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THE EFFECTIVENESS, IMMUNOGENICITY, AND SAFETY OF THE *Escherichia coli* BASED BIVALENT HUMAN PAPILLOMAVIRUS (TYPES 16 AND 18) VACCINE PREVENTING CERVICAL CANCER

A Systematic Review

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ABSTRACT

Background: *Cervical cancer is the fourth most prevalent cancer worldwide and ranks second in Indonesia, with a high mortality rate among women. Cervical cancer ranks highest in treatment costs in Indonesia. HPV-16/18 infection causes nearly all cases of cervical cancer. The HPV-16/18 bivalent vaccine made with E. coli holds potential as a more affordable HPV vaccine than other commercial vaccines.*

Objective: *This systematic review aimed to discuss the effectiveness, immunogenicity, and safety of the bivalent HPV-16/18 vaccine produced by E. coli based on evidence from available studies.*

Methods: *This systematic review included valid experimental studies retrieved from PubMed, Cochrane, ScienceDirect, and Taylor and Francais databases that met the inclusion criteria. The search method used Boolean operators, with the literature cited from 2014 to 2024.*

Results and Discussion: *Seven studies met the inclusion criteria. The results of all studies indicate that the bivalent HPV-16/18 vaccine produced by E. coli has a high effectiveness and good immunogenicity. There were no significant side effects associated with vaccination, and most of the side effects were minor.*

Conclusion: *The bivalent HPV-16/18 vaccine produced by E. coli could serve as a reliable and economical alternative to prophylactic HPV vaccination for cervical cancer prevention.*

Keywords: *Escherichia coli, efficacy, human papillomavirus vaccine, immunogenicity, safety*

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1. INTRODUCTION

Nearly all occurrences of cervical cancer globally have been linked to human papillomavirus (HPV), specifically to strains 16 and 18. Cervical cancer is the fourth most frequent malignancy among women in the world, expected to account for 342,000 deaths and 604,000 new cases in 2020. Approximately 90% of these new cases and deaths occur in low- and moderate-income countries.[1] With a 9.2% prevalence rate, cervical cancer ranks second in Indonesia and is expected to account for 21,003 fatalities and 36,633 new cases in 2020.[2] As a result, it is imperative that cervical cancer be prevented and treated quickly.

Cancer remains a significant burden for national health care providers. In 2018, BPJS Kesehatan spent 2.17 trillion rupiahs on cancer treatment, with the highest financing allocated to cervical cancer at 393 million rupiahs (27.03%).[3] In 2021, the expense for cancer treatment amounted to 3.5 trillion rupiahs, with cervical cancer remaining the leading cost driver.[4] Cervical cancer can be prevented through HPV vaccination. The quadrivalent HPV-6/11/16/18 vaccine (Gardasil®), the nonavalent HPV vaccine (Gardasil®9), and the bivalent HPV-16/18 vaccine (Cervarix) are the HPV vaccinations now available on the market.[5] Gardasil and Cervarix, eukaryote-based vaccines, have been shown to reduce the incidence of cervical cancer. However, their high costs and limited availability pose challenges, particularly in lower-middle-income countries.[6] Prokaryote-based vaccines are cost-effective alternatives. The currently available prokaryote-based HPV vaccine is the bivalent HPV-16/18 vaccine developed using *Eschericia coli* (*E. coli*).[7]

The HPV-16/18 vaccine manufactured using E. coli shows promise as an inexpensive HPV vaccine, with acceptable safety, immunogenicity, and efficacy. Numerous phase I–III clinical trials as well as additional investigations have demonstrated its safety, immunogenicity, and efficacy. Based on the information already available from numerous studies, this systematic review addresses the safety, immunogenicity, and effectiveness of the *E.coli* based HPV-16/18 bivalent vaccine.

2. METHODS

This systematic literature review adhered to the protocols outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions.

Search Strategy

A literature search was performed using PubMed, Cochrane, SCOPUS, and Taylor and Francais databases. Literature was searched on February 29, 2024, using the search keywords: (("Escherichia coli" OR "E. coli") AND ("HPV" OR "Human Papillomavirus" OR "Cervical Cancer")). **Figure 1** illustrates the detailed search strategy for each database.

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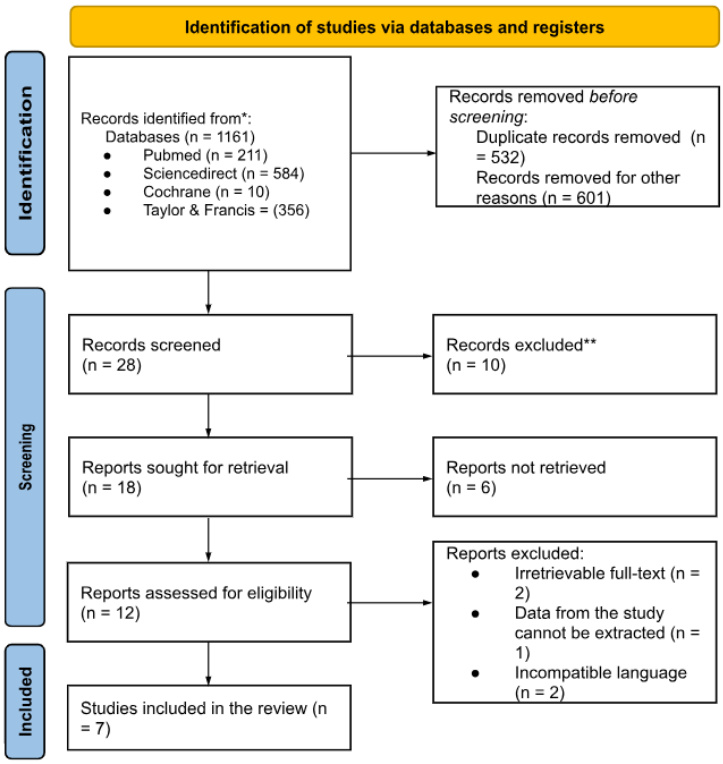

Figure 1. Flowchart of the article screening and selection process.

Inclusion and Exclusion Criteria

To enhance the specificity and relevance of the data, inclusion and exclusion criteria were set up prior to the literature search. The inclusion criteria were defined as follows: 1) Randomized Controlled Trials (RCTs), 2) studies published within the last 10 years, 3) study populations comprising healthy women aged 9-45 years, 4) peer-reviewed journals, and 5) studies involving the intervention of the bivalent HPV-16/18 vaccine produced by *E. coli*. The exclusion criteria were as follows: (1) full-text articles that could not be extracted, (2) incompatible language, and (3) studies other than clinical trials in humans. The PICOS framework was used to structure the inclusion criteria, as shown in **Table 1**.

Population	Intervention	Comparison	Outcome	Study Design
Women in good health aged 9 to 45	Bivalent Human Papilloma Virus (Type 16/18) vaccine produced by *Escherichia coli*	Placebo or other available vaccines	effectiveness, immunogenicity, and safety of the vaccine	Systematic Review of Randomized Controlled Trials

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Assessment of Quality and Publication Bias

The Cochrane Risk of Bias (ROB) tool for Randomized Controlled Trials was utilized to evaluate the risk of bias in the final publications. The results were categorized into three levels: low, unclear, and high risk of bias and recorded in a bias domain file (.xlsx), which was then uploaded to the ROBVIS website. Quality assessments were conducted independently by two reviewers, who resolved any disagreements through discussion.

3. RESULTS AND DISCUSSION

Study Designs and Characteristics

Seven studies met the inclusion criteria with an experimental RCT design discussing the effectiveness, immunogenicity, and safety of *E. coli* based HPV-16/18 vaccine were identified. A summary of the characteristic of the included studies is provided in table **Table 2**.[8–14] The study quality assessment is shown in **Figure 2**.

Pathophysiology of Cervical Cancer

The pathophysiology of cervical cancer is closely associated with Human Papillomavirus (HPV), which is mainly transmitted through sexual contact. Approximately 70% cases of cervical cancer are caused by HPV strains 16 and 18.[15] HPV infects cervical epithelial cells, initiating a process involving internalization, replication, and a potential 10-year incubation period. Most primary infections resolve with a robust immune system, but weakened immunity can lead to persistent infection.[6,17]

Persistent HPV infection reduces pro-inflammatory cytokines, such as TNF-α, and promotes anti-inflammatory cytokines, such as IL-10, to inhibit immune cell migration. Tumor-associated macrophages become pivotal in inducing cancer cell proliferation, migration, angiogenesis, and immune suppression.[17]

The expression of oncogenes E6 and E7 in HPV triggers oncogenesis, disrupting cell regulation and leading to continued division, evasion of apoptosis, and transformation into invasive cancer cells. Infected cells display cervical intraepithelial neoplasia (CIN), which is categorized into grades 1–3. CIN 1 represents low-grade lesions, manageable by the immune system, while CIN 2 and CIN 3 are high-grade lesions involving increasing levels of basal epithelial changes.[16,18]

Mechanism of Action of HPV Prophylactic Vaccine

The *E. coli* based HPV-16/18 vaccine is a virus-like particle (VLP) vaccine, similar to Cervarix and Gardasil. While Cervarix is manufactured from insect cells (Trichoplusia) infected with baculovirus, while Gardasil is made from *Saccharomyces cerevisiae* expressing the L1 gene, both of these methods involve eukaryotic systems which incur high cost. In contrast, prokaryotic-based vaccines, such as *E. coli*-based production of the HPV L1 VLP vaccine, represent a more affordable alternative. [19]

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Table 2. Basic characteristics of the included clinical studies (N =7).

Author, year	Study Design	Study site	Objective	Population	Sample Size	Follow up	Intervention	Control
Qiao et al., 2020[8]	Phase III randomized double-blind, controlled clinical trial	Multicenter	Assesing the effectivenes, safety, and immunogenicity of the HPV-16/18 vaccine produced by *E. coli*	Women 18-45 years old	7372	42 months	HPV-16/18 vaccine produced by *E. coli* (given at months 0, 1, and 6)	Hepatitis E vaccine (at months 0, 1, and 6)
Zhao et al., 2022[9]	Phase III, randomized, double-blind, controlled trial	Multicenter	Providing an analysis of safety and long-term effectiveness following immunization, based on a 66-month follow-up period.	Women 18-45 years old	7372	66 months	HPV-16/18 vaccine produced by *E. coli* (given at months 0, 1, and 6)	Hepatitis E vaccine (at months 0, 1, and 6)
Hu et al., 2020[10]	Randomized	Single-centered	Proving whether the immunogenicity of the vaccine with a schedule of 2 doses or 3 doses in adolescent girls is not inferior to that adult women given a 3-dose regimen.	Women 9-26 years old	979	7 months	Group of children (age 9-17 years) receiving HPV-16/18 vaccine: - Ages 9-14 given 2 doses (months 0 and 6) - Ages 15-17 given 3 doses (months 0, 1, and 6)	Adult women (18-26 years old) given 3 doses of HPV-16/18 vaccine (months 0, 1, 6).
Wu et al., 2015[11]	Phase II, randomized double-blind, clinical trial	Single center	Investigating the immunogenicity and safety of the HPV-16/18 vaccine produced by *E. coli* in three different doses.	Women 18-25 years old	1600	7 months	A recombinant HPV-16/18 vaccine administered three times (at months 0, 1, and 6), divided into three dose groups of 90µg, 60µg, and 30µg.	Hepatitis B vaccine administered three times (at months 0, 1, and 6).
Su et al., 2020[12]	Phase III, randomized double-blind, clinical trial	Multicenter	Analyzed the safety and consistency of immunogenicity of three different vaccine lots.	Women 18-45 years old	7372	42 months	The administration of three doses of HPV-16/18 vaccine given at months 0, 1, and 6 in three different lots.	Hepatitis E vaccine (at months 0, 1, and 6)
Yao et al., 2022[13]	Randomized	Single center	Assessing the long-term immunogenicity and safety of the HPV-16/18 vaccine produced by *E. coli* following a 30-month period.	Healthy women 9-26 years old.	979	30 months	Group of children (aged 9-17 years) receiving the HPV-16/18 vaccine: - Ages 9-14 given 2 doses (at months 0 and 6)	Adult women (18-26 years old) given 3 doses of HPV-16/18 vaccine (months 0, 1, 6).

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							- Ages 15-17 given 3 doses (at months 0, 1, and 6)	
Yu et al., 2020[14]	Phase III, randomized double-blind, clinical trial	Multicenter	Observing the impact of vaccine schedule delay on antibody levels	Women 18-45 years old	7372	30 months	Administered the E. coli-based HPV-16/18 vaccine at months 0, 1, and 6 with varying intervals between doses: - First interval: 28-40 days, 41-50 days, 51-60 days - Second interval: 103-139 days, 140-160 days, 161-198 days	Hepatitis E vaccine (at months 0, 1, and 6)

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Figure 2. Risk of bias analysis.

HPV VLP vaccines can elicit immune responses from both B and T cells, leading to the production of antibodies, particularly immunoglobulin G (IgG). These IgG antibodies can attach to HPV virions, preventing the initial infection. When IgG antibodies are administered through intramuscular injection, they can reach the location of cervicovaginal infection via two main routes. The first route involves IgG passing through the epithelial barrier and entering mucosal secretion (transudation) via the neonatal Fc receptor in the cervix. The second route involves the direct release of serum and interstitial antibodies at the site of injury (exudation), allowing the antibodies to attach to virions on the basement membrane. Both pathways are likely sufficient to prevent infection, cervical cancer, cervical intraepithelial neoplasia (CIN), and adenocarcinoma in situ (AIS).[20,21]

Effectiveness of the HPV-16/18 Vaccine Produced by *E. coli*

The clinical effectiveness of the *E. coli* based HPV-16/18 vaccine was evaluated in two studies. The effectiveness of the vaccine was determined using multicenter, double-blind, Phase III RCTs. The primary effectiveness outcomes of the vaccination were its ability to prevent high-grade genital lesions, which included persistent HPV 16 and 18 infections as well as cervical

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intraepithelial neoplasia grade 2 or higher (CIN2+), vulvar intraepithelial neoplasia grade 2 or higher (VIN2+), or vaginal intraepithelial neoplasia grade 2 or higher (VaIN2+).[8,9] **Table 3** provides an overview of the acquired effectiveness data.

Phase III clinical trials have demonstrated consistently highly effective of the vaccine in preventing low-grade (CIN1+/VIN1+/VaIN1+) and high-grade (CIN2+/VIN2+/VaIN2+) genital lesions linked to HPV 16 and 18. Preliminary research indicated that the HPV 16 vaccine was proven effective against high-grade lesions; however, the HPV 18 vaccine did not demonstrate the same level of effectiveness because there were not as many endpoint data. However, even though the effectiveness level was not as good as HPV 16 protection, this vaccine still worked well to prevent cytological abnormalities, and chronic infections associated with HPV-18. [8,9]

E. coli based HPV-16/18 vaccine showed remarkable efficacy in preventing 100% (95% CI) of CIN2+, VIN2+, and VaIN2+ cases in women aged 18 and 26 in both per-protocol and mITT sets. Furthermore, in women aged 27 to 45, the vaccination was 100% successful in preventing persistent 6-month infections; efficacy rates were 94.4% in the mITT set and 93.9% in the per-protocol set (p<0.0001). Although HPV infection rates are highest in women under 25, the vaccine also sufficient protection to women aged 27 to 45, demonstrating high effectiveness and potential benefits for this older age group.[9]

Table 3. Vaccine effectivenes against high-grade genital lesions and persistent infection.

Subgroup	Analisys	Efficay%, (95% CI)			
		Qiao et al., 2020[8]		Zhao et al., 2022[9]	
		High grade genital lesions	Persistent infection	High grade genital lesions	Persistent infection
Anti-HPV-16 & 18	Per protocol	100 (55.6, 100)	97.8 (87.1, 99.9)	100 (67.2, 100)	97.3 (89.9, 99.7)
	mITT	100 (55.4, 100)	97.9 (88.0, 99.9)	100 (67.1, 100)	97.4 (90.3, 99.7)
Subgroup	Analisys	Zhao et al., 2022[9]			
		Women 18-26 years old		Women 27-45 years old	
		High grade genital lesions	Persistent infection	High grade genital lesions	Persistent infection
Anti-HPV-16 & 18	Per protokol	100 (40.6, 100)	93.9 (76.3, 99.3)	100 (-7.9, 100)	100 (90.6, 100.0)
	mITT	100 (40.4, 100)	94.4 (78.4, 99.3)	100 (7.7, 100)	100 (90.6, 100)

Immunogenicity of the HPV-16/18 Vaccine Produced by *E. coli*

All the included studies assessed the immunogenicity of *E. coli* based HPV-16/18 vaccine. Immunogenecity was evaluated based on seroconversion, seropositivity, geometric mean concentration (GMC), and geometric mean titer (GMT)

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Table 4. Immunogenicity of the vaccine in the included studies.

	Wu et al., 2015[11]							
	30ug		60ug		90ug		Control (Hep E)	
Subgroup	Seroconversion (95% CI) (%)	GMT	Seroconversion (95% CI) (%)	GMT	Seroconversion (95% CI) (%)	GMT	Seroconversion (95% CI) (%)	GMT
HPV-16 IgG	100 (98.6, 100)	5882 (5374, 6438)	100 (98.7, 100)	7977 (7321, 8693)	100 (98.6, 100)	9145 (8383, 9976)	1.6 (0.4, 3.5)	11 (11, 12)
HPV-18 IgG	100 (98.8, 100)	4720 (4305, 5176)	100 (98.8, 100)	5184 (4788, 5612)	100 (98.8, 100)	5657 (5203, 6151)	2 (0.4, 3.5)	10 (10, 11)
HPV 16 Neutralizing Ab	100 (97.1, 100)	7596 (6,395, 9,024)	100 (96.9, 100)	10,548 (9,034, 12,315)	100 (96.7, 100)	12,505 (10,532, 14,848)	0.8 (0, 2.5)	160 (N/A)
HPV 18 Neutralizing Ab	99 (97.7, 100)	6875 (5595, 8448)	100 (97.1, 100)	7261 (6043, 8725)	100 (97, 100)	8097 (6911, 9485)	0 (0, 2.8)	N/A (N/A)

	Qiao et al., 2020[8]		Zhao et al., 2022[9]			
	Month 7		Month 7		Month 66	
Subgroup	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)	Seropositivity (95% CI) (%)	GMC (95% CI) (IU/mL)
Anti-HPV-16	100	790.4 (767.5, 813.9)	100	726.76 (638.49, 827.24)	100	71.42 (59.47, 85.78)
Anti-HPV-18	99.9	267.9 (260.4, 275.6)	100	435.47 (378.02, 501.64)	98.3	33.78 (27.65, 41.28)

	Hu et al., 2020[10]							
	9-14 years (2 doses)		9-14 years (3 doses)		9-17 years (3 doses)		18-26 years (3 doses)	
Subgroup	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)	Seroconversion (95% CI) (%)	GMC (95% CI) (IU/mL)

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Month 6	HPV-16 IgG	100 (98.6, 100)	81 (74, 88)	100 (98.5, 100)	446 (416, 478)	100 (99.0, 100)	402 (378, 428)	100 (97.8, 100)	251 (227, 277)
	HPV-18 IgG	98.5 (96.3, 99.6)	16 (14, 17)	100 (98.6, 100)	79 (73, 86)	99.7 (98.6, 100)	69 (64, 74)	100 (97.9, 100)	42 (38, 47)
Month 7	HPV-16 IgG	100 (98.6, 100)	2219 (2045, 2406)	100 (98.5, 100)	3163 (2914, 3432)	100 (99.0, 100)	2749 (2569, 2941)	100 (97.8, 100)	1560 (1405, 1731)
	HPV-18 IgG	100 (98.7, 100)	397 (365, 431)	100 (98.6, 100)	798 (730, 873)	100 (99.1, 100)	656 (608, 709)	100 (97.9, 100)	340 (306, 378)
	HPV-16 Neutralizing Ab	100 (98.7, 100)	1466 (1339, 1606)	100 (98.7, 100)	2154 (1976, 2347)	100 (99.1, 100)	1903 (1774, 2042)	100 (98.1, 100)	1012 (900, 1136)
	HPV-18 Neutralizing Ab	100 (98.7, 100)	607 (555, 663)	100 (98.7, 100)	1323 (1204, 1453)	100 (99.1, 100)	1099 (1015, 1192)	99.5 (97.2, 100)	503 (443, 571)

Yao et al., 2022[13]

		9-14 years (2 doses)		9-14 years (3 doses)		9-17 years (3 doses)		18-26 years (3 doses)	
		Seropositivity (95% CI) (%)	GMC (95% CI) (IU/mL)	Seropositivity (95% CI) (%)	GMC (95% CI) (IU/mL)	Seropositivity (95% CI) (%)	GMC (95% CI) (IU/mL)	Seropositivity (95% CI) (%)	GMC (95% CI) (IU/mL)
Month 18	HPV-16 IgG	100 (98.6, 100)	128.7 (117.3, 141.1)	99.6 (97.8, 100)	231.5 (211.1, 253.9)	100 (99.0, 100)	206.2 (190.8, 222.9)	100 (97.7, 100)	122.9 (108.7, 139.1)
	HPV-18 IgG	100 (98.6, 100)	45.5 (41.1, 50.3)	100 (98.6, 100)	133.5 (120.0, 148.6)	100 (99.0, 100)	110.3 (100.6, 121.0)	100 (97.8, 100)	50.0 (43.4, 57.5)

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Month 30	HPV-16 IgG	100 (98.5, 100)	73.2 (66.0, 81.1)	100 (98.4, 100)	139.3 (126.3, 153.7)	100 (98.9, 100)	125.3 (115.3, 136.1)	100 (97.5, 100)	72.6 (63.9, 82.6)
	HPV-18 igG	99.6 (97.8, 100)	24.9 (22.4, 27.6)	100 (98.5, 100)	71.2 (63.8, 79.5)	100 (99.0, 100)	60.2 (54.8, 66.2)	100 (97.7, 100)	28.3 (24.6, 32.6)

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in the sample populations.[8–11, 13] The findings related to immunogenicity are summarized in **Table 4.**

A phase II clinical trial was carried out to evaluate the immunogenicity of the vaccine at various doses: 30 µg, 60 µg, and 90 µg. Antibody titers in all dosing groups were 100 times higher than those obtained from spontaneous HPV infection. However, the 30 µg dose resulted in lower neutralizing antibodies against HPV-16 than the 60 µg and 90 µg doses did. In contrast, neutralizing antibodies against HPV-18 remained stable across all three dose levels. [11]

The assessment of vaccine immunogenicity across three age groups—adult women given three doses, children aged 9–14 years given two doses, and children aged 9–17 years given three doses—demonstrated favorable results. The findings showed that children aged 9–14 years were not lower than those in the adult group. Considering that children and adolescents are the main target for the HPV vaccination, the *E. coli* based HPV-16/18 vaccine demonstrated long-term protection against HPV-16/18 infections in children aged 9–14 who administered two doses and 9–17 who administered three doses.[10,11,13]

Phase III clinical trial by Qiao et al. (2020), the vaccine demonstrated a 100% seroconversion rate and induced antibodies 100 times higher for HPV-16 and 50 times higher for HPV-18 compared to those obtained through HPV infection.[8] Long-term immunogenicity was assessed from month 7 to month 66. IgG antibody levels peaked at month 7 (after the third vaccination) and decreased by month 42. Despite the decrease in antibody titers, evaluation at month 66 revealed a seropositivity rate of 98%, with IgG levels still providing adequate protection against HPV-16/18 infections without evidence of waning immunity.[8,9]

Yu et al. (2020) evaluated the impact of vaccination intervals on immunogenicity. Typically, the vaccine is administered three times at months 0, 1, and 6, with standard intervals of 28-40 days between the first and second doses and 140-160 days between the second and third doses. However, in this study, longer intervals were used, with 28-60 days between the first and second doses, and 150-240 days between the second and third doses. The results indicated that variations in these intervals did not significantly affect antibody levels, with the lowest GMC ratios 0.86 for HPV-16 and 0.83 for HPV-18, both above the lower limit of the GMC ratio at 0.64 (95% CI). The study also suggested that optimal antibody responses might be achieved by administering the second dose on schedule and delaying the third dose rather than strictly adhering to the standard vaccination schedule. [14]

Furthermore, Su et al. (2020) conducted a study assessed the stability of the E. coli-based HPV-16/18 vaccine across three different lots to evaluate the quality of each batch. The results demonstrated consistent induction of specific IgG for HPV-16/18 and neutralizing antibodies, with seroconversion rates ranging from 99.9% to 100% at month 7, and remain above 98.8% up to month 42. IgG levels for HPV-16/18 at month 7 ranged from 779.7 to 802.9 IU/mL and 265.7 to 270.3 IU/mL, respectively, across the lots.

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Equivalence analysis showed that the GMC ratios of IgG and neutralizing antibodies among three different lots within the normal range. [12]

Safety and Vaccine Dosage

Safety analysis of *E. coli* based HPV-16/18 vaccine is conducted by examining all adverse events (AE) and serious adverse events (SAE) that occur in the sample population.[8–11] A summary of the safety data from these studies is presented in **Table 5**.

Table 5. Vaccine safety based on adverse events.

Events	Wu et al., 2015[11]			
	30ug	60ug	90ug	Control
All local AEs	24.90%	22.80%	23.10%	19.40%
All systemic AEs	49.50%	49.80%	46.10%	47.60%
SAE	1%	0.30%	1.50%	0.80%
Events	Hu et al., 2020[10]			
	9-14 years (2 doses) (n=301)	9-14 years (3 doses) (n=304)	9-17 years (3 doses) (n=453)	18-26 years (3 doses) (n=225)
All local AEs	24.3%	28.3%	31.1%	34.7%
All systemic AEs	41.9%	48.0%	48.3%	%34.2%
SAE	NA	NA	NA	NA
Events	Qiao et al., 2020[8]		Zhao et al., 2022[9]	
	Vaccine group (n=3691)	Control group (n=3681)	Vaccine group (n=3691)	Control group (n=3681)
All local AEs	37.80%	42.20%	NA	NA
All systemic AEs	45.6	46.2	NA	NA
SAE	5.60%	6.60%	7.20%	7.90%
Pregnancy events	Qiao et al., 2020[8]		Zhao et al., 2022[9]	
	Vaccine group (1187 events)	Control group (1219 events)	Vaccine group (1661 events)	Control group (1684 events)
Ongoing	0.30%	0.60%	0%	0%
Normal delivery	46.70%	50.30%	50.30%	53.10%
Terminal pregnancy	NA	NA	49.70%	46.90%
Spontaneous abortion	5.70%	5.60%	NA	NA

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Stillbirth	0.80%	1.10%	NA	NA
Pregnancy-related complications	0.90%	0.60%	NA	NA
Elective termination	45.50%	41.80%	NA	NA
Normal infant	99.80%	99.70%	99.90%	99.80%
Congenital abnormality	0%	0.30%	0%	0.20%
Other complications or abnormality	0.20%	0%	0.10%	0%

Hu et al. (2014) conducted a clinical trial to assess E. coli based HPV-16/18 vaccine safety. According to the study, 32 out of 38 participants (84.2%) had mild, transient side effects that resolved on their own. No serious adverse events were observed. [22]

Subsequent studies have demonstrated similar safety profiles between the intervention and control groups. [8–11] Research indicated that both the 90 µg and 60 µg doses exhibited better immunogenicity than the 30 µg dose. However, in terms of safety, the 60 µg dose had fewer side effects compared to the 90 µg dose, leading to the selection of the 60 µg dose for further clinical trials.[11]

According to Hu et al. (2020), reported adverse effects in females were mild, with no serious adverse events (SAEs) associated with the vaccine.(10) The incidence of adverse effects was similar between the intervention and control groups. Additionaly, there were no issues with pregnancy, congenital abnormalities, or complications associated with vaccination in either groups.[8,9] These findings confirm that the *E. coli* based HPV-16/18 vaccine is well-tolerated.

Comparison of Immunogenicity, effectiveness, Safety, and Cost-Effectiveness with Commercial HPV Vaccines

Wu et al. (2015) compared the immunogenicity of the E. coli-based HPV-16/18 vaccine (commercialized in China under the name Cecolin) with previous HPV vaccines. The findings revealed that Cervarix elicited the strongest neutralizing antibody response, followed by Cecolin and Gardasil. [11]

Cervarix and Cecolin have the same efficacy in preventing cervical cancer, CIN grades I-III, and AIS caused by HPV-16/18. Meanwhile, Gardasil (quadrivalent vaccine) provides broader protection against HPV-6/11/16/18, but its efficacy is not as high as Cervarix.[23] All three vaccines have demonstrated tolerable side effects, including local reactions such as soreness, erythema, and swelling at the injection area, and systemic side effects like fever, weakness, myalgia, arthralgia, nausea, vomiting, and loss of appetite.[24]

Vaccine availability can be obtained through various means, including independent purchases, purchasing through GAVI/UNICEF, and government contracts with pharmaceutical companies. For

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individual purchase, the cost of Cervarix is US$262 for three doses, Gardasil is US$360 for three doses, and Cecolin is priced at US$47.70 per dose, which is nearly 50% less expensive than Cervarix.[6] Meanwhile, purchasing through GAVI/UNICEF is reasonably priced with each dosage of Cervarix costing US$5.18, Gardasil costing US$4.50, and Cecolin costing $2.90.[25] Thus, the *E. coli* based HPV-16/18 vaccine has a cost-effectiveness advantage over other commercial vaccines with equivalent efficacy.

Strength and Limitation

The current systematic review possesses key strengths, including a large sample size, multicenter trials ensuring diverse representation, and extended follow-up periods of up to 66 months for a comprehensive assessment. Randomized controlled trials increase scientific rigour and reduce bias. Comprehensive assessments that address safety, immunogenicity, and efficacy have advanced our understanding.

Nonetheless, limitations exist, such as the focus on women aged 9-45, potentially limits generalizability. Variable follow-up times could leave out important aspects of long-term efficacy. Research population homogeneity may limit the overall value of the study, and there is currently no research that directly compares the *E. coli* based HPV-16/18 vaccine with commercial vaccines as a control. Biases may persist even after randomization. To gain a more nuanced understanding of these factors, it is essential to be aware of them.

4. CONCLUSION

The *E. coli* based HPV-16/18 vaccine demonstrated high efficacy, robust immunogenicity, and good tolerability. Moreover, it holds more cost-effective than other commercial vaccines, making it viable option for low and middle income countries. Further research is required to explore its efficacy, immunogenicity, and safety in a larger population. Comparative studies using commercial HPV vaccines as controls would enhance our understanding of the profiles of each vaccine.

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