嘉義基督教醫院
實證醫學文獻查證競賽
第D組

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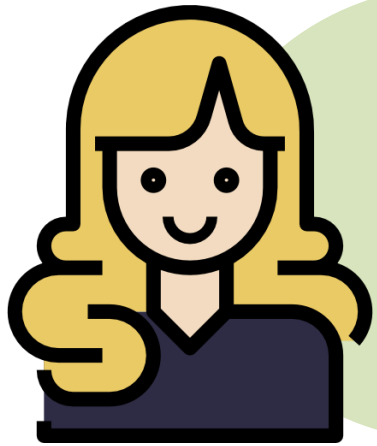
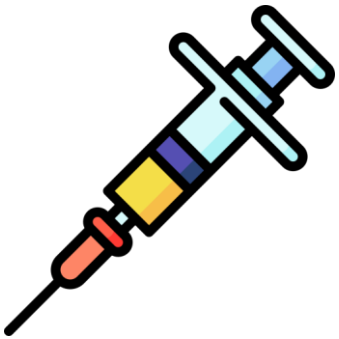
REH 陳慈吟
REH 黃元貞
REH 陳俊佑

臨床情境 Clinical scenario

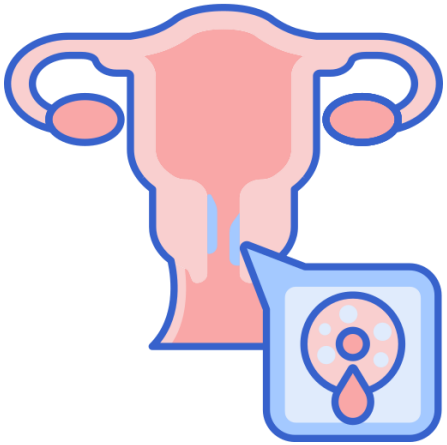
20 y/o
女大學生
未有性行為



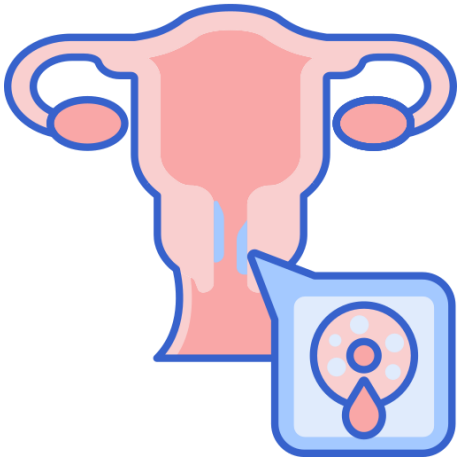
25 y/o
已婚
已生產過



預防 ？？？



背景知識 Background



子宮頸癌
(cervical cancer)

特性

1. 經由**性行為**感染**人類乳突病毒(HPV)**
2. 大部分：自動痊癒
3. 少部分：持續性感染+長期間刺激細胞+其他引發癌症的因子=子宮頸癌

預防

1. 子宮頸抹片檢查
   a. 三十歲以上的婦女，至少每三年做一次
   b. 未滿30歲但已有性行為三年以上的年輕女性
2. 施打**子宮頸癌疫苗(HPV vaccine)**（預防60-70%HPV感染）

治療

1. 目前並無特定藥物可治療HPV感染

臨床問題 PICO -1

	PICO/關鍵字	MeSH同義詞	中文關鍵字
P	• 20歲女性 • 無性經驗	• Female • Sexual experience	• 女性 • 性經驗
I	• 施打子宮頸癌疫苗	• HPV vaccine • Human Papillomavirus Vaccines	• 施打子宮頸癌疫苗
C	• 無施打子宮頸癌疫苗	• -	• 無施打子宮頸癌疫苗
O	• 子宮頸癌發生率	• cervical cancer	• 子宮頸癌發生率

☐治療/預防型問題

臨床問題 PICO -2

	PICO/關鍵字	MeSH同義詞	中文關鍵字
P	• 25歲女性 • 生育過	• Female • Sexual experience	• 女性 • 生育過
I	• 施打子宮頸癌疫苗	• HPV vaccine • Human Papillomavirus Vaccines	• 施打子宮頸癌疫苗
C	• 無施打子宮頸癌疫苗	• -	• 無施打子宮頸癌疫苗
O	• 子宮頸癌發生率	• cervical cancer	• 子宮頸癌發生率

☐治療/預防型問題

文獻搜尋 Acquire

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

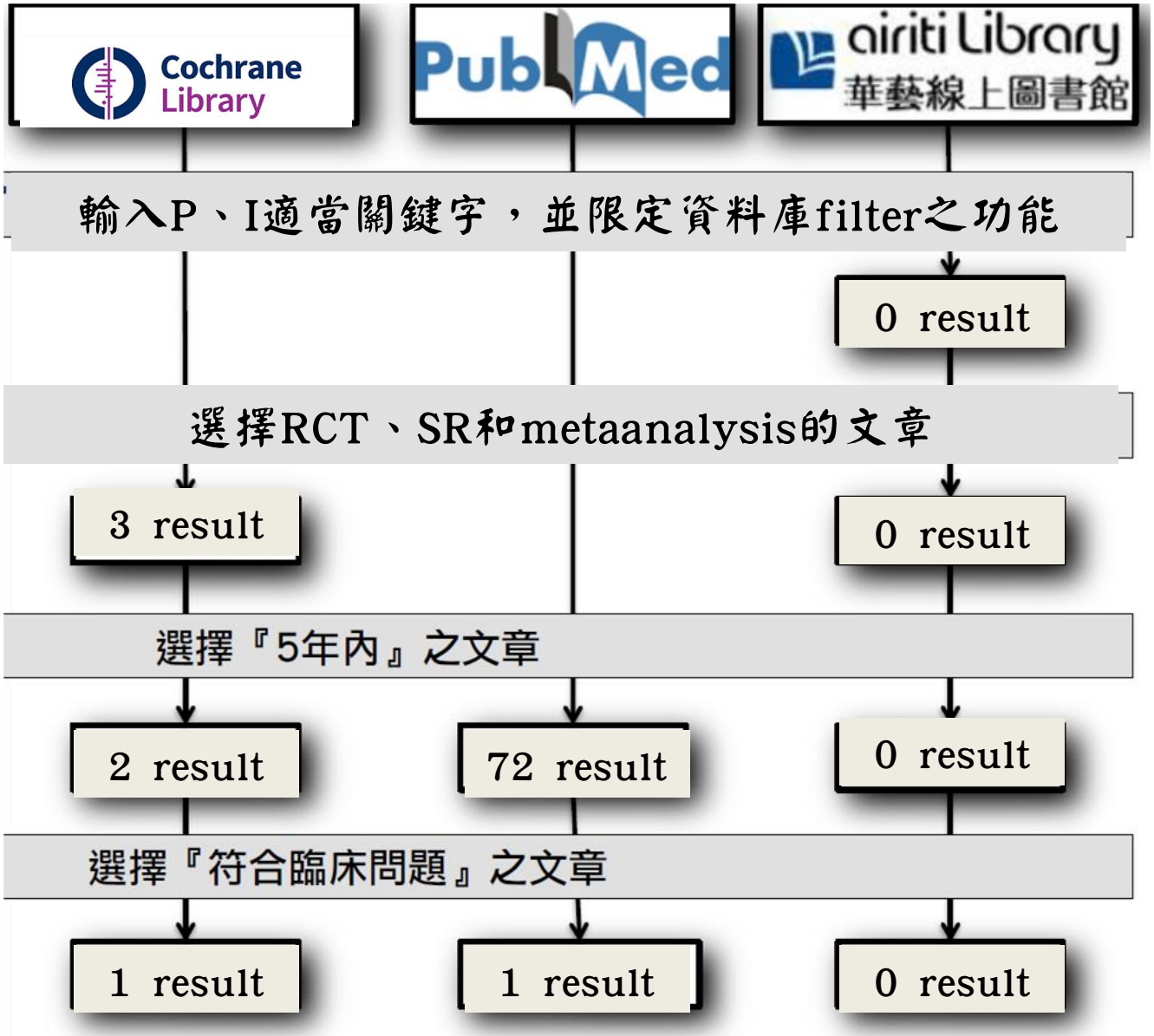
*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

文獻搜尋 Acquire

P	AND	I	AND	C	AND	O
Female Sexual experience		HPV vaccine Human Papillomavirus Vaccines		Placebo		cervical cancer

限定搜尋範圍	Free full text、Within 5 years、Human species
限定研究類型	Systematic review、Meta-analysis
限定語言地區	English、中文[台灣本土文獻]


Cochrane Library
PubMed
airiti Library 華藝線上圖書館
輸入P、I適當關鍵字，並限定資料庫filter之功能
0 result
選擇RCT、SR和metaanalysis的文章
3 result
0 result
選擇『5年內』之文章
2 result
72 result
0 result
選擇『符合臨床問題』之文章
1 result
1 result
0 result

	Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors [2018]		
M	system review		
P	• 20歲女性 • 無性經驗	• Female • Sexual experience	
I	• 施打子宮頸癌疫苗	• HPV vaccine • Human Papillomavirus Vaccines	
C	• 無施打子宮頸癌疫苗	• -	
O	• 子宮頸癌發生率	• cervical cancer	

文獻評讀 Appraise

CASP

1. Did the review address a clearly focused question?
2. Did the authors look for the right type of papers?
3. Do you think the important, relevant studies were included?
4. Did the review’s authors do enough to assess the quality of the included studies?
5. 如果作者將研究結果進行合併，這樣的合併是否合理？

C 文獻評讀 Appraise

CASP

6. What are the overall results of the review?
7. How precise are the results?
8. Can the results be applied to the local population?
9. Were all important outcomes considered?
10. Are the benefits worth the harms and costs?

文獻評讀 Appraise

1. 此篇系統性文獻回顧是否問了一個清楚、明確的問題?

→Yes ・研究族群 ・給予的措施 ・考量的結果

Main results

We included 26 studies involving 73,428 adolescent girls and women. All trials evaluated vaccine safety over a period 0.5 to 7 years and ten trials, with follow-up 3.5 to 8 years, addressed protection against precancer. Cervical cancer outcomes are not available. Most participants enrolled were younger than 26 years of age. Three trials recruited women between 25 to 45 years. The studies compared HPV vaccine with a dummy vaccine.

We assessed protection against precancer in individuals who were free of hrHPV, free of HPV16/18 or those with or without HPV infection at the time of vaccination. We separately assessed precancer associated with HPV16/18 and any precancer.

Protection against cervical precancer

1) Women free of hrHPV

Outcomes were only measured in the younger age group for this comparison (15 to 25 years). HPV vaccines reduce the risk of cervical precancer associated with HPV16/18 from 164 to 2/10,000 women (high certainty). They reduce also any precancer from 287 to 106/10,000 (high certainty).

2) Women free of HPV16/18

The effect of HPV vaccines on risk of precancer differ by age group. In younger women, HPV vaccines reduce the risk of precancer associated with HPV16/18 from 113 to 6/10,000 women (high certainty). HPV vaccines lower the number of women with any precancer from 231 to 95/10,000 (high certainty). In women older than 25, the vaccines reduce the number with precancer associated with HPV16/18 from 45 to 14/10,000 (moderate certainty).

3) All women with or without HPV infection

In those vaccinated between 15 to 26 years of age, HPV vaccination reduces the risk of precancer associated with HPV16/18 from 341 to 157/10,000 (high certainty) and any precancer from 559 to 391/10,000 (high certainty).

In older women, vaccinated between 25 to 45 years of age, the effects of HPV vaccine on precancer are smaller, which may be due to previous exposure to HPV. The risk of precancer associated with HPV16/18 is probably reduced from 145/10,000 in unvaccinated women to 107/10,000 women following HPV vaccination (moderate certainty). The risk of any precancer is probably similar between unvaccinated and vaccinated women (343 versus 356/10,000, moderate certainty).

Pregnancy outcomes

HPV vaccines did not increase the risk of miscarriage or termination of pregnancy. We do not have enough data to be certain about the risk of stillbirths and babies born with malformations (moderate certainty).

P: Female、Sexual experience
I: HPV vaccine、Human Papillomavirus Vaccines
C: -
O: cervical cancer

C 文獻評讀 Appraise

2. 作者是否尋找適當研究型態的文獻?

→Yes

Criteria for considering studies for this review

Types of studies

We considered only phase II and phase III randomised controlled trials (RCTs).

Types of participants

We included studies enrolling female participants, without any age restriction, distinguishing:

1. female participants with no evidence of baseline infection with high-risk human papillomaviruses (hrHPV) types (this group reflects the first target of basic vaccination programmes, i.e. girls before onset of sexual activity);
2. female participants with no evidence of baseline infection with HPV types included in the vaccines (per protocol population);
3. all female participants regardless of baseline infection with HPV (this group reflects the target of catch-up vaccination programs, adolescents or young adult women aged 15 to 26 years, where a considerable proportion may already have been exposed to HPV infection).

The distinction of different participant categories by HPV status at enrolment is essential, since the trial outcomes are expected to differ in women who are already infected with HPV types included in the vaccine and those who are not infected, Further distinction was made by:

1. broad age group (adolescents and young adult women, aged 15 to 26 years) and mid-adult women (25 to 45 years);
2. number of received doses: three doses in agreement with the trial protocol, at least one dose, and fewer than three doses (the latter analysis being a post-hoc assessment);
3. type of vaccine received (mono-, bi- or quadrivalent vaccine).

Valency	Phase	Number	Trial	V1	V2	V3	V4	V5	V6	#Low	#Unclear	#High	%Low	%Unclear	%High
Monovalent	II	1	Phase2 trial (ph2,1v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Bivalent	II	2	Japanese trial (ph2, 2v)	U	U	N	N	N	N	4	2	0	57%	29%	0%
			Phase2 trial (ph2,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
	III	16	African_2 country trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Chinese trial (ph3,v2)_young	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Chinese trial (ph3,v2)_adolescent	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Chinese trial (ph3,v2)_mid_adult	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Co-vaccination_dTpa_IPV trial (ph3,2v)	N	Y	U	U	N	N	3	2	1	43%	29%	14%
			Co-vaccination_HAB trial (Ph3, 2v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Co-vaccination_HepB trial (ph3, 4v)	N	Y	Y	Y	N	N	3	0	3	43%	0%	43%
			CVT(ph3,2v)	N	N	N	N	N	U	5	1	0	71%	14%	0%
			Hong Kong trial (ph3,2v)	N	N	U	U	N	N	4	2	0	57%	29%	0%
			Immunobridging (ph3,2v)	N	Y	N	N	N	N	5	0	1	71%	0%	14%
			Malaysian trial (ph3, 2v)	N	N	U	U	N	N	4	2	0	57%	29%	0%
			Indian Trial (ph3,2v)	N	N	U	U	N	N	4	2	0	57%	29%	0%
			Korean trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Korean trial (ph3b,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			PATRICIA trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			VIVIANE trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Quadrivalent	II	3	Japanese trial (ph2,4v)	U	N	N	N	U	N	4	2	0	57%	29%	0%
			Korean trial (ph2,4v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Phase2 trial (ph2,4v)	N	U	N	N	N	N	5	1	0	71%	14%	0%
	III	4	African_3 country trial (ph3, 4v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			FUTURE I trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			FUTURE II trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			FUTURE III trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Total		26	Nb of Low risk	24	16	16	16	25	25						
			Nb of Unclear risk	2	7	9	9	1	1						
			Nb of High risk	0	3	1	1	0	0						
			% of Low risk	92%	62%	62%	62%	96%	96%						
			% of Unclear risk	8%	27%	35%	35%	4%	4%						
			% of High risk	0%	12%	4%	4%	0%	0%						

作者優先收納證據等級較高的 RCT (randomized controlled trial)

C 文獻評讀 Appraise

3. 你認為所有重要且相關的研究都被納入?

→Yes

Search methods for identification of studies

We searched for papers in all languages and translations were undertaken, if necessary.

Electronic searches

We retrieved published studies from the Cochrane Central Register of Controlled Trials (CENTRAL the Cochrane Library), MEDLINE and Embase.

Cochrane Central Register of Controlled Trials (CENTRAL 2002 to 2017, Issue 5).
MEDLINE (2002 to June Week 1 2017).
Embase (2002 to 2017 week 24).

The search strategies for MEDLINE, CENTRAL and Embase are listed in Appendix 3, Appendix 4 and Appendix 5.

本篇文獻有使用：
1.電子資料庫
2.隨機試驗註冊
3.手動查找文獻

Searching other resources

Registries of randomised trials

We searched the following registries to identify unpublished or ongoing trials: www.clinicaltrials.gov, www.isrctn.com, and www.cancer.gov/clinicaltrials.

Data on adverse effects published in the peer-reviewed literature were complemented by searches in wwww.clinicaltrials.gov for the quadrivalent vaccine and on http://www.gsk-clinicalstudyregister.com/ for the bivalent vaccine. We collected data for the outcomes of serious adverse events, all-cause mortality and pregnancy outcomes from these sources and compared them with data extracted from the primary trial publications.

International public health organisations

We contacted international public health organisations that have investigated questions on HPV vaccine efficacy and safety or that have formulated recommendations on the use of HPV vaccines, to retrieve key documents. Concerned organisations included: the World Health Organization (WHO, Geneva), the US Centers for Disease Control and Prevention (CDC, Atlanta), the European Centre for Disease Prevention and Control (ECDC, Stockholm), and the International Agency for Research on Cancer (IARC, Lyon).

Handsearching

We handsearched the citation lists of included studies.

In addition, we searched the abstracts of the latest conferences of relevant scientific societies related to vaccination, virology (in particular the International Papillomavirus Society), paediatrics, and gynaecology for new or pending information not yet published in peer-reviewed journals.

Correspondence

We contacted study authors to request results on effects separated by gender, if the reports only contained data combined for both genders.

C 文獻評讀 Appraise

3. 你認為所有重要且相關的研究都被納入?

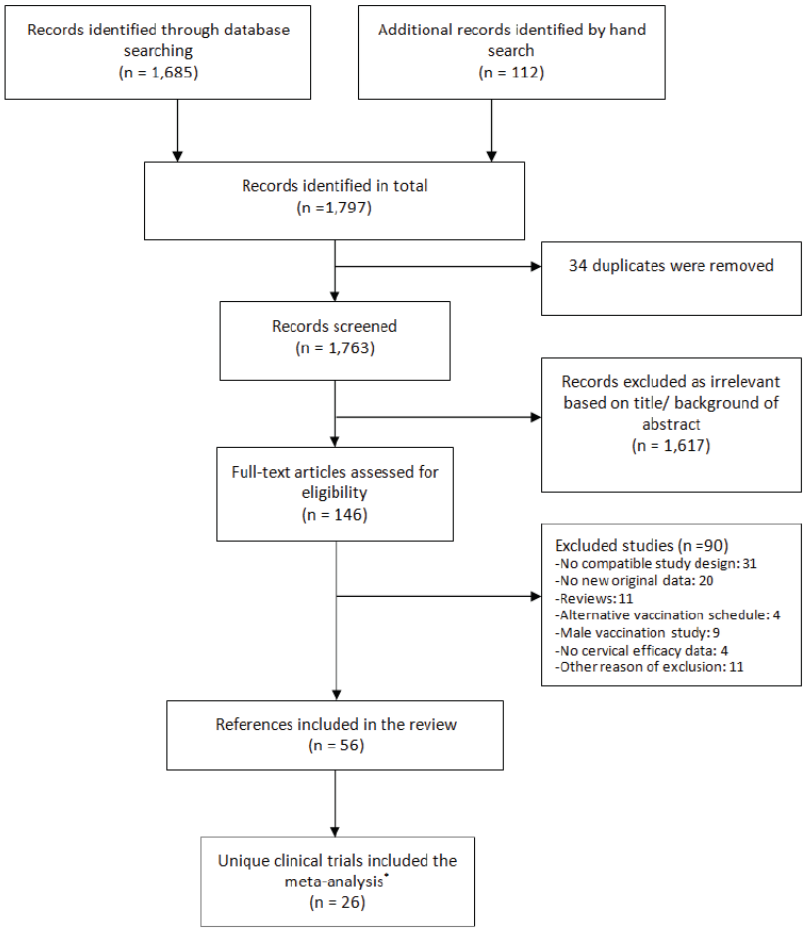
→Yes

Included studies

Twenty-six randomised trials were identified that contained data on vaccine efficacy and/or safety, which all together enrolled 73,428 women. One trial (Phase2 trial (ph2,1v)) evaluated effects of a monovalent HPV16 vaccine, 18 trials evaluated the bivalent vaccine

Excluded studies

A list of 90 excluded studies and reasons for exclusion can be found below (Characteristics of excluded studies). We excluded a Chinese study (Li 2012) and an immuno-bridging study (Reisinger 2007), which contained safety and immunogenicity data reported jointly for men and women. We sent a request to the authors for separate data for women but we did not receive a reply from the former and an answer that gender-separated data were not available from the latter.



C 文獻評讀 Appraise

4. 系統性文獻回顧的作者是否評估所納入研究文獻的品質?→YES

Low risk

Risk of bias in included studies

The assessment of the risk of possible bias present in the selected studies according to the six criteria incorporated in Cochrane's tool for assessing risk of bias in randomised trials (Higgins 2011b) is shown in Characteristics of included studies.

We judged the risk of bias related to the six Cochrane criteria as low in most of the included trials (Figure 2, Figure 3 and Figure 4). We judged the generation of a random sequence as adequate in 24/26 trials (= 92%). In two studies, the system used for randomisation was insufficiently described (unclear risk of bias) (Japanese trial (ph2,4v); Japanese trial (ph2,2v)).

C 文獻評讀 Appraise

4. 系統性文獻回顧的作者是否評估所納入研究文獻的品質?→YES

Valency	Phase	Number	Trial	V1	V2	V3	V4	V5	V6	#Low	#Unclear	#High	%Low	%Unclear	%High
Monovalent	II	1	Phase2 trial (ph2,1v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Bivalent	II	2	Japanese trial (ph2, 2v)	U	U	N	N	N	N	4	2	0	57%	29%	0%
			Phase2 trial (ph2,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
	III	16	African_2 country trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Chinese trial (ph3,v2)_young	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Chinese trial (ph3,v2)_adolescent	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Chinese trial (ph3,v2)_mid_adult	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Co-vaccination_dTpa_IPV trial (ph3,2v)	N	Y	U	U	N	N	3	2	1	43%	29%	14%
			Co-vaccination_HAB trial (Ph3, 2v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Co-vaccination_HepB trial (ph3, 4v)	N	Y	Y	Y	N	N	3	0	3	43%	0%	43%
			CVT(ph3,2v)	N	N	N	N	N	U	5	1	0	71%	14%	0%
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			Korean trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			Korean trial (ph3b,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			PATRICIA trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			VIVIANE trial (ph3,2v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Quadrivalent	II	3	Japanese trial (ph2,4v)	U	N	N	N	U	N	4	2	0	57%	29%	0%
			Korean trial (ph2,4v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			Phase2 trial (ph2,4v)	N	U	N	N	N	N	5	1	0	71%	14%	0%
	III	4	African_3 country trial (ph3, 4v)	N	U	U	U	N	N	3	3	0	43%	43%	0%
			FUTURE I trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			FUTURE II trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
			FUTURE III trial (ph3,4v)	N	N	N	N	N	N	6	0	0	86%	0%	0%
Total		26	Nb of Low risk	24	16	16	16	25	25						
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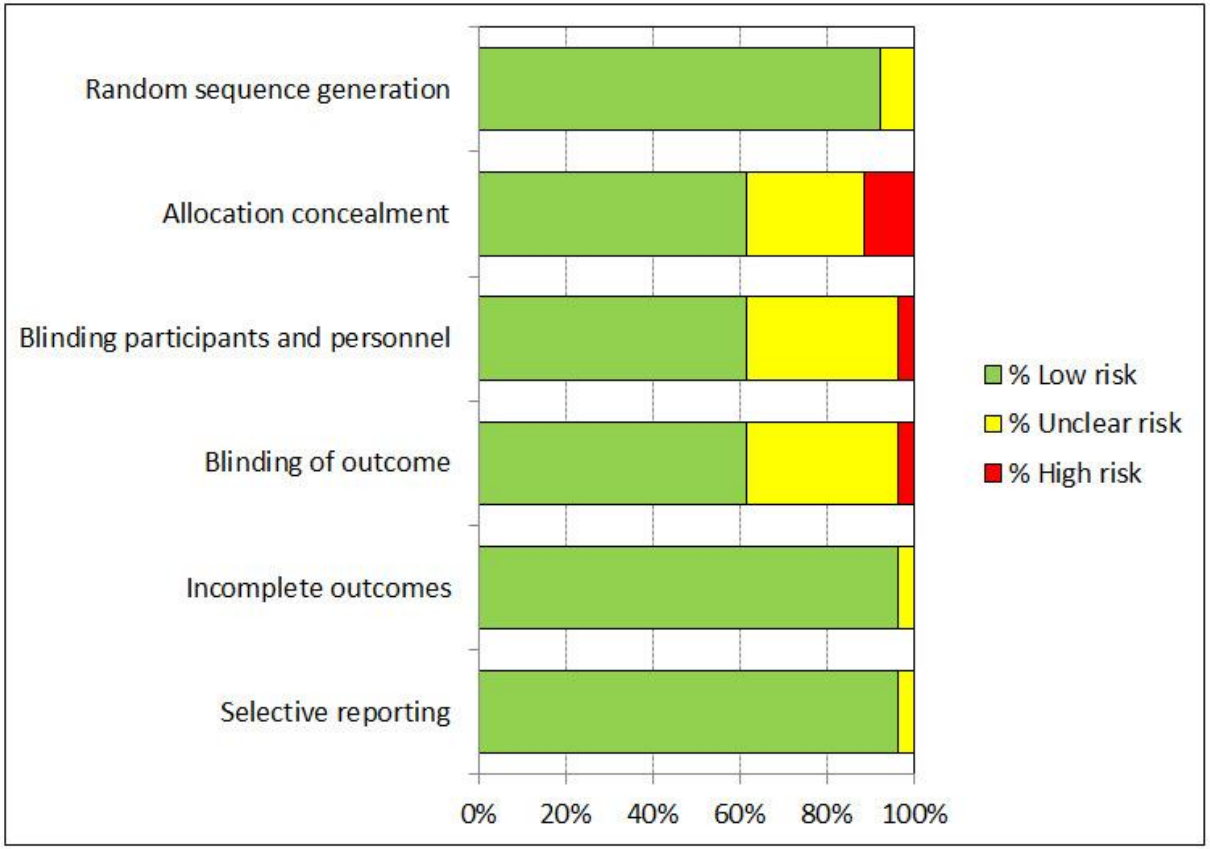
C 文獻評讀 Appraise

4. 系統性文獻回顧的作者是否評估所納入研究文獻的品質?→YES



C 文獻評讀 Appraise

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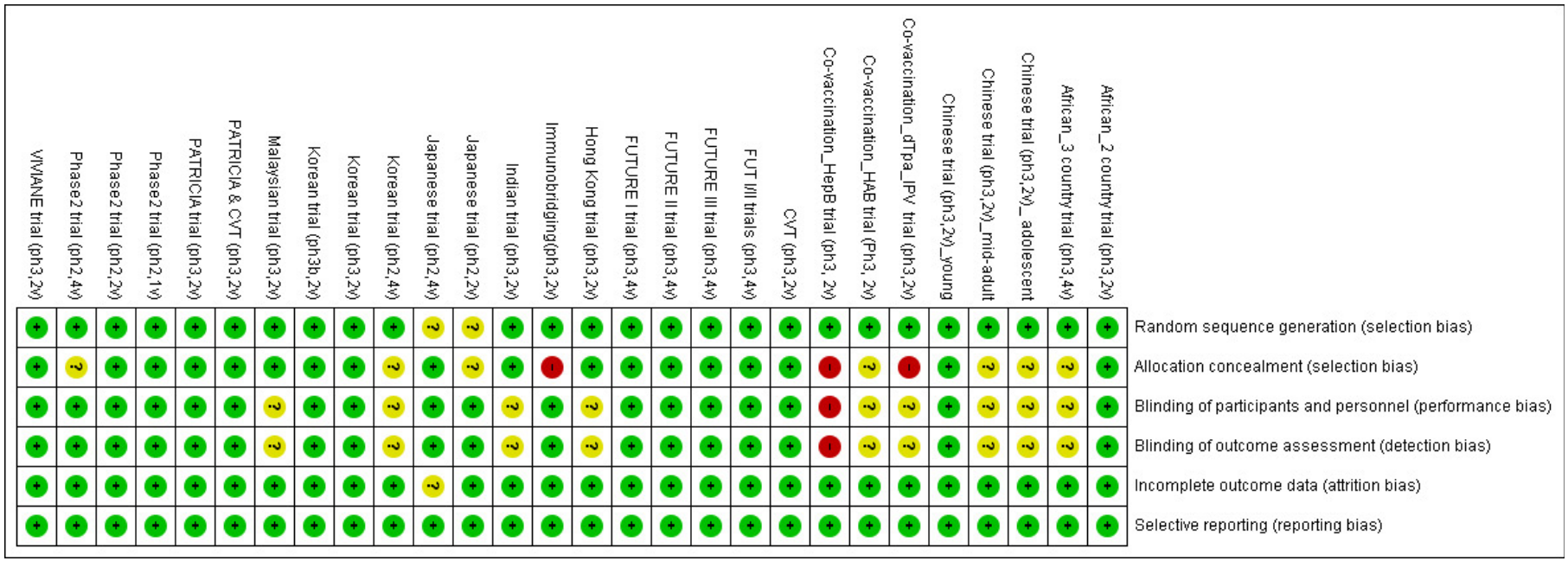


C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

1)未受hrHPV感染之女性

2)未受HPV16/18病毒感染之女性:

3)所有女性，不論有無受到HPV病毒之感染:

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 1.1. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 1 CIN2+ associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=1.47, df=2(P=0.48); Ii=0%

Analysis 1.2. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 2 CIN2+ associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Not applicable

Analysis 1.3. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 3 CIN3+ associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.05, df=1(P=0.82); Ii=0%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 1.4. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 4 CIN3+ associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Not applicable

Analysis 1.5. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 5 AIS associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.09, df=1(P=0.76); Ii=0%

Analysis 1.6. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 6 AIS associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Not applicable

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 1.7. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 7 Any CIN2+ irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0.09; Chii=9.84, df=4(P=0.04); Ii=59.33%

Analysis 1.8. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 8 Any CIN3+ irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.41, df=1(P=0.52); Ii=0%

Analysis 1.9. Comparison 1 High-grade cervical lesions in hrHPV DNA negative women at baseline, Outcome 9 Any AIS irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.14, df=1(P=0.71); Ii=0%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
   →YES

Analysis 2.1. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 1 CIN2+ associated with HPV16/(18), 3 doses.
Heterogeneity: Taui=0; Chii=4.26, df=7(P=0.75); Ii=0%

Analysis 2.2. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 2 CIN2+ associated with HPV16/(18), at least 1 dose.
Heterogeneity: Taui=0; Chii=1.94, df=5(P=0.86); Ii=0%
Heterogeneity: Taui=0; Chii=0.26, df=1(P=0.61); Ii=0%

Total:
Heterogeneity: Taui=0.29; Chii=9.95, df=7(P=0.19); Ii=29.62%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 2.3. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 3 CIN2+ associated with HPV16/(18), 1 or 2 doses (post hoc analysis).
Heterogeneity: Taui=0; Chii=3.51, df=4(P=0.48); Ii=0%
Heterogeneity: Taui=0; Chii=0.5, df=1(P=0.48); Ii=0%

Total
Heterogeneity: Taui=0.47; Chii=8.2, df=6(P=0.22); Ii=26.81%

Analysis 2.4. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 4 CIN2+ associated with HPV6/11/16/18, 3 doses.
Heterogeneity: Taui=1.23; Chii=1.77, df=1(P=0.18); Ii=43.45%18

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
   →YES

Analysis 2.5. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 5 CIN2+ associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Taui=4.8; Chii=4.87, df=1(P=0.03); Ii=79.48%

Analysis 2.6. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 6 CIN2+ associated with HPV6/11/16/18, 1 or 2 doses (post hoc analysis).
Heterogeneity: Taui=3.27; Chii=3.13, df=1(P=0.08); Ii=68.04%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
   →YES

Analysis 2.7. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 7 CIN3+ associated with HPV16/18 or HPV6/11/16/18, 3 doses.
Heterogeneity: Taui=0.41; Chii=2.76, df=2(P=0.25); Ii=27.59%

Analysis 2.8. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 8 CIN3+ associated with HPV 16/18 or HPV6/11/16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=1.15, df=2(P=0.56); Ii=0%

Analysis 2.9. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 9 CIN3+ associated with HPV16/18 or HPV6/11/16/18, 1 or 2 doses (post hoc analysis).
Heterogeneity: Taui=0; Chii=0.05, df=2(P=0.97); Ii=0%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 2.10. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 10 AIS associated with HPV16/18 or HPV6/11/16/18, 3 doses.
Heterogeneity: Taui=0; Chii=0.51, df=2(P=0.78); Ii=0%

Analysis 2.11. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 11 AIS associated with HPV16/18 or 6/11/16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.03, df=1(P=0.86); Ii=0%

Analysis 2.12. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 12 AIS associated with HPV16/18 or HPV6/11/16/18, 1 or 2 doses (post hoc analysis).
Heterogeneity: Not applicable

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 2.13. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 13 Any CIN2+ irrespective of HPV types, 3 doses.
Heterogeneity: Taui=0; Chii=0.63, df=2(P=0.73); Ii=0%

Analysis 2.14. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 14 Any CIN2+ irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.67, df=2(P=0.72); Ii=0%

Analysis 2.15. Comparison 2 High-grade cervical lesions in HPV16/18 DNA negative women at baseline, Outcome 15 Any CIN2+ irrespective of HPV types, 1 or 2 doses (post hoc analysis).
Heterogeneity: Not applicable

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
   →YES

Analysis 3.1. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 1 CIN2+ associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0.04; Chii=8.65, df=4(P=0.07); Ii=53.74%

Analysis 3.2. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 2 CIN2+ associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Taui=0.05; Chii=2.17, df=1(P=0.14); Ii=53.88%

Analysis 3.3. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 3 CIN3+ associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.01, df=1(P=0.92); Ii=0%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 3.4. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 4 CIN3+ associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Not applicable

Analysis 3.5. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 5 AIS associated with HPV16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.13, df=1(P=0.72); Ii=0%

Analysis 3.6. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 6 AIS associated with HPV6/11/16/18, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.01, df=1(P=0.91); Ii=0%

C 文獻評讀 Appraise

5. 如果作者將研究結果進行合併，這樣的合併是否合理？
→YES

Analysis 3.7. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 7 Any CIN2+ irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0.03; Chii=16.25, df=5(P=0.01); Ii=69.24%

Analysis 3.8. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 8 Any CIN3+ HPV type, at least 1 dose.
Heterogeneity: Taui=0.05; Chii=6.5, df=2(P=0.04); Ii=69.23%

Analysis 3.9. Comparison 3 High-grade cervical lesions in women regardless of baseline HPV DNA status, Outcome 9 Any AIS irrespective of HPV types, at least 1 dose.
Heterogeneity: Taui=0; Chii=0.37, df=1(P=0.54); Ii=0%

C 文獻評讀 Appraise

6. 這篇系統性文獻回顧的整體結果為何？

HPV vaccine effects on cervical lesions in adolescent girls and women who are hrHPV DNA negative at baseline

	RR	NNT
associated with HPV16/18		
CIN2+	RR 0.01(0.00 to 0.05)	62
CIN3+	RR 0.01(0.00 to 0.10)	143
AIS	RR 0.10(0.01 to 0.82)	1112
irrespective of HPV type		
Any CIN2+	RR 0.37(0.25 to 0.55)	56
Any CIN3+	RR 0.21(0.04 to 1.10)	
Any AIS	RR 0.10(0.01 to 0.76)	1000

C 文獻評讀 Appraise

6. 這篇系統性文獻回顧的整體結果為何？

HPV vaccine effects on cervical lesions in adolescent girls and women negative for HPV16/18 DNA at baseline

	RR	NNT
associated with HPV16/18		
CIN2+	15-26 y/o RR 0.05(0.03 to 0.10)	94
	24-45 y/o RR 0.30(0.11 to 0.81)	323
CIN3+ (age 15 to 26 years)	RR 0.05(0.02 to 0.14)	186
AIS (age 15 to 26 years)	RR 0.09(0.01 to 0.72)	834
irrespective of HPV type		
Any CIN2+	RR 0.41(0.32 to 0.52)	74
Any CIN3+	-	-
Any AIS	-	-

C 文獻評讀 Appraise

6. 這篇系統性文獻回顧的整體結果為何？

HPV vaccine effects on cervical lesions in adolescent girls and women unselected for HPV DNA status at baseline

	RR	NNT
associated with HPV16/18		
CIN2+	15-26 y/o RR 0.46 (0.37 to 0.57)	55
	24-45 y/o RR 074 (0.52 to 1.05)	
CIN3+ (age 15 to 26 years)	RR 0.55 (0.45 to 0.67)	136
AIS (age 15 to 26 years)	RR 0.36 (0.17 to 0.78)	1112
irrespective of HPV type		
Any CIN2+	15-26 y/o RR 0.70 (0.58 to 0.85)	60
	24-45 y/o RR 1.04 (0.83 to 1.30)	
Any CIN3+	RR 0.67 (0.49 to 0.93)	114
Any AIS	RR 0.32 (0.15 to 0.67)	834

C 文獻評讀 Appraise

6. 這篇系統性文獻回顧的整體結果為何？

HPV vaccine effects on cervical lesions in adolescent girls and women unselected for HPV DNA status at baseline

	RR	NNT
Serious adverse events	RR 0.98 (0.92 to 1.05)	
Deaths	RR 1.29 (0.85 to 1.98)	

C 文獻評讀 Appraise

7. 結果精準嗎？→Yes

		A	B	C
		Relative risks according to enrolment status among women who received ≥ 1 dose		
	Outcome	hr HPV DNA- ≥ 1 dose	HPV16/18 DNA- ≥ 1 dose	Regardless of HPV ≥ 1 dose
	Age group 15-26			
	High-grade intraepithelial neoplasia associated with HPV16/18			
1	CIN2+	0.01 (0.00 to 0.05)[b2q1] [1.1 ⊕⊕⊕⊕	0.05 (0.03 to 0.10)[b4q2] [2.2.1 ⊕⊕⊕⊕	0.46 (0.37 to 0.57)[b1q2] [3.1.1 ⊕⊕⊕⊕
2	CIN3+	0.01 (0.00 to 0.10)[b1q1] [1.3] ⊕⊕⊕⊕	0.05 (0.02 to 0.14)[b1q2] [2.8] ⊕⊕⊕⊕	0.55 (0.45 to 0.67)[b1q1] [3.3] ⊕⊕⊕⊕
3	AIS+	0.10 (0.01 to 0.82)[b1q1] [1.5 ⊕⊕⊕	0.09 (0.01 to 0.72)[q2] [2.11] ⊕⊕⊕	0.36 (0.17 to 0.78)[b1q1] [3.5] ⊕⊕⊕
	Any high-grade intraepithelial neoplasia irrespective of HPV types			
4	CIN2+	0.33 (0.25 to 0.43)[b4] [1.7.1 ⊕⊕⊕⊕ 0.57 (0.44 to 0.76)[q1] [1.7.2 ⊕⊕⊕	0.41 (0.32 to 0.52)[b2] [2.14] ⊕⊕⊕⊕	0.70 (0.58 to 0.85)[b2q1] [3.7.1 ⊕⊕⊕⊕
5	CIN3+	0.08 (0.03 to 0.23)[b2] [1.8.1 ⊕⊕⊕⊕ 0.54 (0.36 to 0.82)[q1] [1.8.2 ⊕⊕⊕	-	0.55 (0.43 to 0.71)[b2] [3.8.1] ⊕⊕⊕⊕ 0.81 (0.69 to 0.96)[q1] [3.8.2] ⊕⊕⊕
6	AIS+	0.10 (0.01 to 0.76)[b1q1] [1.9 ⊕⊕⊕	-	0.32 (0.15 to 0.67)[b1q1] [3.9] ⊕⊕⊕⊕
	Persistent HPV16/18 infection			
7	6M persisting	0.07 (0.05 to 0.90)[b1] [4.3] ⊕⊕⊕	0.10 (0.08 to 0.12)[b4] [5.5.1] ⊕⊕⊕⊕	0.44 (0.38 to 0.51)[b2] [6.2.1] ⊕⊕⊕

C 文獻評讀 Appraise

7. 結果精準嗎？→Yes

Age group 24-45

	High-grade intraepithelial neoplasia associated with HPV16/18				
8	CIN2+	-	0.30 (0.11 to 0.81)[b1q1] [2.2.2 ⊕⊕⊕	0.74 (0.52 to 1.05)[b1q1] [3.1.2 ⊕⊕⊕	
9	CIN3+	-	-	-	
10	AIS+	-	-	-	
	Any high-grade intraepithelial neoplasia irrespective of HPV types				
11	CIN2+	-	-	1.04 (0.83 to 1.30)[b1q1] [3.7.2] ⊕⊕	
12	CIN3+	-	-	-	
13	AIS+	-	-	-	
	Persistent HPV16/18 infection				
14	6M persisting	-	0.17 (0.10 to 0.29)[b1q1] [5.5.2 ⊕⊕⊕⊕	0.57 (0.47 to 0.69)[b1q1] [6.2.2 ⊕⊕⊕⊕	

多數結果 P<0.01有達到統計學上的顯著差異，多數95%信賴區間 上下值差異不大→還可算精確度

C 文獻評讀 Appraise

8. 此研究結果是否可應用到當地的族群？→Yes

Included studies

Twenty-six randomised trials were identified that contained data on vaccine efficacy and/or safety, which all together enrolled 73,428 women. One trial (Phase2 trial (ph2,1v)) evaluated effects of a monovalent HPV16 vaccine, 18 trials evaluated the bivalent vaccine (African_2 country trial (ph3,2v); Chinese trial (ph3,2v)_ adolescent; Chinese trial (ph3,2v)_mid-adult; Chinese trial (ph3,2v)_young; Co-vaccination_dTpa_IPV trial (ph3,2v); Co-vaccination_HAB trial (Ph3, 2v); Co-vaccination_HepB trial (ph3, 2v); CVT (ph3,2v); Hong Kong trial (ph3,2v); Immunobridging(ph3,2v); Indian trial (ph3,2v); Japanese trial (ph2,2v); Korean trial (ph3,2v); Korean trial (ph3b,2v); Malaysian trial (ph3,2v); PATRICIA trial (ph3,2v); Phase2 trial (ph2,2v); VIVIANE trial (ph3,2v)) and seven others the quadrivalent vaccine (African_3 country trial (ph3,4v); FUTURE III trial (ph3,4v); FUTURE II trial (ph3,4v); FUTURE I trial (ph3,4v); Japanese trial (ph2,4v); Korean trial (ph2,4v); Phase2 trial (ph2,4v)). Six studies were phase II trials and 20 others were phase III trials. No phase I trials were included.

有包含中華女性的資料，且收錄年紀與我們病人年紀相符
→可採用於我們的病人

C 文獻評讀 Appraise

9. 是否所有重要的臨床結果都有被考量到？→Yes

Primary outcomes

1. Histologically-confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3 and adenocarcinoma in situ (AIS)) or worse, associated with the HPV types included in the vaccine or any lesions irrespective of HPV type. Association between HPV types and a diagnosed lesion means that the particular type or types have been detected in that lesion. These primary outcomes were judged by WHO to be adequate endpoints (Pagliusi 2004).
2. Invasive cervical cancer.
3. Safety/occurrence of adverse effects:
    i. local adverse effects (redness, swelling, pain, itching at the injection site);
    ii. mild systemic effects;
    iii. serious systemic effects;
    iv. mortality;
    v. pregnancy outcomes observed during the trials, in particular occurrence of congenital anomalies.

Secondary outcomes

1. Incident infection with vaccine HPV types (HPV16 and HPV18, jointly; and HPV6, HPV11, HPV16 and HPV18 jointly).
2. Persistent infection (persisting during at least six months or at least 12 months) with vaccine HPV types.

C 文獻評讀 Appraise

10.付出的傷害和花費換得介入措施所產生的益處是否值得？→Yes

		A	B	C
		Relative risks according to enrolment status among women who received ≥ 1 dose		
	Outcome	hr HPV DNA- ≥ 1 dose	HPV16/18 DNA- ≥ 1 dose	Regardless of HPV ≥ 1 dose
	Age group 15-26			
	High-grade intraepithelial neoplasia associated with HPV16/18			
1	CIN2+	0.01 (0.00 to 0.05)[b2q1] [1.1] ⊕⊕⊕⊕	0.05 (0.03 to 0.10)[b4q2] [2.2.1] ⊕⊕⊕⊕	0.46 (0.37 to 0.57)[b1q2] [3.1.1] ⊕⊕⊕⊕
2	CIN3+	0.01 (0.00 to 0.10)[b1q1] [1.3] ⊕⊕⊕⊕	0.05 (0.02 to 0.14)[b1q2] [2.8] ⊕⊕⊕⊕	0.55 (0.45 to 0.67)[b1q1] [3.3] ⊕⊕⊕⊕
3	AIS+	0.10 (0.01 to 0.82)[b1q1] [1.5] ⊕⊕⊕	0.09 (0.01 to 0.72)[q2] [2.11] ⊕⊕⊕	0.36 (0.17 to 0.78)[b1q1] [3.5] ⊕⊕⊕
	Any high-grade intraepithelial neoplasia irrespective of HPV types			
4	CIN2+	0.33 (0.25 to 0.43)[b4] [1.7.1] ⊕⊕⊕⊕ 0.57 (0.44 to 0.76)[q1] [1.7.2] ⊕⊕⊕	0.41 (0.32 to 0.52)[b3] [2.14] ⊕⊕⊕⊕	0.70 (0.58 to 0.85)[b2q1] [3.7.1] ⊕⊕⊕⊕
5	CIN3+	0.08 (0.03 to 0.23)[b2] [1.8.1] ⊕⊕⊕⊕ 0.54 (0.36 to 0.82)[q1] [1.8.2] ⊕⊕⊕	-	0.55 (0.43 to 0.71)[b2] [3.8.1] ⊕⊕⊕⊕ 0.81 (0.69 to 0.96)[q1] [3.8.2] ⊕⊕⊕
6	AIS+	0.10 (0.01 to 0.76)[b1q1] [1.9] ⊕⊕⊕	-	0.32 (0.15 to 0.67)[b1q1] [3.9] ⊕⊕⊕⊕
	Persistent HPV16/18 infection			
7	6M persisting	0.07 (0.05 to 0.90)[b1] [4.3] ⊕⊕⊕	0.10 (0.08 to 0.12)[b4] [5.5.1] ⊕⊕⊕⊕	0.44 (0.38 to 0.51)[b2] [6.2.1] ⊕⊕⊕

預防性接種人類乳突病毒疫苗，是否可預防子宮頸癌，或子宮頸癌前病變以及有哪些害處?

	對象 (女性)	罹患HPV16/18病毒相關子宮頸癌前病變之風險	其他相關原因之罹患癌前病變風險
未受hrHPV感染之女性	15-25歲	164/10,000降低至2/10,000 (高度證據等級) PICO_ 1	287/10,000降至 106/10,000 (高度證據等級)
未受HPV16/18病毒感染之女性	<25歲	113/10,000降低至6/10,000 (高度證據等級)	231/10,000降低至 95/10,000 (高度證據等級)
	>25歲	45/10,000降低至14/10,000 (中度證據等級) PICO_ 2	
所有女性，不論有無受到HPV病毒之感染	15-26歲 已接種疫苗	341/10,000降低至157/10,000 (高度證據等級)	559/10,000降低至 391/10,000 (高度證據等級)。
	25-45歲 已接種疫苗	未接種疫苗女性之145/10,000降至已接種疫苗女性之107/10,000 (中度證據等級)	有無接種疫苗之罹患風險性相似（343與356/10,000，中度證據等級）

成本效益-藥價、藥效

HPV 疫苗	效力	預防病毒類別	接種對象(公費)	接種對象(自費)	健保自費單價
二價(Cervarix 保蓓)	9.4年	16、18型	我國國籍之: 1. 國中一年級女生 2. 國中二年級女生 3. 國中三年級女生 4. 91 年 9 月 1 日至 93 年 9 月 1 日出生之離島、原住民族地區、低收入戶及中低收入戶之青少 女。	10~25歲女性	2600 /劑*3
~~四價(Gardasil 嘉喜)~~	~~8年~~	~~6、11、16、18型~~		~~9-26歲女性及16-26歲男性~~	~~3500 /劑*3~~
九價	?	6、11、16、18、31、33、45、52、58 型		9-26歲男女性	5500 /劑*3

應用 Apply

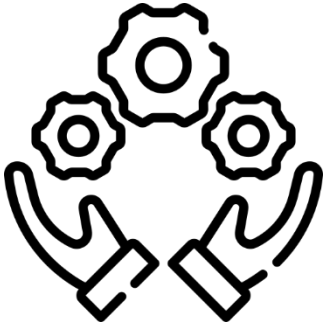
以我們個案20歲來看，並以CIN 2的結果來說，以最好的情況NNT=55的情況下

公費施打 1080030元 (以9價來算)	疫苗費用(四價)：10500(三劑) x 55=577500 or 疫苗費用(九價)：16500(三劑) x 55=907500 門診掛號費：350 x 54=18900元 LEEP：2810(點) x 0.9*54=136566元 不能工作的損失(以兩小時計算)：158 x 2 x 54=17064
不公費施打 175725元	門診掛號費：350 x 55=19250元 LEEP：2810(點) x 0.9 x 55=139095元 不能工作的損失(以兩小時計算)：158 x 2 x 55=17380

應用 Apply

Evidence

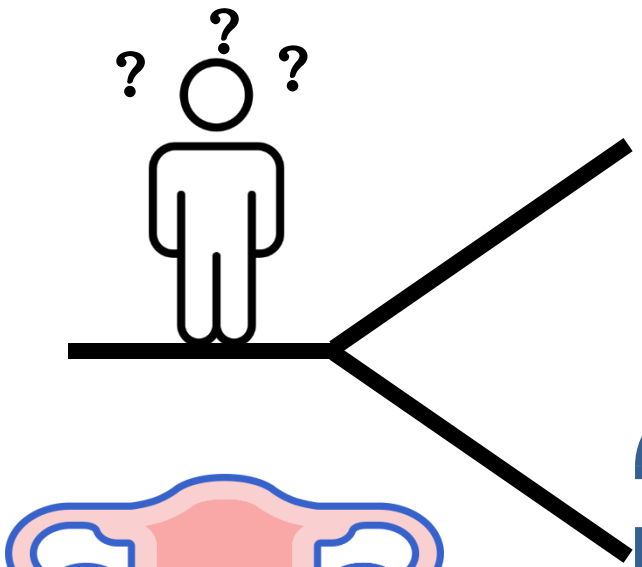
Expectation



Experience

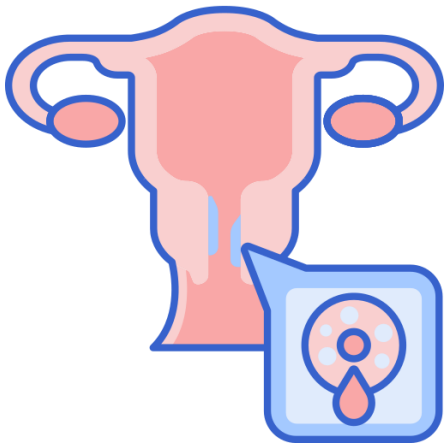
Environment

應用 Apply



施打：
子宮頸癌前病變的機率顯著性降低
子宮頸癌得到的機率也會降低

不施打：
子宮頸癌前病變的機率相對顯著性提高
子宮頸癌得到的機率也會相對提高
(台灣發生率約17/100000)



應用 Apply

Share Decision Making

根據研究可以看出子宮頸癌疫苗的確可以顯著的降低癌前病變以及子宮頸癌的發生率，因此在經濟允許的情況下，我們建議您可以施打子宮頸癌疫苗來避免子宮頸癌的發生。


THANK
YOU