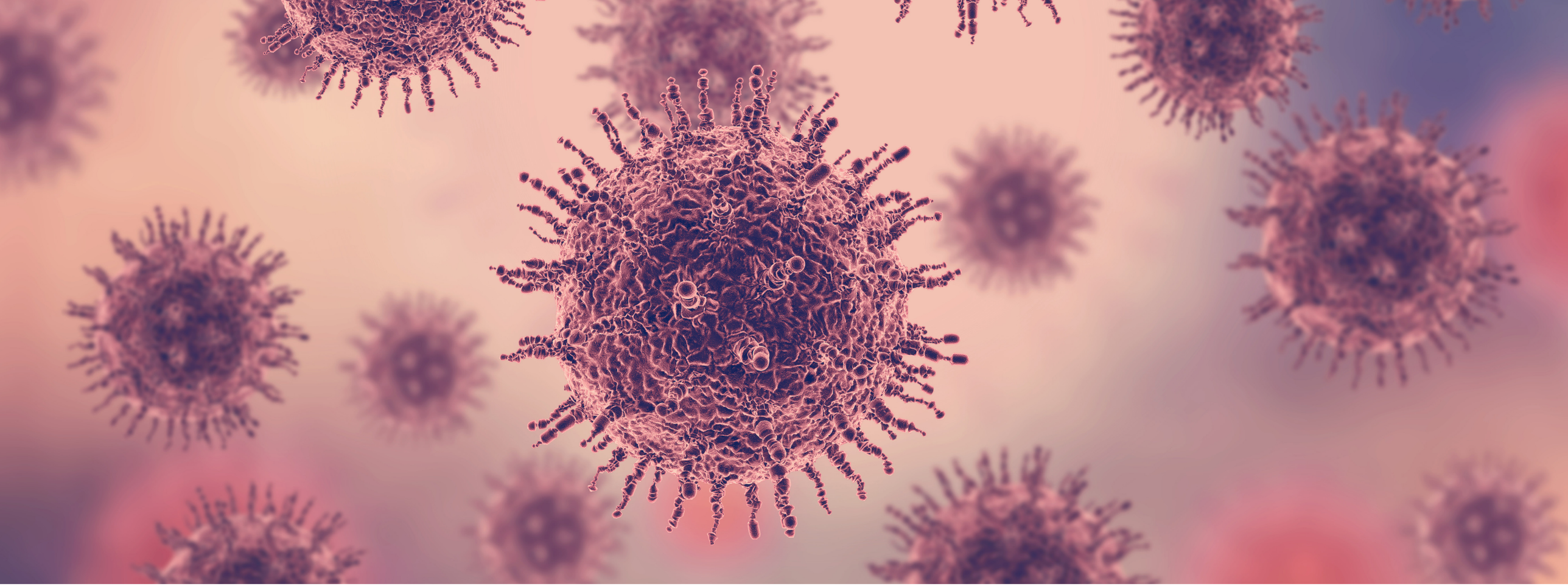
CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Immunogenicity and safety of Cervarix HPV-16/18 AS04-adjuvant vaccine against HPV induced cervical cancer in women (15+ years)
Authors	Zagoneanu, Adina Elena
Publication date	2023
Original Citation	Zagoneanu, A. E. (2023) 'Immunogenicity and safety of Cervarix HPV-16/18 AS04-adjuvant vaccine against HPV induced cervical cancer in women (15+ years)', UCC Student Medical Journal, Vol. 3, pp. 50-61. https://doi.org/10.33178/SMJ.2023.1.5
Type of publication	Peer-reviewed Article
Link to publisher's version	https://journals.ucc.ie/index.php/smj/article/view/4323/6488 - 10.33178/SMJ.2023.1.5
Rights	© 2023, the Author(s). This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License. - https://creativecommons.org/licenses/by-nc/4.0
Download date	2026-11-07 02:22:38
Item downloaded from	https://hdl.handle.net/10468/16563



UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh



Immunogenicity and safety of Cervarix HPV-16/18 AS04-adjuvant vaccine against HPV induced cervical cancer in women (15+ years)

ADINA ELENA ZAGONEANU

Abstract

BACKGROUND: The incidence of cervical cancer has decreased by over 50% from the mid-1970s to the mid-2000s. This is due in part to an increase in screening, which can identify cervical changes before they turn cancerous. Decreasing incidence rates in young women may be due to the use of the HPV vaccine [1]. There are currently three types of HPV vaccines on the market: bivalent, quadrivalent and nine-valent HPV vaccines. These are administered in three-doses to both sexes from age 15 upwards to prevent HPV infection. Many medical systems support the vaccination of teenage girls and boys with HPV vaccines during their secondary school years in order to reduce the incidence of HPV-related cervical cancer in women. Despite the discovery of the link between HPV and cervical cancer in 1985, the beginning of vaccine production in 2002, and promotion of screening procedures since the 1960's, cervical cancer is still the fourth most common cancer in women worldwide today [2].

OBJECTIVE: This review aims to analyse the immunogenicity and safety of Cervarix®, also known as HPV-16/18 AS04-adjuvant vaccine, in women (15+ years) against cervical cancer.

METHODS: The literature review analysing the effectiveness and immunogenicity of HPV-16/18 AS04-ADJUVANTED Vaccine against cervical cancer, was conducted by using two main databases: EbescoHost (Medline and Academic Search) and PubMed. Advanced searches were conducted using specific key words, various filters and Boolean operators 'OR' and 'AND' to find the most suitable literature. This process resulted in over 100 results. From this cohort, clinical trials were selected in accordance with the specific inclusion and exclusion criteria determined for the review. After duplicates from both databases were removed, the studies were assessed in order or title, population and objective relevance, and the top 10 most relevant articles to the title of the literature review, were selected for the literature review.

RESULTS: The 10 clinical trials selected all obtained a minimum of 10 out of the 11 CASP[3] requirements indicating good study quality. All 10 studies were successful in proving the immunogenicity and safety of the HPV-16/18 AS04-adjuvant vaccine in protecting women 15+ (15-55 years) from developing HPV-induced cervical cancer [15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. This confers that vaccination against HPV-16/18 virus proves to be effective in preventing HPV-induced CIN and cervical cancer and is a safe to administer vaccine.

Introduction

Cervical cancer is the fourth most common cancer affecting women globally [2]. It is diagnosed in more than 500,000 women every year and leads to 250,000 deaths [4]. Statistics show, a woman dies from cervical cancer every two minutes [4]. 99% of cervical cancer are due to human papillomavirus [HPV] infection [6], most commonly HPV-16 and HPV-18 [5].

Given the knowledge that most cervical cancers are caused by HPV, for which there are already vaccination programmes in place, the above figures are startling.

Anti-HPV vaccinations began in the early 2000's leading to a marked decrease of 50% in yearly cervical cancer rates.

Currently we have three HPV vaccines on the market, namely the "9-valent HPV vaccine (Gardasil® 9, 9vHPV), quadrivalent HPV vaccine (Gardasil®, 4vHPV), and bivalent HPV vaccine (Cervarix®, 2vHPV)" [12] that protect against HPV-16 & -18.

However, despite the FDA approval and medical recommendation that all teenage girls and women should avail of HPV vaccines general acceptance of HPV vaccines are low in many countries [12] due to lack of public health education, public health funding or drive for this campaign or vaccine availability, which is reflected by the high number of infections and subsequent cervical cell abnormalities.

The vaccine is developed based on a virus-like particle (VLP) of the major papillomavirus capsid protein L1" [14] that doesn't contain the active virus and is thus non-infectious and safe. "Cervarix comprises HPV16 and 18 VLPs, monophosphoryl lipid A (MPL), and aluminium hydroxide (together called adjuvant system 04, AS04) as an adjuvant" [14].

In my literature review I aim to assess the immunogenicity and safety of Cervarix® HPV Vaccine against cervical cancer in women, aged 15 and over. This aims to see if "AS04-adjuvanted HPV 16/18 vaccine administered in a three-dose schedule over 6 months elicits a high immunogenic response and is highly protective against cervical intraepithelial neoplasia and infection causally related to high-risk oncogenic HPV types" [13].

OBJECTIVES

- Review the literature for evidence of the immunogenicity of Cervarix® vaccine in protecting women against cervical cancer.
- Review the literature regarding the safety of Cervarix® vaccine.

METHODOLOGY

i) Search Database

Two Databases were used to conduct this literature review, namely:

EBSCOhost (Academic Search Complete & Medline) & PubMed.

ii) Key Words Identified

"HPV Vaccine 16/18", "bivalent HPV Vaccine", "AS04-adjuvant HPV vaccine", "AS04-adjuvant vaccine" , "Cervarix", "efficacy", "protection", "effectiveness", "immunogenicity", "immunity", "Cervical Cancer", "Cervical Carcinoma" and "CIN".

iii) Search Criteria

a] The following search criteria was implemented into EbescoHost [Academic Search & Medline] and PubMed:

EbescoHost had 276 results and Pubmed had 196 results for the initial search.

Table 1: Search Criteria Used for EbescoHost & PubMed

Term 1	"Efficacy" **OR** "Effectiveness" **OR** "Efficiency"
Command	**AND**
Term 2	"Immunogenicity" **OR** "Immunity" **OR** "Immune Response"
Command	**AND**
Term 3	"Cervarix" **OR** ""Bivalent HPV 16/18 Vaccine" **OR** "AS04-adjuvant vaccine" **OR** "16/18 AS04 Vaccine" **OR** "AS04 HPV Vaccine"
Command	**AND**
Term 4	"Cervical Cancer" **OR** "Cervical Carcinoma" **OR** "CIN"

iv) Filters Used

The following filters were applied to ensure the studies found were relevant and suitable. After filter application, EbescoHost had 84 results and PubMed had 21 results, for a total of 105 research papers.

Table 2: Advanced Search Filters for EbescoHost & PubMed

EbescoHost [Academic Search Complete & Medline]	PubMed
• Full Text • Peer Reviewed • Language: English • Published: 2000 – 2021 **Special Limiters for Academic Search Complete** • PDF Full Text **Special Limiters for Medline** • Human • Abstract Available • Sex: Female • Age: Adolescent 13-18, Adult 19+ Years • Publication Type: Clinical Study	• Full Text • Peer Reviewed • Language: English • Results by Year: 2000 – 2021 • Clinical Trials • Randomised Control Trial **Additional Filters** • Species: Human • Sex: Female • Age: Adolescent 13-18, Adult 19+ Years

v) Inclusion & Exclusion Criteria

Mendeley was used to save the 105 results and remove duplicates resulting in 67 papers to be assessed following inclusion and exclusion criteria below.

vi) Screening Exclusion Process

Out of the 58 research papers left to be examined, 6 papers were removed due to their titles not being fully relevant to the study, leaving 52 studies to be assessed for their eligibility. 42 studies were excluded for various reasons listed in the table below leaving 10 articles [12,13,14,15,16,17,18,19,20,21] as the most relevant to use in the literature review.

Table 3: Inclusion & Exclusion Criteria for Papers

Inclusion Criteria	Exclusion Criteria
• Original Research • Pilot study • Free PDFs • Full Free Text • Research Published between 2000 - 2021 • Research Conducted on Humans • Women aged 15 years and over • Cervarix® vaccine clinical trials • Different ethnicities • Peer Reviewed Research	• Case Reports • Review Articles • Meta Analysis • Research Published before 2000 • Research conducted on animals • Not available in English • Not scholarly reviewed articles • Protocols • Studies on male participants • Studies on females under 15.

Table 4: Study Exclusion Criteria

Research Paper Exclusion Reasons	# of Papers
Title didn't include all 4 search items together	6
Study didn't have full free text/PDF online	7
Case Study/Review	4
Study analysed financial efficacy of vaccine as opposed to prophylactic efficacy	2
Title didn't include 'AS04-adjuvant vaccine'	5
Study involved teenage girls & boys	4
Study involved men	2
Study involved women under 15 years of age	6
Study involved vaccine administration as protection against other diseases, not cervical cancer	3
Study didn't have results published	2
Study involved vaccination in patients already suffering from HPV induced cervical cancer	4
Total Excluded with Reason	**42**
Remaining Studies	**10**

vii) Data Extraction & Management

The data obtained from the studies included author name, publication year, study title, population, intervention, control, duration, design, methodology, objectives, key findings and strengths and limitations. Mendeley was the reference manager of choice for this literature review.

Results

In this literature review, 10 clinical trials were included [15,16,17,18,19,20,21,22,23,24] 8 of which were randomized and double-blinded except for two studies; one which was partially randomized and partially blinded [23] and one which was non-randomized and open label [16]. All data obtained and analysed by the clinical trials was quantitative. The findings resulted from multicentre trials and single centre studies which ranged from India [12], Japan [14], Brazil [15], China [16,19], Malaysia [21], South Africa [20] and Korea [24]. All study participants were female and study populations ranged from 120 [20] to 6051 [22]. The age range of the participants was 15-55+ years and no participants studies on women under 15 years were assessed, as per inclusion & exclusion criteria (Table 4). Controls were used in all bar one study [16] which assessed the immunogenicity and safety of the HPV-16/18 AS04-adjuvant vaccine in age stratified cohorts and discussed the differences in these groups. 9 out of the 10 studies used parallel placebo groups to help determine the immunogenicity of the HPV 16/18 AS04 Adjuvant vaccine. Placebo vaccines did not pose any harm to the wellbeing of the population. Study duration varied from 7 months [15,17,19,24] – 9.4 years [18]. All 10 studies used in this review had the same objectives analysing the immunogenicity and safety of HPV 16/18 AS04 vaccine against CIN1+, irrespective of HPV infection. All 10 studies had the same method of vaccine administration – 3 vaccine doses at months 0, 1 and 6 [15,16,17,18,19,20,21,22,23,24]. All 10 studies had the same safety recording measures to record AEs, SAEs, NOCDs and other MSCs [15,16,17,18,19,20,21,22,23,24]. All 10 papers performed the same methods of data analysis, namely ELISA and PBNA to determine GMTs [15,16,17,18,19,20,21,22,23,24].

STUDY VALIDITY & QUALITY

The study population, objectives, methodology and data analysis were all appropriate and indicative of a good quality study, according to the CASP Checklist [3]. Confounding variables were assessed in all 10 papers by PIs. The validity of these studies was analysed in accordance to CASP Clinical Trials Review [3], in Table 7 included in the appendix. All the articles assessed for the review were of a very high standard, having a minimum of 10 out of the 11 requirements as stated on CASP [3] form.

Discussion

IMMUNOGENICITY

All participants in all the 10 studies selected were seropositive for anti-HPV 16 & anti-HPV-18 antibodies post vaccination, meaning that the vaccine induced an antibody producing immune response to prevent HPV infection [15,16,17,18,19,20,21,22,23,24]. This serostatus can be detected at one month post vaccination dose 1, 2 or 3. All data provided shows how the vaccine elicits a similar GMT response in all participants, spiking at month 7 of study, exactly one month after vaccination with dose 3 of the HPV-16/18 AS04 adjuvant [15,16,17,18,19,20,21,22,23,24]. The vaccine has this effect on women irrespective of their age, serostatus at

Table 4: Summary of results

Author [Year], Title	Objective	Study Type, Population, Sample Size	Study Methodology	Key Findings	Strengths and Limitations
Neerja Bhatla et al. [2015] "Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women"[15]	Assess the **immunogenicity and safety** of HPV-16/18 AS04-adjuvanted vaccine against cervical cancer	Study type: Double-blind, randomized [1:1], controlled and multicentre trial with two parallel groups. P= women [18-35 years] N = 330	Participants were randomly divided into two groups. Group 1 = HPV vaccine Group 2 = Placebo [aluminium hydroxide] Women were vaccinated at month 0, 1 and 6. Immunogenicity: -Serum samples collected at pre-vaccination, month 0, and at month 7 -Analysed using ELISA method & PBNA Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	Immunogenicity: - All participants seropositive for HPV-16 & HPV-18 antibodies post vaccination. - Anti HPV-16 GMT: 10226.5 EL.U/ml [95% confidence interval: 8847.1–11821.0] -Anti HPV-18 GMT: 3953.0 EL.U/ml [95% confidence interval: 3421.8–4566.8], Safety: - 6 SAEs detected, non-vaccine related - Equal no. of reported vaccine related local AEs in both groups >97% Compliance to vaccination course . The AS04-adjuvanted HPV-16/18 cervical cancer vaccine resulted in being highly immunogenic and easily tolerable.	Limitation: None mentioned in the papers which is a limitation in itself. Limitation: Short study [7 months] Limitation: Local AE numbers not reported.
Tino F Schwarz et al. [2008] "Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years"[16]	Assess the efficacy, **immunogenicity and safety** of an HPV-16/18 AS04-adjuvanted vaccine in women.	Study Type: Multicentre, Phase III, non-randomized, open-label, age-stratified study. P=Women [15-55 years] N= 676	Women were divided into three groups by age Group 1: [15-25], Group 2: [26-45], Group 3: [46-55]. All women got three doses of the Cervarix Vaccine at month 0,1 and 6. Immunogenicity: -Phase 1: Follow up visits at month 0,1,2,6,7,12. -Serum samples collected and assessed at months [0,2,7,12] using ELISA method. -Phase 2: Follow up visits at months 18 and 24. -Serum samples collected at month 18 & 24 -Data analysed using ELISA method & PBNA -GMTs calculated Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	Immunogenicity: -Study findings reported high immunogenicity and tolerability of HPV-16/18 AS04 vaccine in study population. -Vaccine induced a high immune response against both HPV-16 & -18 for 24 months, in women >26 years, after first vaccination [month 0]. -Seropositivity = 100% from months [0-24] -Peak antibody titres at months 7 for all participants. -Antibody levels in women >26 years reached a plateau 24 months after first vaccination [month 0] -Site-specific immunity [at cervix] induced by vaccine supported by high antibody levels present in secretions at month 24. Safety: - Compliance to vaccination course was 98.7 to 99.3% in the respective phases. -Approximately 11% of participants experienced medically significant adverse effects [bronchitis, depression, hypertension] -Approximately 5% of participants [14 women] experienced serious adverse effects, out of which only 1 was a side-effect of the vaccine.	Limitation: Ethnic demographic of women not specified. Limitation: No identified serological correlate of protection,

Table 4: Summary of results (continued)

Author [Year], Title	Objective	Study Type, Population, Sample Size	Study Methodology	Key Findings	Strengths and Limitations
Ryo Konno et al. [2014] "Efficacy of the human papillomavirus [HPV]-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women"[17]	Assess HPV 16/18 AS04-adjuvanted vaccine efficacy, **immunogenicity and safety** up to 4 years after first vaccination in Japanese women aged 20-25 years.	Study Type: multicentre phase II double blinded, parallel group RCT. P = Women [20-25 years] N = 752	Women were split in [1:1] manner into two groups. Group 1 = HPV-16/18 L1 VLP AS04 vaccine Group 2 = Placebo [Aluminum hydroxide] Vaccine administrations at months 0, 1, and 6. Immunogenicity: -Cervical liquid-based cytology samples were collected at the yearly follow-up visits[months 12, 24, 36, 48] -Analysed using ELISA method & PBNA -GMTs calculated. Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	A Immunogenicity: -All participants seropositive for HPV-16 & -18 antibodies at 48 months. -GMTs HPV-16 = 1283.2 EL.U/mL [95% CI: 1150.1–1431.7] -GMTs HPV-18 = 473.0 EL.U/mL [95% CI: 416.8–536.8] -GMTs for antibodies peaked at month seven, declined until month 18 and then plateaued. Safety: -The number of SAEs/AEs were similar between the two groups.	Strength: Vaccine efficiency also calculated
Paulo S. Naud et al. [2014] "Sustained efficacy, **immunogenicity, and safety** of the HPV-16/18 AS04-adjuvanted vaccine"[18]	Assess the efficacy, **immunogenicity and safety** of an HPV-16/18 AS04-adjuvanted vaccine in women from 5 Brazilian centres during 9.4 years.	Study Type: Double-blind, randomized [1:1], placebo-controlled study. P= Women [25-55 years] N=437	Women were randomized [1:1] into two groups. Group 1 received 3 doses of HPV-16/18 vaccine. Group 2 received 3 doses of placebo [Al[OH]3] Vaccine administrations occurred at months 0, 1, and 6. Immunogenicity: -Cervical swabs & cytology specimen collections were performed every 6 months and 12 months respectively for HPV testing, for 113 months. -Anti HPV 16/18 antibodies were measured via ELISA and PBNA. -VE was determined based of HPV, cytological lesions and histopathological abnormalities detected at months 6 and 12 throughout the 113 month study. Safety: -AEs were reported by participants up to 7 days post vaccination. -Reports of SAEs, pregnancies, etc. were recorded up to 30 days post vaccination. -All other SAEs, AEs etc. were recorded during 113 month study.	Immunogenicity: - All women seropositive for HPV-16/18 at month 113. - GMTs HPV 16 =180·1 ED50 [95% CI: [153·3 to 211·4]] - GMTs HPV 18 = 137·3 ED50 [95% CI: [112·2 to 168·0]] - Antibody titres [HPV vaccine induced] x10 above natural infection levels. Safety: -Safety profile is acceptable. -All reported SAEs, AEs and pregnancy outcomes in this study were not associated to the vaccine.	Strength: Longest follow-up reported for a licensed HPV vaccine.



Table 4: Summary of results (continued)

Author [Year], Title	Objective	Study Type, Population, Sample Size	Study Methodology	Key Findings	Strengths and Limitations
Hextan Y S Ngan et. al [2010] "Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: **immunogenicity and safety** in healthy Chinese women from Hong Kong"[19]	To assess the **immunogenicity and safety** of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in Chinese women aged 18 to 35 years enrolled from Hong Kong.	Study Type: Double-blind, randomized controlled trial with vaccine and placebo groups. P = Women [18-35 years] N = 300	Women were randomized [1:1] into two groups. Group 1 received 3 doses of HPV-16/18 vaccine. Group 2 received 3 doses of placebo [Al[OH]3] Vaccine administrations occurred at months 0, 1, and 6. Immunogenicity: HPV-16/18 antibodies, seroconversion rates and geometric mean titres were measured at month 7. -Data analysed using ELISA method & PBNA Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	Immunogenicity: Group 1 seropositive for HPV-16/18 antibodies by month 7. Anti HPV-16/18 GMT mean titres = 10 422 [95% confidence interval, 8730-12 442] EL.U/mL for HPV 16and 4649 [3975-5437] EL.U/mL, for HPV18. Safety: -High vaccination compliance among both groups [99%] and well tolerated vaccine. -Post-vaccination local injection reactions at site were higher in the vaccine than placebo group; Most common symptom: pain. - Other symptoms = fatigue and myalgia, frequent in both groups. SAEs = 5/300: 4 in Group 1, 1 in group 2. All unrelated to HPV vaccine or placebo.	Limitation: Not a very lengthy study considering peak titres occur at month 7 post initial vaccination at month 0. Limitation: Single Site study including only 300 participants from the same population – not representative.
Cosette M Wheeler et. Al [2016] "Efficacy, **safety, and immunogenicity** of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study"[20]	To assess the efficacy, **safety, and immunogenicity** of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women,	Study Type: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. P = Women [25-49 years] N = 5747	Participants were split in [1:1] manner into two groups. Group 1 received the HPV-16/18 L1 VLP AS04 vaccine and group 2 received the Hepatitis A vaccine [control]. Vaccine administrations occurred at months 0, 1, and 6. Immunogenicity: Cytology testing performed for HPV DNA testing every 6 months and Pap cytology testing every 12 months via PBNA. Antibody responses assessed by ELISA19 every 6-months, for the 2 year study duration. [24 months]. Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	Immunogenicity: -Geometric peaked at approximately month 7 and plateaued thereafter. ->95% participants seropositive for HPV-16 /18 at month 84. -GMTs similar in all age groups. Safety: Serious adverse events related to vaccination occurred in 5 [0·2%] participants in Group 1 and 8 [0·3%] participants in Group 2 [Control].	Strength: Multi-Site, Ethnically diverse study with a large subject co-hort. Limitation: The ratio of women with a history of HPV infection or disease and women with no history of disease used in VIVIANE study might not be representative general population.

Table 4: Summary of results (continued)

Author [Year], Title	Objective	Study Type, Population, Sample Size	Study Methodology	Key Findings	Strengths and Limitations
B K Lim et. al [2014] **"Immunogenicity and Safety** of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18–35 years: A Randomized Controlled Trial"[21]	To evaluate the vaccine **immunogenicity against HPV-16 and HPV-18 as well as its safety** and reactogenicity in Malaysian women.	Study type: Phase IIIb, double-blind, randomized [1:1] and placebo controlled trial P = Women [18-35 years] N = 271	Participants were randomized [1:1], divided into two groups, to receive three doses of HPV-16/18 vaccine or Al[OH]$_3$ [control] at M 0, 1, 6. Group 1 – HPV vaccine, Group 2 – Control. Immunogenicity: -Antibody titters were measured at month 7 by [ELISA] method & PBNA. -Gynaecological examination and cervical swab performed at month 7. Safety: -Any local or general, solicited symptoms were recorded in diary cards for 7 days after each vaccination. -Unsolicited symptoms were recorded for 30 days after each vaccination. -SAEs were reported throughout the study.	Vaccine was immunogenic and well tolerated in Malaysian women aged 18-35 years. Immunogenicity: - 100% seroconversion, in initially seronegative participants, one month post-dose-3 for anti HPV-16 and anti-HPV-18 antibodies. - GMTs HPV 16 = 11107.5 [95% CI: 9727.3-12683.4] EL.U/mL - GMTs HPV 18 = 4273.5 [95% CI: 3771.8-4841.9] EL.U/mL Safety: -Vaccine compliance >96% -AEs such as local injection pain and post vaccine general symptoms [fatigue etc.] present equally among both groups. - 8 SAEs reported [5 in group 1, 3 in group 2], not connected to HPV vaccine.	Limitation: Vaccine efficiency not assessed. Limitation: Relatively small sample size Limitation: Short Study [7 months].
Feng-Cai Zhu et al. [2014] "Efficacy, **immunogenicity and safety** of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: results from a randomized controlled trial"[22]	Efficacy, **immunogenicity and safety** of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: results from a randomized controlled trial	Study Type: randomized, double-blind, controlled trial P = Women [18-25 years] N = 6051	Participants were randomized [1:1], divided into two groups, to receive three doses of HPV-16/18 vaccine or Al[OH]$_3$ [control] at M 0, 1, 6. Group 1 – HPV vaccine, Group 2 – Control. Immunogenicity: -Blood samples at months 0, 7, 12, 24, 36 and 48. HPV-16 and HPV-18 antibodies were measured [ELISA] & PBNA. -Gynaecological examination with cervical samples collected at day 0 and at 6-month intervals until month 48. -VE assessed Safety: -Any local or general, solicited symptoms were recorded in diary cards for 7 days after each vaccination. -Unsolicited symptoms were recorded for 30 days after each vaccination. -SAEs were reported throughout the study. -Data was analysed accordingly.	Immunogenicity: -Seroconversion was 100% for anti-HPV-16 and 99.7% for anti-HPV-18, in initially seronegative participants. -GMTs[95% CI] were 6,996 [6,212 to 7,880] against HPV 16 and 3,309 [2,942 to3,723] EU/mL, against HPV 18. -All initially seropositive women in the vaccine group remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies at month 7 and GMTs were 5,698 [4,703 and 6,904] and 3,242 [2,736 and 3,842]EU/mL, respectively. Safety: -Similar AEs were reported among both groups, - Group 1 reported more local injection site symptoms. -1 SAE, GIT infection associated with HPV vaccine. -1 fatal SAE, suicide, reported but unrelated to HPV vaccine.	Limitation: SAE & AE incidences not reported numerically.

Table 4: Summary of results (continued)

Author [Year], Title	Objective	Study Type, Population, Sample Size	Study Methodology	Key Findings	Strengths and Limitations
Denny L et. al [2013] **"Safety and immunogenicity** of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: A partially-blind randomised placebo-controlled study"[23]	Evaluated the **safety and immunogenicity** of the HPV-16/18 AS04-adjuvanted vaccine in women in South Africa.	Study type: Phase I/II, partially-blind, partially-randomised, placebo-controlled trial at a single centre in Khayelitsha, Cape Town, Republic of South Africa. P = Women [18-25 years] N = 120	Participants were divided into HIV positive and HIV negative groups. Women in the HIV positive group were randomised [1:1] to receive the HPV-16/18 AS04-adjuvanted vaccine [Group 1] or control [Group 2]. Women in the HIV negative group were given the HPV vaccine also [Group 3]. Immunogenicity: -Blood samples for assessment of HPV-16/18 antibody and CD4+ T-cell responses were collected at months 0, 2, 7, and 12 and analysed. -Data analysed using ELISA method & PBNA -GMTs calculated Safety: -Solicited adverse events were recorded by a trained field worker daily for 7 days after each vaccination. Severity of solicited adverse events was graded on a scale of 0 [absent] to 3 [preventing normal activities]. -Data was analysed accordingly	Immunogenicity: All participants seropositive for HPV-16 and HPV-18 after their vaccinations and at month 12. -GMTs peaked in both group 1 and 3 at month 7. Group 1 HPV-16 :3558.2 [95% CI: 2723.6; 4648.6] EL.U/ml Group 1 HPV-18: 1945.8 [95% CI: 1451.4; 2608.6] Group 3 HPV-16: 8168.8 [95% CI: 6341.0; 10,523.5]EL.U/ml Group 3 HPV-18 : 3703.0 [95% CI: 2502.5; 5479.4] EL.U/ml -GMTs at Month 12: Group 1 HPV-16: 748.1 [95% CI: 520.0; 1076.3] EL.U/ml Group 1 HPV-18: 343.1 [95% CI: 236.2; 498.2] Group 3 HPV-16: 2793.6 [95% CI: 2087.8; 3738.0] EL.U/ml Group 3 HPV-18: 210.3 [95% CI: 627.4; 1662.6] EL.U/ml. In placebo group – no change was seen in GMT levels. Safety: Administration of the HPV-16/18 vaccine did not influence HIV disease progression. The HPV-16/18 vaccine had a clinically acceptable safety and reactogenicity profile. AEs: 30 days post vaccine 86.9% [group 1], 78.0% [group 2], 86.7% [group 3] including headache, local injection pain. SAEs: 1 SAE, rhinitis associated with HPV vaccine in group 1.	Limitation: immunogenicity was assessed in young adult women, many of whom were already seropositive for HPV-16 and/or HPV-18 prior to vaccination, Limitation: Small study population. Small number of participants [approx. 40] in each group.
Seung Cheol Kim et. al [2011] "Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: **Immunogenicity and safety** in 15-25 years old healthy Korean women"[24]	The study assessed the **immunogenicity and safety** of human papillomavirus [HPV]-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Korean women.	Phase IIIB, double-blind, randomised [2:1], multi-centre clinical trial. P: Women [15-25 years] N = 225	Women were divided into two groups HPV vaccine [N=149] and placebo [N=76]. Vaccine administrated at month 0, 1, and 6 months. Patient assessment happened monthly until month 7. Immunogenicity: -Serum samples were collected pre-vaccination and one month post-dose 3. - Blood samples [5 mL] were collected before vaccination and one month post-dose 3 to evaluate the antibody response against HPV-16 and HPV-18 using ELISA & PBNA. Safety: -Safety log diaries were given to participants on the day of vaccination to record solicited and unsolicited [local/general] symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively. -SAEs NOCDs and MSCs were recorded throughout. - Data was analysed accordingly	Immunogenicity: At month 7, all initially seronegative women had seroconverted for HPV-16 and HPV-18 antibodies with anti-HPV-16 and anti-HPV-18 GMTs of 9,351.4 El.U/mL [95% CI, 8,145.5 to 10,735.8] and 4204.1 El.U/mL [95% CI, 3,626.5 to 4,873.6], respectively. Safety: Vaccination compliance 95.3% in HPV and 89.5% in placebo group. AEs: Symptoms of local pain, headache, fatigue were reported in both groups in equal proportion. SAEs: 3 were reported [2 in HPV group; 1 in placebo group]. AEs were tabulated with exact 95% confidence intervals [CIs] for all vaccine doses and overall. All SAES unrelated to vaccination.	Limitation: Relatively short study duration – 7 months. Limitation: No VE calculated.

month 0 or underlying health conditions such as HIV [15,16,17,18,19,20,21,22,23,24].

Thereafter follows the decline of the serum GMT levels until month 18 post initial vaccination, where antibody levels reach a plateau [15,16,17,18,19,20,21,22,23,24]. However, this result has been challenged in one of the 10 studies in use, which stated women vaccinated at age 26+ had their GMT levels reach a plateau at month 24, approximately 6 months later than the 15+ age cohort [16]. The 10 studies selected were based in different countries and included different ethnicities. This diverse population cohort allowed for an inclusive and globally representative analysis to be conducted [15,16,17,18,19,20,21,22,23,24]. There was no significant difference in the GMT levels induced by HPV vaccine among populations with no underlying health conditions [15,16,17,18,19,20,21,22,24].

HIV-positive individuals have an impaired or reduced immune response to routine vaccines [2], however, the adjuvant in Cervarix is an important contributor towards the immunogenicity induced by the vaccine. Factors affecting immunogenicity in the case of the review, are age [16] and autoimmune diseases i.e. HIV [23]. These factors either affect the plateau period of serum GMT levels [16] or quantity of serum GMTs at any given time [23], respectively.

Although these factors contribute to overall immunogenicity, they don't suppress the effectiveness of the vaccine. Therefore according to the mentioned papers, women vaccinated at 26+ years or women that are HIV positive can acquire immunity against HPV 16 and HPV 18 on vaccination with HPV-16/18 AS04-adjuvant [16]. On the other hand, in both studies mentioned, which included parameters affecting the immunogenicity of the study (in this age, older age and HIV positive status), these may invite scepticism as their population cohorts were relatively small and they were not fully double blinded and randomized, which can lead to biased results [16][23].

SAFETY

The HPV-16/18 AS04-adjuvant vaccine was approved for use by the FDA in 2009, indicating it's a safe and efficacious vaccine

[25]. Among the 10 studies listed, each study carefully analysed any adverse effects of the vaccine up to day 7 post vaccination and then up to day 30 post vaccination, by allowing participants to record their details in a diary [15,16,17,18,19,20,21,22,24]. Only 1 study involves personnel gathering this information from the participants themselves [23], which although may be a more scientifically reliable method, can be a confounding variable given possible 'white coat syndrome' amongst participants, as this may influence participants to give biased answers regarding side effects of the vaccine.

Current literature promotes the HPV-16/18 AS04 adjuvant vaccine as safe and tolerable among patients, as we've seen with a vaccine compliance rate with an average of 97% among the 10 studies selected [15,16,17,18,19,20,21,22,23,24]. The majority of adverse effects reported were related to the injection itself and certain symptoms such as headache and fatigue [15,16,17,18,19,20,21,22,23,24] are usual Cervarix side effects [26]. The accuracy of self-reported symptoms is something that can be questioned regarding AEs reported, as some participants may over-report/under-report their symptoms as self-reporting bias is a concerning aspect in research [27]. The time of year of symptom reporting would also be interesting to determine and see if there were any confounding variables present which may have coincided with any presenting symptoms e.g. head cold caught during winter at the same time of vaccine, which may influence reported side effects of the vaccine. Only 3 out of the 10 papers showed SAEs as a result of the HPV vaccine. These were all easily treatable and the participants recuperated without sequalae.

STRENGTHS & LIMITATIONS OF REVIEW

Among the 10 studies selected, many were found set in Asia: China, Japan, Malaysia, India, one in Europe – France, one in America, South America – Brazil, and one in Africa [15,16,17,18,19,20,21,22,23,24].

Studies on Caucasian women or Asian [Indian, Chinese, Japanese and Malaysian] women were the most abundant, which although is a great discovery among women of these populations, is limited to only representing specified groups. Finding studies that included more than one ethnic group and analysing the immunogenic effect of the vaccine and its safety for the patients was difficult. Equally only one study investigating the immunogenicity of the vaccine in black women[23] was found on both databases used [EbescoHost & PubMed]. This one paper then went to analyse the immunogenicity and safety of the vaccine in a small population of equal numbers of HIV positive & negative participants in South Africa – which is not an accurately representative of the South African demographic [23] due to the small sample size.

Another limitation of this research topic is that it was difficult to find 10 papers featuring populations of the same broad age bracket (15 – 55 years). Although a review was possible to conduct given the scope specified (15+ years) it would have been preferable to have 10 articles including the exact same age cohort, preferably age stratified.

GAPS IN LITERATURE

Based on the overall limitations mentioned it would be great to see a clinical trial analysing the immunogenicity and safety of HPV-16/18 AS04-Adjuvant vaccine on women of different ethnicities and see how their results compare. There should be more studies performed on women of colour, especially black women as they're grossly under-represented in the current literature. For increased statistical accuracy and bias elimination all studies should be double-blinded and randomised. It would also be very interesting to assess the immunogenicity and safety of the Cervarix vaccine against another HPV vaccine brand i.e. bi-valent but without AS04 adjuvant, Gardasil, quadrivalent or nine valent. This would be an interesting analysis and would help determine which vaccine induces more immunogenicity, as the stronger the immune response against the HPV induced virus the less likely it is for dyskaryosis, CIN and Cervical cancer to progress. As we can observe from the literature, HPV vaccination is an effective prophylactic treatment against cervical cancer with its immunogenicity present up to 9.4 years[18], and perhaps beyond. Therefore, the question of why cervical cancer is the 4th most common cancer among women[2] is not answered by the lack of vaccine protection & safety, but rather by the lack of vaccination, regular screening and awareness.

Conclusion

The administration of Cervarix, HPV-16/18 AS04-adjuvant vaccine is highly immunogenic, safe and tolerable among women aged 15+ and protects them against HPV induced cervical cancer, which counts for approximately 90% of all cases [15,16,17,18,19,20,21,22,23,24].

All women, regardless of initial HPV-16/18 serostatus prior to vaccination, tested seropositive for both HPV-16/18 antibodies post vaccination [15,16,17,18,19,20,21,22,23,24]. GMTs level reach their peak at month 7, exactly 1 month post dose 3 vaccination, after which they decrease to hit a plateau at month 18 [15,16,17,18,19,20,21,22,23,24]. The antibody induced response is still present post month 18 and the longest study to confirm presence of GMT levels is 9.4 years [18]. Despite local injection site AEs, the Cervarix vaccine is highly tolerable among women and has a high administration compliance. The majority of SAEs detected at any time post vaccination are rarely vaccine associated [15,16,17,18,19,20,21,22,23,24]. However, even those that are vaccine associated are generally easily treatable. Therefore, along with proven immunogenicity, the Cervarix HPV-16/18 AS04-adjuvant vaccine is also safe and an appropriate prophylactic treatment in women aged 15+ to prevent the development of HPV induced cervical cancer [15,16,17,18,19,20,21,22,23,24].

Appendix A: Abbreviations

AE[s]	Adverse Events/Effects
SAE[s]	Serious Adverse Events/Effects
CIN1+	Cervical Intraepithelial Neoplasia [grade one or grater]
GMT[s]	Geometric Mean Titre[s]
NOCD[s]	New Onset Chronic Disease
MSC[s]	Medically Significant C
IM	Immunogenicity
VE	Vaccine Efficiency
ELISA	Enzyme-linked immunoassay
PBNA	Pseudovirion-based Neutralization Assay
CASP	Critical Appraisal Skills Program [3]

Appendix B: CASP Checklist for Clinical Trials [3]

CASP Checklist: Clinical Trial Based Checklist	Neerja Bhatla et al. [2015]	Tino F Schwarz et al. [2008]	Ryo Konno et al. [2014]	Paulo S. Naud et al. [2014]	Hextan Y S Ngan et. al [2010]	Cosette M Wheeler et. Al [2016]	B K Lim et. al [2014]	Feng-Cai Zhu et al. [2014]	Denny L et. al [2013]	Seung Cheol Kim et. al [2011]
1. Did the study address a clearly focused research question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the assignment of participants to interventions randomised?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
3. Were all participants who entered the study accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4a. Were the participants 'blind' to intervention they were given?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4b. Were the investigators 'blind' to the intervention they were giving to participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4c. Were the people assessing/analyzing outcome/s 'blinded'?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were the study groups similar at the start of the randomised controlled trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.Apart from the experimental intervention, did each study group receive the same level of care [that is, were they treated equally]?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were the effects of intervention reported comprehensively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the precision of the estimate of the intervention or treatment effect reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Do the benefits of the experimental intervention outweigh the harms and costs?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Can the results be applied to your local population/in your context?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total Score:	**11/11**	**10/11**	**11/11**	**11/11**	**11/11**	**11/11**	**11/11**	**11/11**	**10/11**	**11/11**

References

1. Cervical Cancer: Statistics | Cancer.Net [Internet]. [cited 2021 Nov 10]. Available from: https://www.cancer.net/cancer-types/cervical-cancer/statistics
2. Buskwofie A, David-West G, Clare CA. A Review of Cervical Cancer: Incidence and Disparities. Journal of the National Medical Association [Internet]. 2020 Apr;112[2]:229–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0027968420300432
3. CASP_RCT_Checklist_PDF_Fillable_Form.
4. Cervical Cancer: An NCD We Can Overcome [Internet]. [cited 2021 Nov 9]. Available from: https://www.who.int/director-general/speeches/detail/cervical-cancer-an-ncd-we-can-overcome
5. Walsh RJ, Tan DSP. The Role of Immunotherapy in the Treatment of Advanced Cervical Cancer: Current Status and Future Perspectives. Journal of Clinical Medicine [Internet]. 2021 Sep 29 [cited 2021 Nov 9];10[19]:4523. Available from: https://www.mdpi.com/2077-0383/10/19/4523
6. Cervical cancer [Internet]. [cited 2021 Nov 9]. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1
7. Cervarix HPV vaccine can cut cervical cancer rates by almost 90%, new study says [Internet]. [cited 2021 Nov 9]. Available from: https://www.thejournal.ie/hpv-vaccine-effectiveness-study-the-lancet-5590855-Nov2021/
8. Panatto D, Amicizia D, Trucchi C, Casabona F, Lai PL, Bonanni P, et al. Sexual behaviour and risk factors for the acquisition of human papillomavirus infections in young people in Italy: suggestions for future vaccination policies. BMC Public Health [Internet]. 2012 [cited 2021 Nov 24];12[1]:623. Available from: /pmc/articles/PMC3490840/
9. Who should have cervical screening - HSE.ie [Internet]. [cited 2021 Nov 24]. Available from: https://www2.hse.ie/screening-and-vaccinations/cervical-screening/when-you-should-have-cervical-screening/who-should-have-cervical-screening.html
10. Treatment decisions | Cervical cancer | Cancer Research UK [Internet]. [cited 2021 Nov 9]. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/treatment/treatment-decisions
11. Yang A, Farmer E, Wu TC, Hung CF. Perspectives for therapeutic HPV vaccine development. Journal of Biomedical Science [Internet]. 2016 Nov 4 [cited 2021 Nov 9];23[1]:1–19. Available from: https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-016-0293-9
12. HPV Vaccination: What Everyone Should Know | CDC [Internet]. [cited 2021 Nov 9]. Available from: https://www.cdc.gov/vaccines/vpd/hpv/public/index.html
13. McKeage K, Romanowski B. AS04-adjuvanted human papillomavirus [HPV] types 16 and 18 vaccine [Cervarix®]: a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. Drugs [Internet]. 2011 Mar 5 [cited 2021 Nov 9];71[4]:465–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21395359
14. Cheng L, Wang Y, Du J. Human Papillomavirus Vaccines: An Updated Review. Vaccines [Internet]. 2020 Jul 16;8[3]:391. Available from: https://www.mdpi.com/2076-393X/8/3/391
15. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. Journal of Obstetrics and Gynaecology Research [Internet]. 2010 Feb;36[1]:123–32. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1447-0756.2009.01167.x
16. Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Perona P, et al. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15–55 years. Vaccine. 2009 Jan 22;27[4]:581–7.
17. Konno R, Yoshikawa H, Okutani M, Quint W, v Suryakiran P, Lin L, et al. Efficacy of the human papillomavirus [HPV]-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women. Human Vaccines & Immunotherapeutics. 2014 Jul 7;10[7].
18. Naud PS, Roteli-Martins CM, de Carvalho NS, Teixeira JC, de Borba PC, Sanchez N, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Human vaccines & immunotherapeutics [Internet]. 2014 Aug 1 [cited 2021 Nov 16];10[8]:2147–62. Available from: https://pubmed.ncbi.nlm.nih.gov/25424918/
19. Ngan HYS, Cheung ANY, Tam KF, Chan KKL, Tang HW, Bi D, et al. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. Hong Kong medical journal = Xianggang yi xue za zhi. 2010 Jun;16[3].
20. Wheeler CM, Skinner SR, del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. The Lancet Infectious diseases [Internet]. 2016 Oct 1 [cited 2021 Nov 16];16[10]:1154–68. Available from: https://pubmed.ncbi.nlm.nih.gov/27373900/
21. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, et al. Immunogenicity and Safety of the AS04-adjuvanted Human Papillomavirus-16/18 Cervical Cancer Vaccine in Malaysian Women Aged 18–35 years: A Randomized Controlled Trial.
22. Zhu F, Hu S-Y, Hong Y, Hu Y-M, Zhang X, Zhang Y-J, et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18-25 years: event-triggered analysis of a randomized controlled trial. Cancer Medicine. 2017 Jan;6[1].
23. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: A partially-blind randomised placebo-controlled study. Vaccine [Internet]. 2013 Nov 19 [cited 2021 Nov 16];31[48]:5745–53. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0264410X13012735
24. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: Immunogenicity and safety in 15-25 years old healthy Korean women. Journal of Gynecologic Oncology. 2011;22[2]:67–75.
25. FDA Licensure of Bivalent Human Papillomavirus Vaccine [HPV2, Cervarix] for Use in Females and Updated HPV Vaccination Recommendations from the Advisory Committee on Immunization Practices [ACIP] [Internet]. [cited 2021 Nov 25]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm
26. Side Effects of Cervarix [Human Papillomavirus Bivalent Vaccine], Warnings, Uses [Internet]. [cited 2021 Nov 25]. Available from: https://www.rxlist.com/cervarix-side-effects-drug-center.htm
27. Rosenman R, Tennekoon V, Hill LG. Measuring bias in self-reported data. International Journal of Behavioural and Healthcare Research. 2011;2[4]:320.