D, Wakhungu I, Congo O. Efficacy of single-dose human papillomavirus vaccination among young African women. *NEJM evidence*. 2022 Apr 26;1(5):EVIDoA2100056.
3. Lehtinen M, Gray P, Luostarinen T, Eriksson T, Apter D, Bly A, Harjula K, Heikkilä K, Hokkanen M, Kuortti M, Nieminen P. Head-to-head comparison of two human papillomavirus vaccines for efficacy against cervical intraepithelial neoplasia grade 3 and adenocarcinoma in situ—population-based follow-up of two cluster-randomized trials. *Frontiers in Cellular and Infection Microbiology*. 2024 Sep 9;14:1437704.
4. Lehtinen M, Apter D, Eriksson T, Harjula K, Hokkanen M, Natunen K, Nieminen P, Paavonen J, Palmroth J, Petäjä T, Pukkala E. Effectiveness of various human papillomavirus vaccination strategies: A community randomized trial in Finland. *Cancer medicine*. 2021 Nov;10(21):7759-71.
5. Zhao C, Zhao Y, Li J, Li M, Su Y, Mi X, La Tu SY, Shen D, Ren L, Li Y, Wang L. The eight-year long-term follow-up on the effectiveness of the quadrivalent human papillomavirus vaccine in Chinese women 20-45 years of age. *Human Vaccines & Immunotherapeutics*. 2022 Nov 30;18(5):2052700.
6. Kreimer AR, Sampson JN, Porras C, Schiller JT, Kemp T, Herrero R, Wagner S, Boland J, Schussler J, Lowy DR, Chanock S. Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial. *JNCI: Journal of the National Cancer Institute*. 2020 Oct;112(10):1038-46.
7. Artemchuk H, Eriksson T, Poljak M, Surcel HM, Dillner J, Lehtinen M, Faust H. Long-term antibody response to human papillomavirus vaccines: up to 12 years of follow-up in the Finnish maternity cohort. *The Journal of infectious diseases*. 2019 Jan 29;219(4):582-9.
8. Watson-Jones D, Changalucha J, Whitworth H, Pinto L, Mutani P, Indangasi J, Kemp T, Hashim R, Kamala B, Wiggins R, Songoro T. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. *The Lancet Global Health*. 2022 Oct 1;10(10):e1473-84.



9. Shing JZ, Hu S, Herrero R, Hildesheim A, Porras C, Sampson JN, Schussler J, Schiller JT, Lowy DR, Sierra MS, Carvajal L. Precancerous cervical lesions caused by non-vaccine-preventable HPV types after vaccination with the bivalent AS04-adjuvanted HPV vaccine: an analysis of the long-term follow-up study from the randomised Costa Rica HPV Vaccine Trial. *The Lancet Oncology*. 2022 Jul 1;23(7):940-9.
10. Shu Y, Yu Y, Ji Y, Zhang L, Li Y, Qin H, Huang Z, Ou Z, Huang M, Shen Q, Li Z. Immunogenicity and safety of two novel human papillomavirus 4-and 9-valent vaccines in Chinese women aged 20–45 years: a randomized, blinded, controlled with Gardasil (type 6/11/16/18), phase III non-inferiority clinical trial. *Vaccine*. 2022 Nov 15;40(48):6947-55.
11. Qiao YL, Wu T, Li RC, Hu YM, Wei LH, Li CG, Chen W, Huang SJ, Zhao FH, Li MQ, Pan QJ. Efficacy, safety, and immunogenicity of an Escherichia coli-produced bivalent human papillomavirus vaccine: an interim analysis of a randomized clinical trial. *JNCI: Journal of the National Cancer Institute*. 2020 Feb 1;112(2):145-53.
12. Lehtinen M, Lagheden C, Luostarinen T, Eriksson T, Apter D, Bly A, Gray P, Harjula K, Heikkilä K, Hokkanen M, Karttunen H. Human papillomavirus vaccine efficacy against invasive, HPV-positive cancers: population-based follow-up of a cluster-randomised trial. *BMJ open*. 2021 Dec 1;11(12):e050669.
13. Ayatollahi H, Rajabi E, Yekta Z, Jalali Z. Efficacy of oral zinc sulfate supplementation on clearance of cervical human papillomavirus (HPV); a randomized controlled clinical trial. *Asian Pacific journal of cancer prevention: APJCP*. 2022 Apr;23(4):1285.
14. Olsson SE, Restrepo JA, Reina JC, Pitisuttithum P, Ulied A, Varman M, Van Damme P, Moreira Jr ED, Ferris D, Block S, Bautista O. Long-term immunogenicity, effectiveness, and safety of nine-valent human papillomavirus vaccine in girls and boys 9 to 15 years of age: Interim analysis after 8 years of follow-up. *Papillomavirus Research*. 2020 Dec 1;10:100203.
15. Long-term follow-up data on sustained immunogenicity and safety for Gardasil®9 published in *Pediatrics*. Merck.com. (2024, December 26). <https://www.merck.com/news/long-term-follow-up-data-on-sustained-immunogenicity-and-safety-for-gardasil9-published-in-pediatrics/>. . Accessed October 2024.
16. Restrepo J, Herrera T, Samakoses R, Reina JC, Pitisuttithum P, Ulied A, Bekker LG, Moreira Jr ED, Olsson SE, Block SL, Hammes LS. Ten-year follow-up of 9-valent human papillomavirus vaccine: immunogenicity, effectiveness, and safety. *Pediatrics*. 2023 Oct 1;152(4):e2022060993.
17. Montroy J, Salvadori MI, Forbes N, Dubey V, Almasri S, Jirovec A, Yan C, Gusic K, Stevens A, Young K, Tunis M. Efficacy, effectiveness and immunogenicity of reduced HPV vaccination schedules: A review of available evidence. *Canada Communicable Disease Report*. 2024 Jun 28;50(6):166.

