

# 實證醫學

Evidence-Based Medicine

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內科部

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# 臨床場景

蘇小姐，25歲，已婚。因台灣目前核准九價子宮頸疫苗上市，想詢問目前不同價數的**子宮頸疫苗對於癌症的預防效果**如何，以及是否值得自費施打**效價高的疫苗**？

# Background Knowledge

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## 子宮頸

### 特性

1. 建議年紀<26歲的女性施打預防效果最好
2. 所有的子宮頸疫苗，都能有效降低子宮頸頸癌

### 疫苗

1. 主要降低HPV 16,18的CIN
2. 目前有2,4,9價三種劑型
3. 9價疫苗於2015年開始於美國上市

# 病人的主要**問題**是

2 5 歲 **女 性** 介 入 效 果  
家 族 病 史 不 同 效 價 子 宮 頸 疫 苗

→ 這是一個 **介入型** 的問題

# 提出可以回答的臨床問題

P : Young female with family history

I : HPV vaccine (9)

C : qHPV vaccine, bHPV vaccine

O : Result in any increased **benefit** or **harm**?

# PICO 1

	P I C O / 關鍵字	MeSH同義詞	中文關鍵字
P	<ul style="list-style-type: none"><li>• 25y/F with family history</li><li>• Asian</li></ul>	<ul style="list-style-type: none"><li>• Female with high risk</li><li>• Taiwan, chinese</li></ul>	<ul style="list-style-type: none"><li>• 年輕女性有家族史</li></ul>
I	<ul style="list-style-type: none"><li>• 9vHPV Vaccination</li></ul>	<ul style="list-style-type: none"><li>• Prevention vaccines</li><li>• 9vHPV vaccines</li></ul>	<ul style="list-style-type: none"><li>• 高效價子宮頸疫苗</li></ul>
C	<ul style="list-style-type: none"><li>• qHPV, bHPV</li></ul>	<ul style="list-style-type: none"><li>• comparison</li></ul>	<ul style="list-style-type: none"><li>• 二價或者四價</li></ul>
O	Major <ul style="list-style-type: none"><li>• Cervical epithelial neoplasia</li><li>• Adverse events</li></ul> Minor <ul style="list-style-type: none"><li>• Cervical, vulvar, vaginal disease</li><li>• Discontinued event</li></ul>	<ul style="list-style-type: none"><li>• CIN</li><li>• AE</li><li>• Fatal outcome</li></ul>	<ul style="list-style-type: none"><li>• 子宮頸癌症發生率</li><li>• 副作用</li><li>• 生殖道疾病</li></ul>

# PICO 2

	P I C O / 關鍵字	MeSH同義詞	中文關鍵字
P	<ul style="list-style-type: none"> <li>&lt;16y F with family history</li> <li>Asian</li> </ul>	<ul style="list-style-type: none"> <li>Female with high risk</li> <li>Taiwan, chinese</li> </ul>	<ul style="list-style-type: none"> <li>&lt;16歲女性有家族史</li> </ul>
I	<ul style="list-style-type: none"> <li>9vHPV Vaccination</li> </ul>	<ul style="list-style-type: none"> <li>Prevention vaccines</li> <li>9vHPV vaccines</li> </ul>	<ul style="list-style-type: none"> <li>高效價子宮頸疫苗</li> </ul>
C	<ul style="list-style-type: none"> <li>qHPV, bHPV</li> </ul>	<ul style="list-style-type: none"> <li>comparison</li> </ul>	<ul style="list-style-type: none"> <li>二價或者四價</li> </ul>
O	<p>Major</p> <ul style="list-style-type: none"> <li>Cervical epithelial neoplasia</li> <li>Adverse events</li> </ul> <p>Minor</p> <ul style="list-style-type: none"> <li>Cervical, vulvar, vaginal disease</li> <li>Discontinued event</li> </ul>	<ul style="list-style-type: none"> <li>CIN</li> <li>AE</li> <li>Fatal outcome</li> </ul>	<ul style="list-style-type: none"> <li>子宮頸癌症發生率</li> <li>副作用</li> <li>生殖道疾病</li> </ul>

# Search Skills

(**Female with high risk**) AND

((**HPV-vaccine**) OR (**9vHPV**) OR (**New HPV**)) AND ((**benefit**)

OR (**harm**))

Recent 5 years, Systemic review, Meta-Analysis,

Randomized clinical trial



# 檢索策略-提升檢索效率

首先以『P』、『I』做搜尋，再依據結果適當加入關鍵字及同義詞

P

AND

I

AND

C

AND

O

Female  
OR  
Young female  
OR  
Female with high risk

HPV vaccination  
OR  
9vHPV vaccine

qHPV  
bHPV

CIN incidence  
OR  
Adverse event  
OR  
mortality

限定搜尋範圍

Free full text、Within 5 years、Human species

限定研究類型

Systematic review、Meta-analysis、Randomized controlled trial

限定語言地區

English、中文[台灣本土文獻]

# 搜尋Cochrane Library-提升檢索效率

**Cochrane Library** Trusted evidence. Informed decisions. Better health. [Log in / Register](#)

Search Search Manager Medical Terms (MeSH) Browse

Search Scope: Title, Abstract, Keywords

Search Query: female\* HPV vaccin\*

Buttons: Go Save

**Database**

- Cochrane Reviews
  - All
  - Review
  - Protocol
- Other Reviews
  - Trials
  - Methods Studies
  - Technology Assessments
  - Economic Evaluations
  - Cochrane Groups

**Dates**

Publication Year (available for all databases)  
Year (YYYY) the article was originally published  
\*\*For Cochrane Reviews, this is the year of the last update

All Years

Between  and

輸入關鍵字、適當使用Truncation  
『female\* 9vHPV vaccin\*』

使用Limit功能  
限定『Review or clinical』之文章  
限定『2012-2017』文章

# 搜尋Pubmed-利用限定縮小檢索範圍

**Builder**

All Fields   [Show index list](#)

AND    [Show index list](#)

or [Add to history](#)

輸入關鍵字、適當使用Truncation  
『female \* 9vHPV vaccin\*』

適當使用布林運算  
『AND』、『OR』

**Article types**

- ✓ **Meta-Analysis**
- ✓ **Randomized Controlled Trial**
- ✓ **Systematic Reviews**
- Customize ...

**Text availability**

- Abstract
- Free full text
- ✓ **Full text**

**Publication dates**

- ✓ **5 years**
- 10 years
- Custom range...

**Species**

- ✓ **Humans**
- Other Animals

限定適當文章類型  
『Meta-Analysis』、『Systematic Reviews』  
『Randomized Controlled Trial』

限定適當搜尋範圍  
限定『5年』內之文章  
限定『Full text』有全文可供評讀  
限定『Humans』 species

# 搜尋Pubmed-再利用My NCBI 篩選器提升效率

All (77)

Chinese (0)

[Clinical Trial \(41\)](#)

[Costs/Narrow \(5\)](#)

Diagnosis/Narrow (0)

[Economics/Narrow \(3\)](#)

[Etiology/Narrow \(12\)](#)

Japanese (0)

Korean (0)

[Meta-analysis \(9\)](#)

[Practice Guideline \(7\)](#)

[Prognosis/Narrow \(13\)](#)

[Published in the last 5 years \(77\)](#)

[Randomized Controlled Trial \(41\)](#)

[Systematic Reviews \(37\)](#)

[Therapy/Narrow \(43\)](#)

根據臨床問題類型篩選

『治療型問題』

『診斷型問題』

『預後型問題』

『病因型問題』

同時注意含有經濟效益分析之文章

『Costs/Narrow』

『Economics/Narrow』

找出可能含亞洲族群文章納入考慮

『Chinese』

Secondary

Primary database

**Cochrane**

**EMBASE**

**PubMed**

**華藝線上**

Key words and Synonyms

6

60

81

0

Systematic Review or Randomized Controlled Trial

1

18

33

0

Within 5 years

1

6

5

0

Match PICO

**1**




**1**

**2**

**0**

Results

# 各資料庫收納結果

來源	標題	年份
	Vaccines for preventing HPV diarrhoea: vaccines in use (Review) [2014]	2014
	A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil in 9–15-Year-Old Girls [2015]	2015
	A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women [2015]	2015
	Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence [2017]	2017

# 比較收納文獻-選出最佳文獻，並提出我們的理由



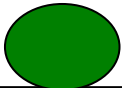
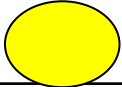
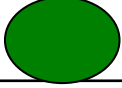
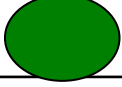
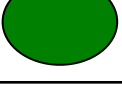

## Vaccines for preventing HPV diarrhoea: vaccines in use (Review) [2014]

M	Systematic review	
P	Female aged less than 26 year	
I	HPV vaccination	
C	Other HPV vaccination	
O	CIN incidence AE	
T	2month-2years	

# 比較收納文獻-選出最佳文獻，並提出我們的理由

Embase®

A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil in 9–15-Year-Old Girls [2015]

M	Randomized clinical trial	
P	Female between 9-15 years	
I	9vHPV vaccine	
C	qHPV	
O	CIN incidence AE	
T	Follow up at least 1 years	



# 比較收納文獻-選出最佳文獻，並提出我們的理由

Embase<sup>®</sup>

## A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women [2015]

M	Randomized clinical trials	
P	Female between 16 – 26 years	
I	9vHPV vaccine	
C	qHPV	
O	CIN incidence rate Adeverse events	
T	Follow up duration at least 2 years	

# 比較收納文獻-選出最佳文獻，並提出我們的理由



Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence [2017]

M	Systematic review (not meta analysis)	
P	Female and male	
I	9vHPV	
C	qHPV, bHPV	
O	CIN incidence, AE	
T	1 year	

# 收納文獻比較總整理-選出最佳文獻

收 納 文 章	M	P	I	C	O	T
Vaccines for preventing HPV diarrhoea: vaccines in use	●	●	●	●	●	●
A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil in 9–15-Year-Old Girls [2015]	●	●	●	●	●	●
A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women [2015]	●	●	●	●	●	●
Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence [2017]	●	●	●	●	●	●



# 解讀證據 Critical Appraisal

◆ 文獻結果是否有效度：Validity

◆ 文獻結果是否有臨床重要性：Importance

◆ 文獻結果是否適用於我們的病人：Applicability

# 嚴格評讀工具

## Critical Appraisal Tool

**CASP Checklists** (click to download)



<a href="#"><u>CASP Systematic Review Checklist</u></a>	<a href="#"><u>CASP Qualitative Checklist</u></a>
<a href="#"><u>CASP Randomised Controlled Trial Checklist</u></a>	<a href="#"><u>CASP Case Control Checklist</u></a>
<a href="#"><u>CASP Diagnostic Checklist</u></a>	<a href="#"><u>CASP Cohort Study Checklist</u></a>
<a href="#"><u>CASP Economic Evaluation Checklist</u></a>	<a href="#"><u>CASP Clinical Prediction Rule Checklist</u></a>

# 嚴格評讀 critical appraisal

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women

E.A. Joura, A.R. Giuliano, O.-E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, E.D. Moreira, Jr., Y. Ngan, L.K. Petersen, E. Lazcano-Ponce, P. Pitisuttithum, J.A. Restrepo, G. Stuart, L. Woelber, Y.C. Yang, J. Cuzick, S.M. Garland, W. Huh, S.K. Kjaer, O.M. Bautista, I.S.F. Chan, J. Chen, R. Gesser, E. Moeller, M. Ritter, S. Vuocolo, and A. Luxembourg, for the Broad Spectrum HPV Vaccine Study\*

這篇文獻「納入理由」

年份為2015年，Randomise Clinical Trial

- ✓ 最符合PICO
- ✓ 最佳的研究設計

- ✓ 可以回答臨床問題
- ✓ 有全文可供評讀

# Did the trial address a clearly focused issue?

此研究是否問了一個清楚明確的問題？

## BACKGROUND

The investigational 9-valent viruslike particle vaccine against human papillomavirus (HPV) includes the HPV types in the quadrivalent HPV (qHPV) vaccine (6, 11, 16, and 18) and five additional oncogenic types (31, 33, 45, 52, and 58). Here we present the results of a study of the efficacy and immunogenicity of the 9vHPV vaccine in women 16 to 26 years of age.

## METHODS

We performed a randomized, international, double-blind, phase 2b–3 study of the 9vHPV vaccine in 14,215 women. Participants received the 9vHPV vaccine or the qHPV vaccine in a series of three intramuscular injections on day 1 and at months 2 and 6. Serum was collected for analysis of antibody responses. Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue were obtained and used for HPV DNA testing, and liquid-based cytologic testing (Papanicolaou testing) was performed regularly. Tissue obtained by means of biopsy or as part of definitive therapy (including a loop electrosurgical excision procedure and conization) was tested for HPV.

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P: female between 16-26 yrs

I: 9vHPV

C: qHPV

O: CIN incidence, AE

therapy (including  
tested for HPV.



Yes



Can't tell



No

l conization) was



# Was the assignment of patients to treatments randomised?

此研究是否適當的隨機分派病患？

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# Was the assignment of patients to treatments randomised?

此研究是否適當的隨機分派病患？

## *Vaccine randomization*

An Interactive Voice Response System (IVRS) was used to allocate study subjects and balance randomization between sites. Subjects were assigned an allocation number from an allocation schedule via the IVRS. Study personnel utilized IVRS at each vaccination visit for assignment of the clinical material from the appropriate vaccination group to be administered to the subject.

本實驗使用IVRS亂數電話表,



Yes



Can't tell

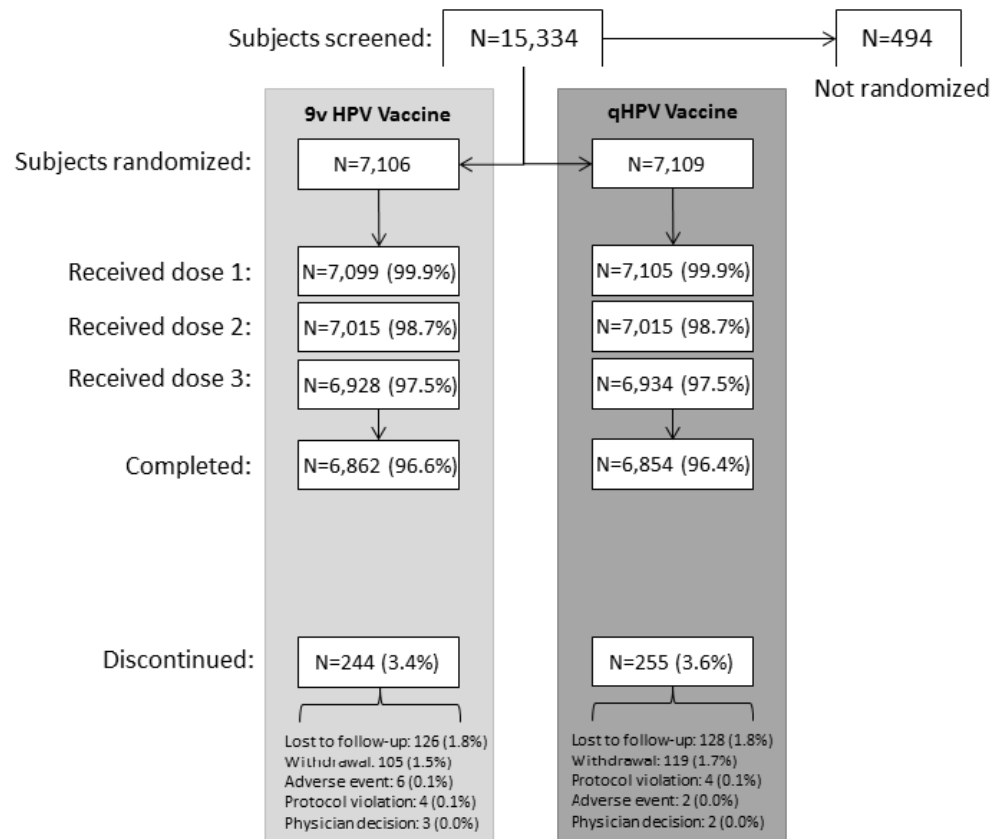


No

# Were all of the patients who entered the trial properly accounted for at its conclusion?

是否所有的病患都有納入結果中去分析？

Figure S1. Efficacy substudy; disposition of subjects from day 1 to month 7



本文章為採用intention to treat analysis,且明確交代lost of follow up rate,兩組相當。



Yes



Can't tell



No

## Were patients, health workers and study personnel “ blind ” to treatment ?

病患、(給藥、測量結果的)醫療照護者、分析數據人員是否都是「盲性的」？

The investigational 9-valent viruslike particle vaccine against human papillomavirus (HPV) includes the HPV types in the quadrivalent HPV (qHPV) vaccine (6, 11, 16, and 18) and five additional oncogenic types (31, 33, 45, 52, and 58). Here we present the results of a study of the efficacy and immunogenicity of the 9vHPV vaccine in women 16 to 26 years of age.

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本實驗為 randomized, international, triple-blind.

was performed regularly. Tissue obtained by means of biopsy or as part of definitive therapy (including conization) was tested for HPV.



Yes



Can't tell



No

# Were the groups similar at the start of the trial?

隨機分派後的兩組病患是否具有可比性？

**Table 1. Baseline Characteristics of the Participants.\***

Characteristic	9vHPV Vaccine (N=7106)	qHPV Vaccine (N=7109)	Total (N=14,215)
<b>Age — yr</b>			
Mean	21.9±2.5	21.8±2.5	21.9±2.5
Median	22.0	22.0	22.0
Range	16–26	16–26	16–26
Age at first sexual intercourse — yr	17.4±2.2	17.4±2.2	17.4±2.2
<b>Region — no. (%)</b>			
Asia-Pacific	905 (12.7)	909 (12.8)	1,814 (12.8)
Europe	2406 (33.9)	2409 (33.9)	4,815 (33.9)
Latin America	2372 (33.4)	2372 (33.4)	4,744 (33.4)
North America	1423 (20.0)	1419 (20.0)	2,842 (20.0)
<b>Smoking status — no. (%)</b>			
Current smoker	1071 (15.1)	1005 (14.1)	2,076 (14.6)
Former smoker	382 (5.4)	358 (5.0)	740 (5.2)
Never smoked	5647 (79.5)	5744 (80.8)	11,391 (80.1)
Unknown	6 (0.1)	2 (0)	8 (0.1)
<b>Lifetime sexual partners — no. (%)†</b>			
1	2063 (29.0)	2023 (28.5)	4,086 (28.8)
2	1691 (23.8)	1698 (23.9)	3,389 (23.8)
3	1648 (23.2)	1646 (23.2)	3,294 (23.2)
4	1520 (21.4)	1527 (21.5)	3,047 (21.4)
>4	11 (0.2)	15 (0.2)	26 (0.2)
<b>Non-HPV-related cervicovaginal infections or sexually transmitted diseases</b>			
Any	298 (4.2)	292 (4.1)	590 (4.2)
Chlamydia	284 (4.0)	285 (4.0)	569 (4.0)
Gonorrhea	19 (0.3)	11 (0.2)	30 (0.2)
<b>Contraceptive use‡</b>			
Barrier	2318 (32.6)	2303 (32.4)	4,621 (32.5)
Behavior	1014 (14.3)	1035 (14.6)	2,049 (14.4)
Hormonal	4273 (60.2)	4292 (60.4)	8,565 (60.3)
<b>Day 1 composite HPV positivity — no./total no. (%)§</b>			
Serologic test	2771/7082 (39.1)	2647/7078 (37.4)	5418/14,160 (38.3)
PCR assay	1887/6919 (27.3)	1920/6943 (27.7)	3807/13,862 (27.5)
Serologic test or PCR assay	3365/6970 (48.3)	3345/6983 (47.9)	6710/13,953 (48.1)

分派後的基本特性皆有清楚羅列,於文章內文有提及基本特性的差異性皆不大.



Yes



Can't tell



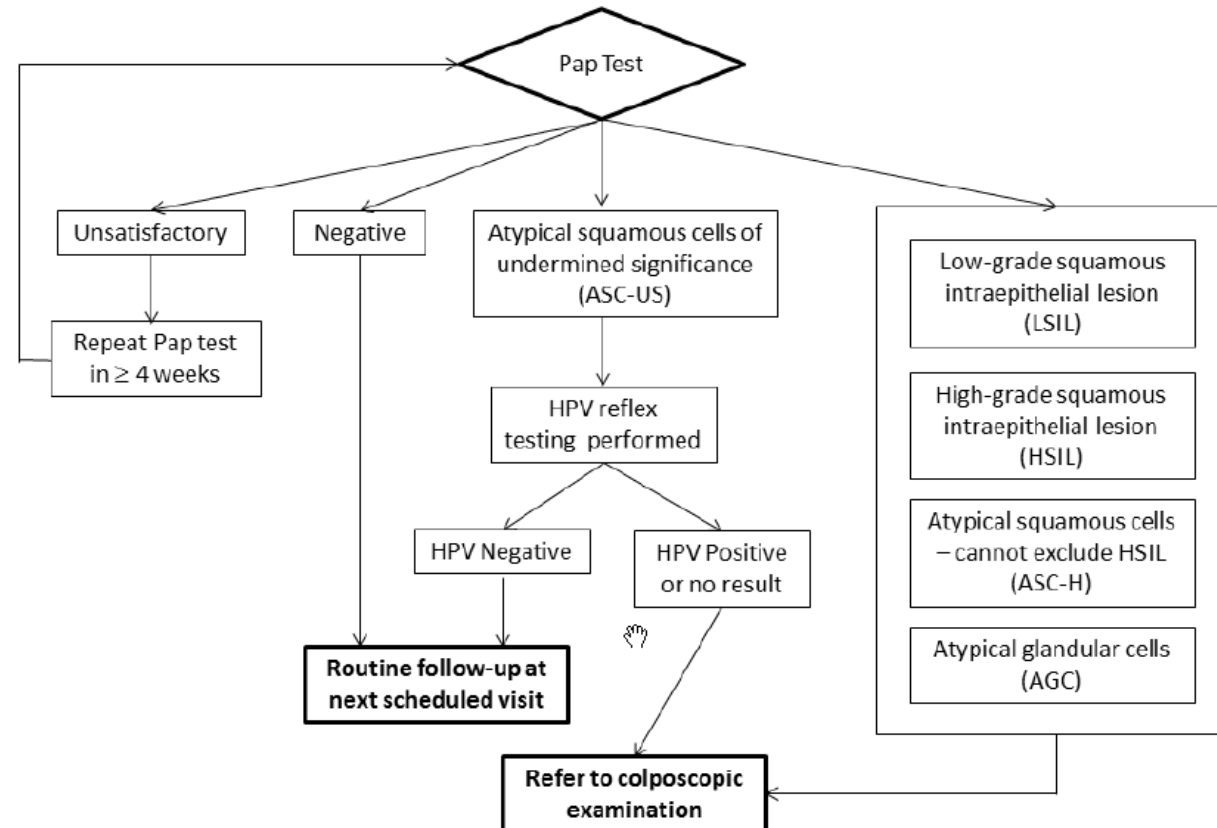
No



# Aside from the experimental intervention, were the groups treated equally?

除了研究介入 (intervention) 的差別，兩組間其他的治療是否相等？

Figure S3. Mandatory regimen for triage of abnormal Papanicolaou tests to colposcopic examination.

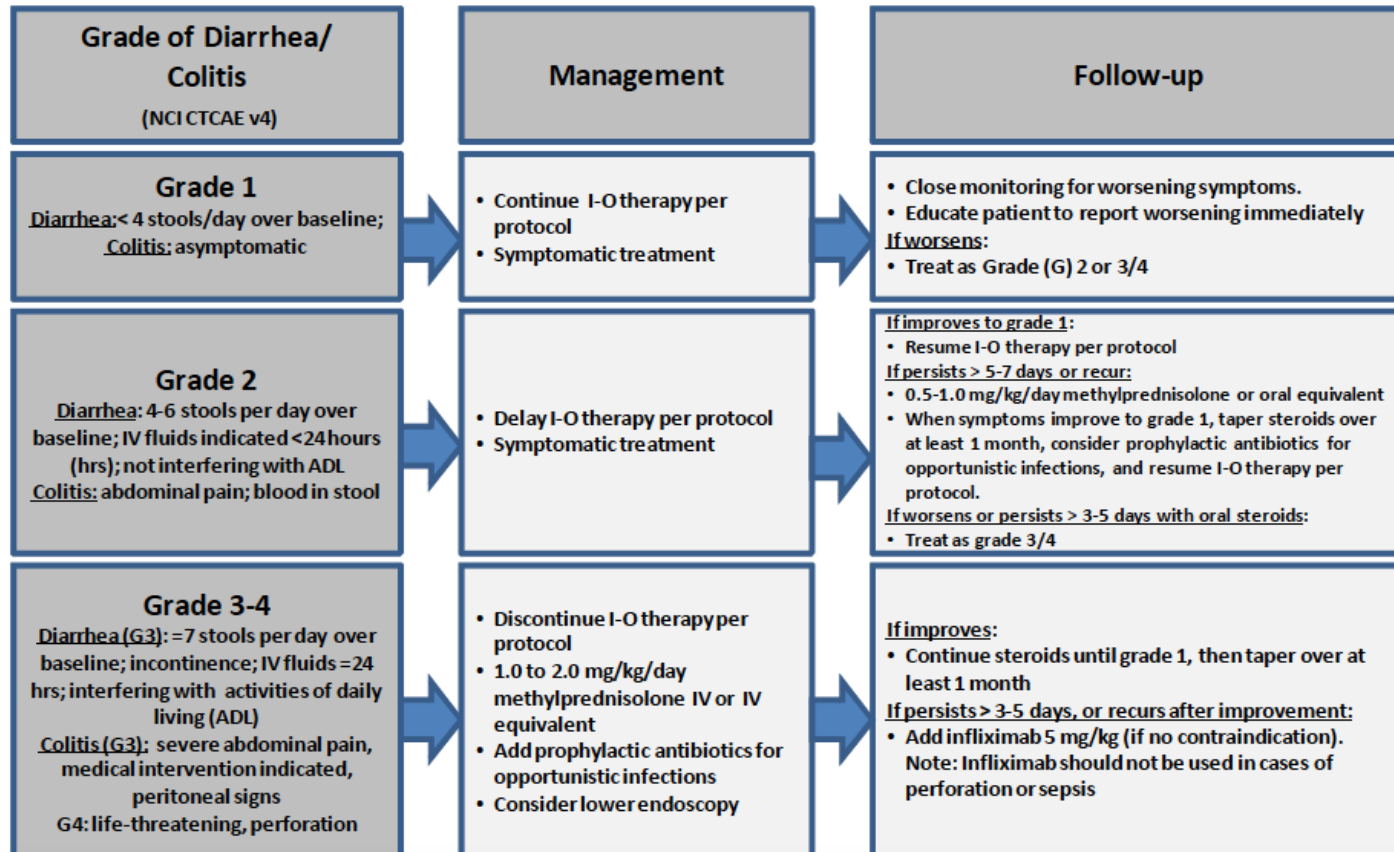


# Aside from the experimental intervention, were the groups treated equally?

除了研究介入 (intervention) 的差別，兩組間其他的治療是否相等？

## GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



除了major intervention外,副作用的management皆有明確的Protocol,應該可以認為組間治療大致相同。



Yes



Can't tell



No

# How large was the treatment effect?

介入的治療效果有多大？

End Point	9vHPV Vaccine (N=7099)		qHPV Vaccine (N=7105)		Risk Reduction (95% CI)
	no./total no.	cases/1000 person-yr	no./total no.	cases/1000 person-yr	
<b>Modified intention-to-treat population</b>					
High-grade cervical, vulvar, and vaginal disease†					
All participants	340/7027	14.0	344/7027	14.0	0.7 (-15.7 to 14.8)
HPV-uninfected on day 1	26/3032	2.4	46/3077	4.2	42.5 (7.9 to 65.9)
Not related to 9 vaccine HPV types‡	26/3032	2.4	33/3077	3.0	19.7 (-34.5 to 52.5)
Related to 9 vaccine HPV types‡	0/3032	0.0	13/3076	1.2	100 (70.4 to 100)
HPV-infected on day 1	314/3995	23.1	298/3950	22.1	-4.8 (-23.3 to 10.8)
Not related to 9 vaccine HPV types‡	141/3995	10.0	137/3950	9.8	-2.0 (-30.0 to 19.9)
Related to 9 vaccine HPV types‡	173/3992	12.4	161/3946	11.6	-6.8 (-33.2 to 14.3)
Average risk reduction§	—	—	—	—	19.0 (-1.6 to 35.3)
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
All participants	325/6882	14.1	326/6871	14.1	-0.3 (-17.3 to 14.3)
HPV-uninfected on day 1	26/2976	2.5	44/3009	4.2	39.7 (1.8 to 64.3)
Not related to 9 vaccine HPV types‡	26/2976	2.5	31/3009	3.0	14.3 (-49.1 to 49.1)
Related to 9 vaccine HPV types‡	0/2976	0.0	13/3009	1.2	100 (70.3 to 100)
HPV-infected on day 1	299/3906	23.3	282/3862	22.2	-5.3 (-24.1 to 10.8)
Not related to 9 vaccine HPV types‡	131/3906	10.1	132/3862	10.3	1.8 (-26.0 to 23.5)
Related to 9 vaccine HPV types‡	168/3906	13.0	150/3862	11.7	-11.3 (-39.6 to 11.0)
Average risk reduction§	—	—	—	—	17.1 (-4.2 to 34.0)

CIN incidence rates在9vHPV組沒有顯著的 benefit ( $p>0.05$ ), **Average risk reduction 17.1 (-4.2 to 34.0)** Side effect 一樣沒有顯著差異 ( $p>0.05$ )



Yes



Can't tell



No



# How precise was the estimate of the treatment effect?

## 治療效果的估計值有多精確？

High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
All participants	325/6882	14.1	326/6871	14.1	-0.3 (-17.3 to 14.3)
HPV-uninfected on day 1	26/2976	2.5	44/3009	4.2	39.7 (1.8 to 64.3)
Not related to 9 vaccine HPV types‡	26/2976	2.5	31/3009	3.0	14.3 (-49.1 to 49.1)
Related to 9 vaccine HPV types‡	0/2976	0.0	13/3009	1.2	100 (70.3 to 100)
HPV-infected on day 1	299/3906	23.3	282/3862	22.2	-5.3 (-24.1 to 10.8)
Not related to 9 vaccine HPV types‡	131/3906	10.1	132/3862	10.3	1.8 (-26.0 to 23.5)
Related to 9 vaccine HPV types‡	168/3906	13.0	150/3862	11.7	-11.3 (-39.6 to 11.0)
<b>Average risk reduction§</b>	—	—	—	—	<b>17.1 (-4.2 to 34.0)</b>

The study used a fixed-event design whereby the primary efficacy analysis would be performed when at least 30 primary efficacy end-point events had been observed. With at least 30 such events, the study would have **power of 90% or more to**

**show a lower boundary of the 95% confidence interval for the estimate of vaccine efficacy of more than 25%, with a one-sided type I error rate of 0.025,** assuming that the true efficacy of the 9vHPV vaccine relative to qHPV vaccine is 83%.

# How precise was the estimate of the treatment effect?

治療效果的估計值有多精確？

High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
All participants	325/6882	14.1	326/6871	14.1	-0.3 (-17.3 to 14.3)
HPV-uninfected on day 1	26/2976	2.5	44/3009	4.2	39.7 (1.8 to 64.3)
Not related to 9 vaccine HPV types‡	26/2976	2.5	31/3009	3.0	14.3 (-49.1 to 49.1)
Related to 9 vaccine HPV types‡	0/2976	0.0	13/3009	1.2	100 (70.3 to 100)
HPV-infected on day 1	299/3906	23.3	282/3862	22.2	-5.3 (-24.1 to 10.8)
Not related to 9 vaccine HPV types‡	131/3906	10.1	132/3862	10.3	1.8 (-26.0 to 23.5)
Related to 9 vaccine HPV types‡	168/3906	13.0	150/3862	11.7	-11.3 (-39.6 to 11.0)
<b>Average risk reduction§</b>	—	—	—	—	<b>17.1 (-4.2 to 34.0)</b>

The study used a fixed-event design whereby the primary efficacy analysis would be performed when at least 30 primary efficacy end-point events had been observed. With at least 30 such events, the study would have power of 90% or more to

show a 1  
interval  
more than  
rate of 0.  
the 9vHPV vaccine relative to qHPV vaccine is 65%.

採用較嚴格的信效度標準  
Power 90-95%, RReduction : 17.1  
CI : -4.2-32 窄區間

Yes

Can't tell

No

## Can the results be applied in your context?

此研究是否可應用到你的病患？

此實驗雖然是美國研究，但有納入各洲人種(台灣也有加入)，因此種族特性應該不會成為影響的原因。

**Basic Characteristics :**

- a. 收案年齡 16-26yr (25yr)
- b. 第一次性行為年紀 17.4+/- 2yr(25yr有一對女兒6歲與4歲)
- c. 未抽菸比例 79.5%

適用上應該無太大問題



Yes



Can't tell



No

# Can the results be applied in your context?

## *Study and population*

The study was initiated on September 26<sup>th</sup>, 2007 and data are current through visits that occurred before or on April 10<sup>th</sup>, 2013. Subjects were randomized from 105 study sites located in 18 countries (Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States [including Puerto Rico]).

# Were all clinically important outcomes considered ?

是否所有重要的臨床結果都被考量到？

**Table 2. Effect of 9vHPV Vaccine on the Incidence of Cervical, Vulvar, and Vaginal Disease and of Persistent HPV-Related Infection.\***

End Point	9vHPV Vaccine (N=7099)		qHPV Vaccine (N=7105)		Risk Reduction (95% CI)
	no./total no.	cases/1000 person-yr	no./total no.	cases/1000 person-yr	
<b>Modified intention-to-treat population</b>					
High-grade cervical, vulvar, and vaginal disease†					
All participants	340/7027	14.0	344/7027	14.0	0.7 (-15.7 to 14.8)
HPV-uninfected on day 1	26/3032	2.4	46/3077	4.2	42.5 (7.9 to 65.9)
Not related to 9 vaccine HPV types‡	26/3032				
Related to 9 vaccine HPV types‡	0/3				
HPV-infected on day 1	314/7027				
Not related to 9 vaccine HPV types‡	141/7027				
Related to 9 vaccine HPV types‡	173/7027				
Average risk reduction§					
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
All participants	325/7027				
HPV-uninfected on day 1	26/7027				
Not related to 9 vaccine HPV types‡	26/7027				
Related to 9 vaccine HPV types‡	0/2				
HPV-infected on day 1	299/7027				
Not related to 9 vaccine HPV types‡	131/7027				
Related to 9 vaccine HPV types‡	168/7027				
Average risk reduction§					
<b>Per-protocol efficacy population</b>					
High-grade cervical, vulvar, and vaginal disease†					
Related to HPV-31, 33, 45, 52, or 58	1/6				
Related to HPV-6, 11, 16, or 18	1/5				
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
Related to HPV-31, 33, 45, 52, or 58	1/5				
Related to HPV-6, 11, 16, or 18	1/5				
Persistent infection ≥6 months' duration¶					
Related to HPV-31, 33, 45, 52, or 58	35/5812	3.6	80/5830	5.0	26.4 (-4.3 to 47.5)
Related to HPV-6, 11, 16, or 18	59/5812				

**Table 3. Geometric Mean Titer (GMT) and Seroconversion for HPV Types 6, 11, 16, and 18 in Noninferiority Analyses at Month 7 in the Per-Protocol Immunogenicity Population.\***

Anti-HPV Type	9vHPV Vaccine (N=6792)		qHPV Vaccine (N=6795)		GMT Ratio (95% CI)
	Participants	GMT	Participants	GMT	
HPV-6 cLIA ≥24 mMU/ml	4539	4532 (99.8)	4541	4528 (99.7)	1.02 (0.99 to 1.06)
HPV-11 cLIA ≥24 mMU/ml					0.80 (0.77 to 0.83)
HPV-16 cLIA ≥24 mMU/ml					0.99 (0.96 to 1.03)
HPV-18 cLIA ≥24 mMU/ml	4539	4532 (99.8)	4541	4528 (99.7)	1.19 (1.14 to 1.23)
					<b>Difference (95% CI)</b>
					percentage points
					0 (-0.3 to 0.2)
					0 (-0.1 to 0.2)
					0 (-0.1 to 0.2)
					0.1 (-0.1 to 0.4)

According to the geometric mean titer, the **noninferiority** of the response to the 9vHPV vaccine as compared with the response to the qHPV vaccine for HPV-6, 11, 16, and 18 was established at 1 month after dose 3

**Benefit outcome**



Yes



Can't tell



No

# Were all clinically important outcomes considered ?

是否所有重要的臨床結果都被考量到？

**Table 2. Effect of 9vHPV Vaccine on the Incidence of Cervical, Vulvar, and Vaginal Disease and of Persistent HPV-Related Infection.\***

End Point	9vHPV Vaccine (N = 7099)		qHPV Vaccine (N = 7105)		Risk Reduction (95% CI)
	no./total no.	cases/1000 person-yr	no./total no.	cases/1000 person-yr	
<b>Per-protocol efficacy population</b>					
High-grade cervical, vulvar, and vaginal disease†					
Related to HPV-31, 33, 45, 52, or 58	1/6016	0.1	30/6,017	1.6	96.7 (80.9 to 99.8)
Related to HPV-6, 11, 16, or 18	1/5883	0.1	3/5898	0.2	66.6 (-203.0 to 98.7)



Yes



Can't tell



No

# Are the benefits worth the harms and costs?

利弊得失是否值得？

**Table 4. Adverse Events.\***

Event	9vHPV Vaccine (N = 7071)	qHPV Vaccine (N = 7078)
	no. of participants (%)	
Participants with one or more adverse events†	6640 (93.9)	6419 (90.7)
Injection-site event‡	6414 (90.7)	6012 (84.9)
Pain§	6356 (89.9)	5910 (83.5)
Mild	3754 (53.1)	4043 (57.1)
Moderate	2300 (32.5)	1682 (23.8)
Severe	302 (4.3)	185 (2.6)
Swelling	2830 (40.0)	2035 (28.8)
Mild: 0 to ≤2.5 cm	1958 (27.7)	1594 (22.5)
Moderate: >2.5 cm to ≤5.0 cm	597 (8.4)	332 (4.7)
Severe: >5.0 cm	272 (3.8)	109 (1.5)
Unknown	3 (0)	0 (0)
Erythema	2407 (34.0)	1810 (25.6)
Mild: 0 to ≤2.5 cm	1921 (27.2)	1555 (22.0)
Moderate: >2.5 cm to ≤5.0 cm	370 (5.2)	197 (2.8)
Severe: >5 cm	114 (1.6)	57 (0.8)
Unknown	2 (0)	1 (0)
Pruritus¶	388 (5.5)	282 (4.0)
Mild	301 (4.3)	223 (3.2)
Moderate	80 (1.1)	56 (0.8)
Severe	7 (0.1)	3 (0)
Systemic event¶¶	3948 (55.8)	3883 (54.9)
Any vaccine-related systemic event	2086 (29.5)	1929 (27.3)
Headache	1031 (14.6)	969 (13.7)
Pyrexia	357 (5.0)	301 (4.3)
Nausea	311 (4.4)	261 (3.7)
Dizziness	211 (3.0)	197 (2.8)
Fatigue	166 (2.3)	150 (2.1)
Serious event	233 (3.3)	183 (2.6)
Vaccine-related event	2 (0)	2 (0)
Death	5 (0.1)	5 (0.1)
Discontinuation due to adverse event**	8 (0.1)	4 (0.1)
Vaccine-related event	5 (0.1)	3 (0)
Serious event	3 (0)	1 (0)
Serious vaccine-related event	1 (0)	0 (0)

Adverse events related to **injection site** were **more common** in the **9vHPV** group than in the qHPV group.

The frequency of **systemic adverse events** was generally **similar** in the two groups



Yes



Can't tell



No

# Are the benefits worth the harms and costs?

利弊得失是否值得？

藥品	Cervarix 保蓓	Gardasil 4 嘉喜	Gardasil 9 嘉喜
價數	兩價	四價	九價
病毒	16、18	6、11、16、18	6、11、16、18、31、33、45、52、58
接種次數/價格	三劑 (0、1、6個月)，3,000元/劑，共9,000元	三劑 (0、2、6個月)，3,500元/劑，共10,500元	三劑 (0、2、6個月)，5,000元/劑，共15,000元





# Are the benefits worth the harms and costs?

利弊得失是否值得？

## Calculation

To calculate the NNT, you need to know the Absolute Risk Reduction (ARR); the

$$\text{NNT} = 1/\text{ARR}$$

Where  $\text{ARR} = \text{CER (Control Event Rate)} - \text{EER (Experimental Event Rate)}$ .

NNTs are always rounded up to the nearest whole number.

For a more detailed look at the NNT measure, and an interactive nomogram for  
NNTs, see Zapletal E, LeMaitre D, Menard J and Degoulet P, The Number Needed  
its proper context, BMJ 1996;312:426-9.

根據RCT結果,我們換算CIN  
incidence的NNT

NNT : 6 ( 3- 24 )

表示約每6人使用,即有一個人會明顯  
增加CIN預防率.

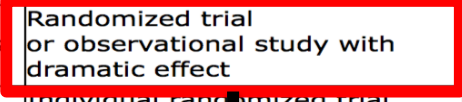
費用 = NNT x 疫苗費用 x time

=> 6 x 5000 x 3 = 約9萬



# 評定證據等級-OCEBM Level of Evidence, 2011

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<b>How common is the problem?</b>	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
<b>Is this diagnostic or monitoring test accurate?</b> (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
<b>What will happen if we do not add a therapy?</b> (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
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -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
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -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	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided	Case-series, case-control, or historically controlled	Mechanism-based reasoning
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study			
<b>Is this (early detection) test worthwhile?</b> (Screening)	Systematic review of randomized trials	Randomized trial		case-control, or historically controlled	Mechanism-based reasoning



【介入型問題】  
RCT之隨機分配臨床試驗  
證據等級為 **Level 2**  
※經嚴格評讀，無其他需要考慮降階理由

考慮降階之理由

- 研究品質差
- 絕對效果小
- PICO和臨床情境不相符
- 證據間沒有一致性
- 研究不精確(95%CI過大)

# 評定證據等級 GRADEpro online

● 不嚴重

● 嚴重

● 很嚴重

臨床問題: 輪狀病毒疫苗的效果如何?

輪狀病毒預防的效果		『主要』結果	『次要』結果
		子宮頸癌發生率	副作用率
		RiskReduction:17.1(95%CI) [-4.2,34.0]	RR:1.02(95%CI) [0.97,1.05]
研究設計		RCT	RCT
降階	1. 存在誤差風險	●	●
	2. 結果不一致	●	●
	3. 證據不具直接性	●	●
	4. 結果不精準	●	●
	5. 存在發表誤差	●	●
升階	1. 效果顯著		
	2. 降低干擾因素		
	3. 具劑量-反應效果		
<b>證據等級</b>		⊕⊕⊕⊕ HIGH	⊕⊕⊕⊕ HIGH

Reference:



# 臨床回覆

李先生您好，依據我們團隊嚴格的實證醫學文獻搜尋的結果。

目前有大型臨床試驗研究顯示，使用9價子宮頸疫苗與4價疫苗相比，於常規保護力上無明顯差異，但對特定族群可提供額外顯著效益，副作用亦無差異；費用需自費約15000\$。

然而影響子宮頸癌並非單一因素，除預防接種外，仍需要定時接受抹片檢查。

就目前最佳證據，如果沒有經濟上的問題，9價疫苗接種是值得推薦的。

A blue stethoscope is positioned diagonally across the frame, resting on a folded blue cloth. Below the cloth is a white medical form with various fields and text. The background is a soft, out-of-focus blue.

Evidence-Based Medicine

實證是守護病患最好的工具

感謝您的指導與聆聽