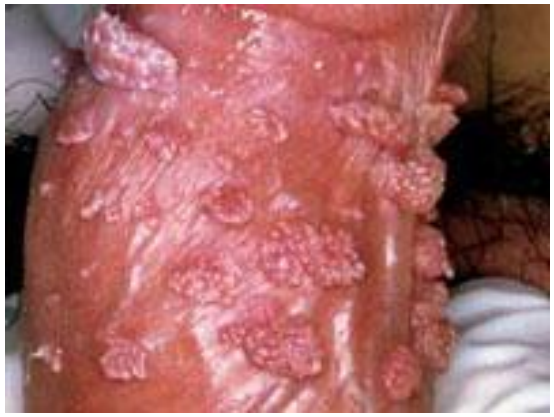
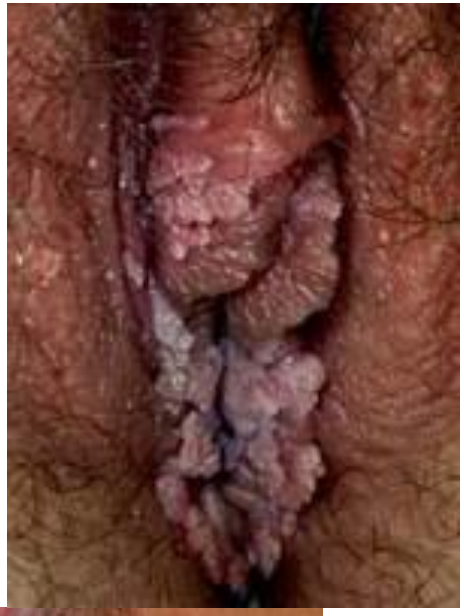
尖锐湿疣的治疗与预防进展

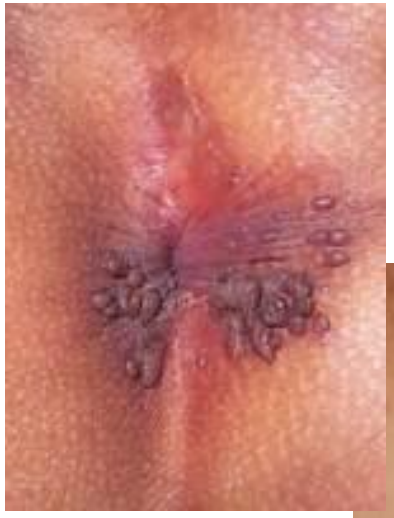
程浩

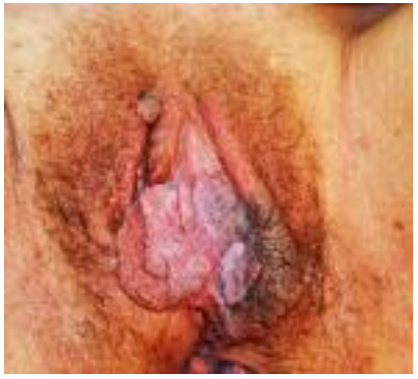
浙江大学医学院附属邵逸夫医院 皮肤科

典型尖锐湿疣









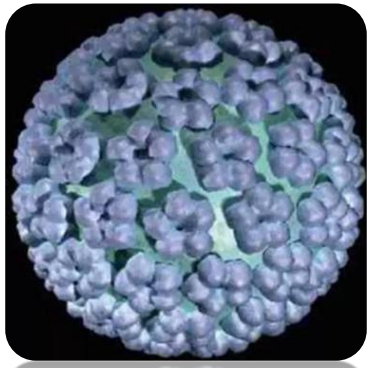
尖锐湿疣概述

- 人乳头瘤病毒HPV感染引起疣状病变[1]
- HPV：200多亚型，约170余型感染人类[2]

  40种亚型—粘膜型：与生殖器部位感染有关[3]

  尖锐湿疣**90%上由HPV6或11型**引起

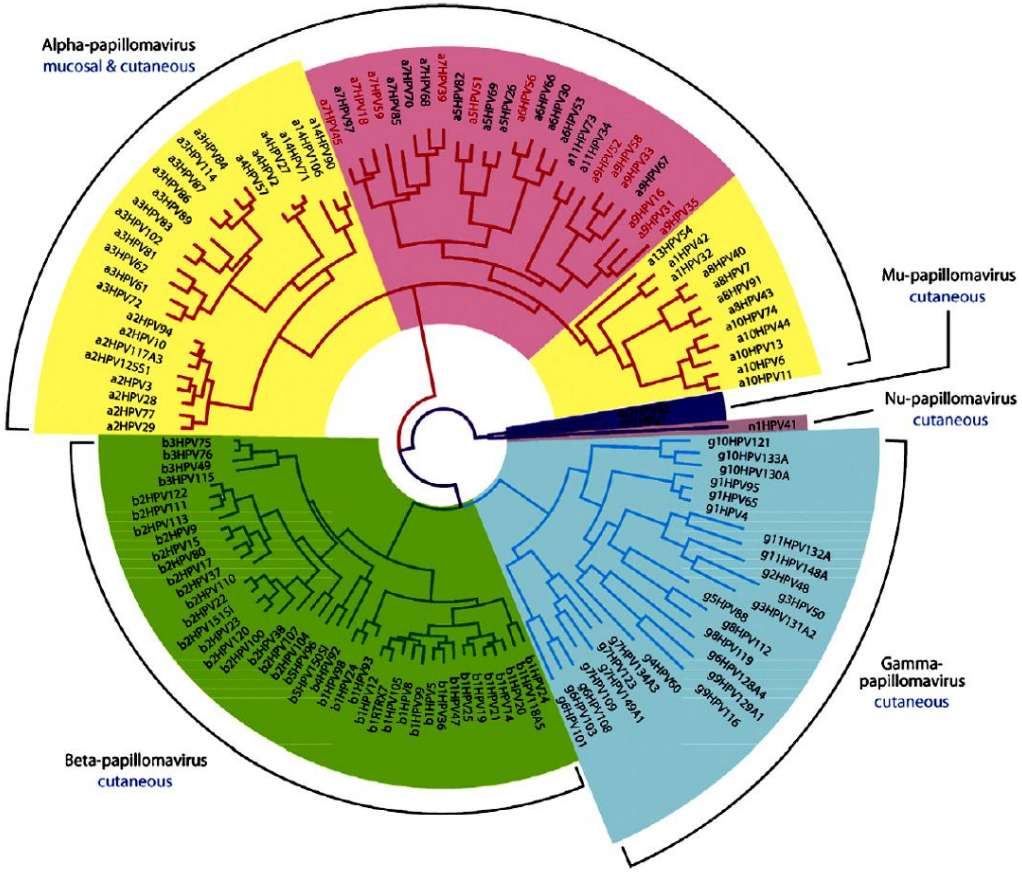
致癌风险	HPV分型	主要相关疾病[4]
高风险	16,18	宫颈鳞状细胞癌；宫颈腺癌；口咽癌
	31, 33, 35, 39, 45, 51, 52, 56, 58, 59	宫颈鳞状细胞癌；少数口咽癌
低风险	**6, 11**	**尖锐湿疣**；呼吸道乳头瘤病
	13,32	口腔局部上皮增生



人乳头瘤病毒

1.中华医学会皮肤性病学分会性病学组. 中华皮肤科杂志.2014; 47(8) : 598-599.
2.De Villiers EM. Virology,2013, 445(1-2) : 2 -10.
3.Workowski KA, et al. MMWR Recomm Rep. 2015,64(03):1-137.
4. Ghittoni R, Accardi R, Chiocca S, et al. Ecancermedicalscience. 2015 Apr 29;9:526.

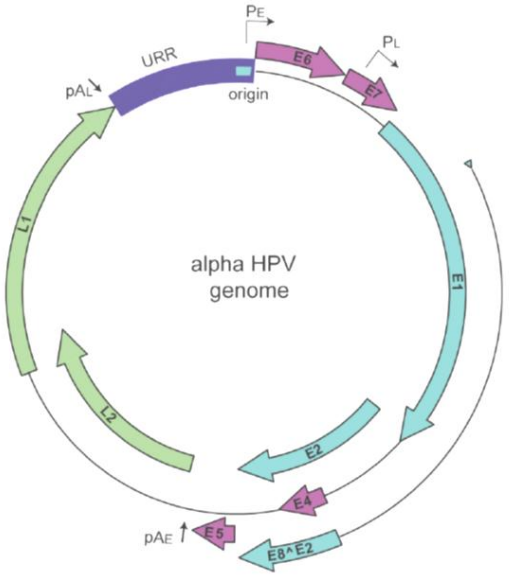
HPV病毒生物学



HPV-双链DNA病毒

*早期蛋白E6和E7：致癌蛋白

*结构蛋白L1，L2



HPV流行病学：

- 全球，HPV 感染是最常见 STD； HPV感染估计12%
- HPV高感染地区：非洲、东欧、拉美
- 全球女性的HPV 感染率为6.1% ~ 33.5%
- 不发达国家感染率高：缺乏宫颈脱落细胞学筛查

  HPV筛查可以降低宫颈癌的发病和死亡率
- **尖锐湿疣感染人群：全世界 3千万**
- 高危型HPV感染率 ：

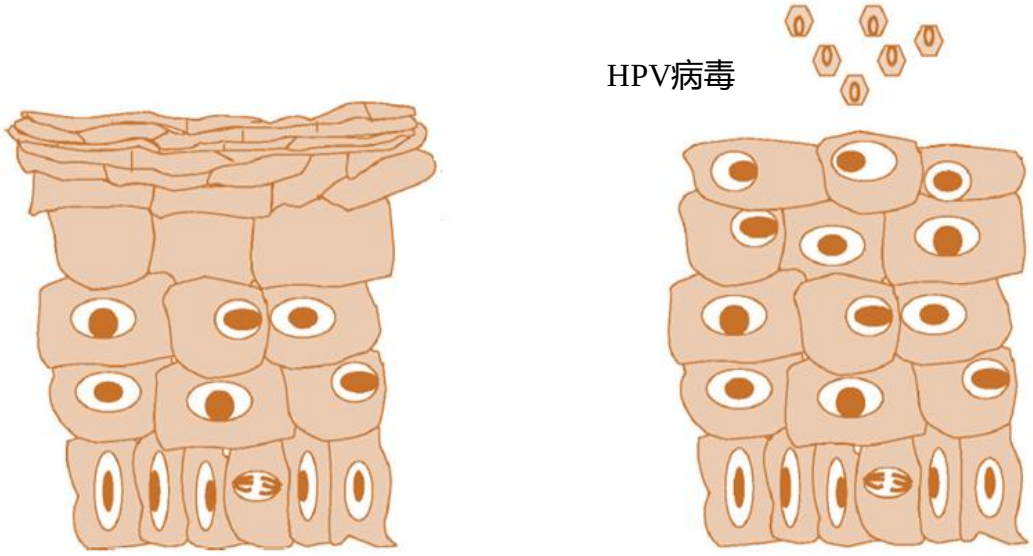
  正常宫颈细胞学的人群感染率也各不相同

  发达中国家--宫颈癌是妇女肿瘤第一位

  全球--妇女肿瘤最常见的第二位

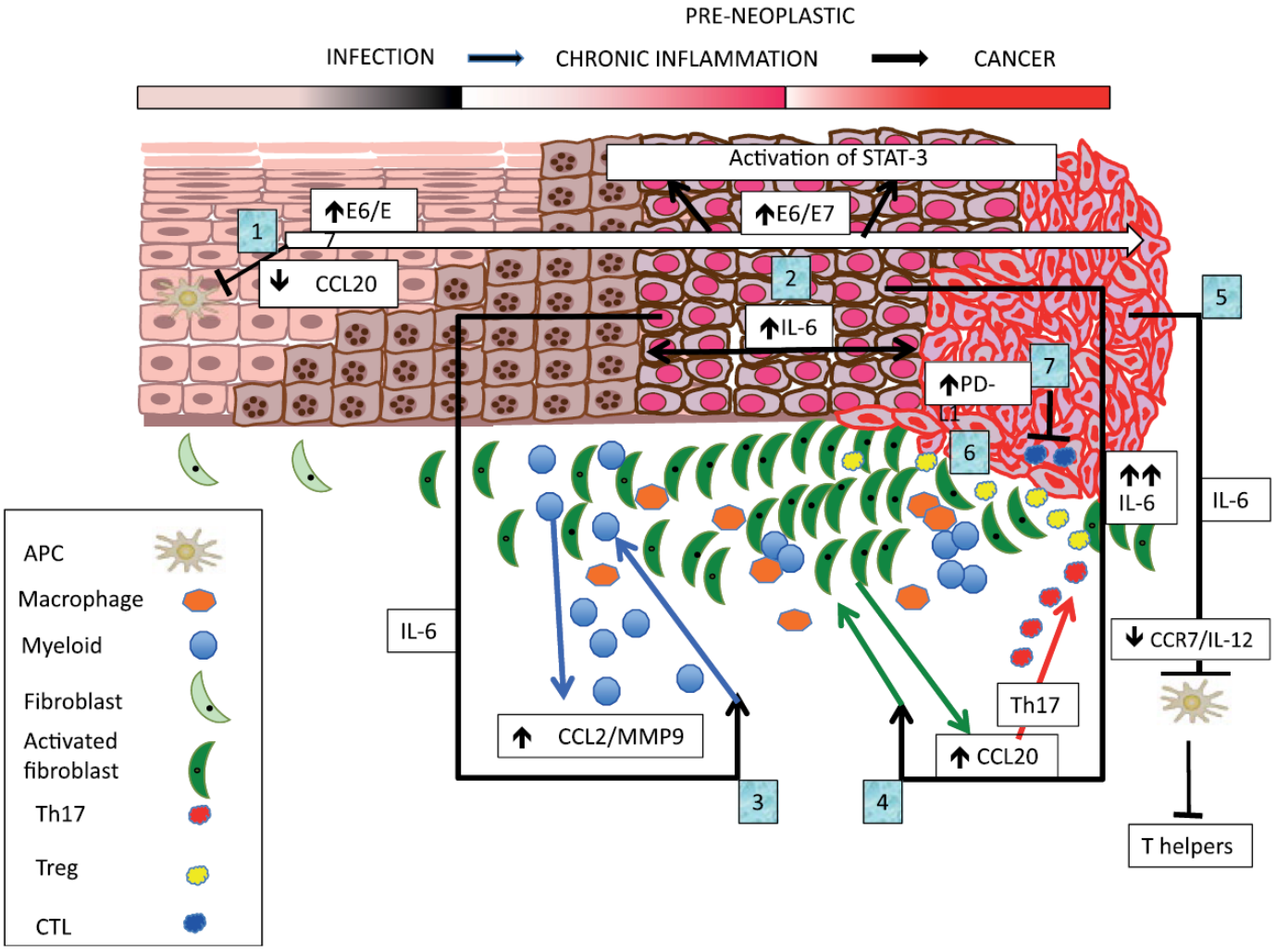
尖锐湿疣发病机制

- HPV是一种微小、无包膜DNA病毒，外生殖器皮肤/粘膜或口腔粘膜微破坏，感染基底层上皮细胞
- 进入宿主的HPV病毒逃避**“免疫监视”**
- HPV病毒引起皮肤和黏膜上皮增殖，形成增生性病灶



1.Bhatia N, et al. J Cutan Med Surg. 2013 Dec;17 Suppl 2:S47-54.
2.Longworth MS, et al. Microbiol Mol Biol Rev. 2004 Jun;68(2):36.

HPV感染致癌机制-免疫逃逸



HPV 感染的自然史

- 女性宫颈HPV清除的中位时间：9.4个月
- 男性生殖器HPV清除的中位时间：7.5个月（致癌和非致癌亚型）
- 异性伴侣间HPV传播率：

  3项研究：女性到男性的HPV传播率高于男性到女性的传播

  一项研究：男性与女性间以及女性与男性之间的HPV传播率相似
- HPV 6或11感染后发展为疣的中位时间：6-10个月（最长18个月）

  比先前报告6型或11型HPV女性的中位时间长2.9个月
- 患HIV/ AIDS的女性和HIV阴性女性的疣消退即使不治疗也很常见：

  诊断后第一年60％HIV / AIDS妇女和80％HIV阴性妇女的疣可以消退

尖锐湿疣的诊断

Table 1 Checklist for initial consultation

Checklist
• Duration of genital warts
• History of genital warts
• Location of other warts: anal and/or oral
• Previous treatment(s) and clinical result(s)
• Patient with steady partner or with several partners
• Smoking status
• Immune suppression status and comorbidities
• Diabetes
• Allergy to anaesthetics
• History of other sexually transmitted infections

O'Mahony et al. Position statement for the diagnosis and management of anogenital warts.JEADV 2019, 33, 1006–1019

尖锐湿疣患者最常问的问题

Table 2 Frequently asked questions and answers to guide discussion with patients

Questions	Answers
How did I get AGW?	AGW are caused by HPV.[1] Usually, HPV is contracted via sexual interactions: indirect acquisition is rare[5]
What is the risk of HPV transmission?	The risk of HPV transmission is very high (1.6 sexual interactions are enough to get the infection). The infection is very common and the vast majority of people have the virus during their lifetime
Is there a treatment?	Discuss the modalities and the limitations of treatment, explaining this will not eradicate the virus
Does smoking increase my risk of developing AGW?	Explain that smokers are at an increased risk of developing AGW and therefore, smoking cessation should be encouraged[15]
How long will I have AGW for?	AGW can recur several times but with appropriate treatment, most warts should clear within 3 months[5]
Is this the end of my sex life?	Reassure the patient that this is not the case
Should I disclose to my current and previous partner?	It is important to disclose you have AGW to your current partner in order to allow him/her to be checked
Should I always use a condom?	Explain that data have shown that increased levels of condom use is associated with increased clearance of HPV.[88] It is therefore advisable to use condoms routinely
What are the risks during pregnancy?	AGW can become large during pregnancy[5] but will usually disappear within weeks of delivery. In rare cases, HPV can be transmitted during child birth resulting in recurrent respiratory papillomatosis in the infant[73,78]
Will I develop cancer?	AGW are not related to cancer. AGW are caused by certain types of HPV, other types of HPV can cause cancer[5]
Can AGW spread to other parts of the body?	It is very uncommon for AGW to spread to other body locations

AGW, anogenital warts; HPV, human papillomavirus.

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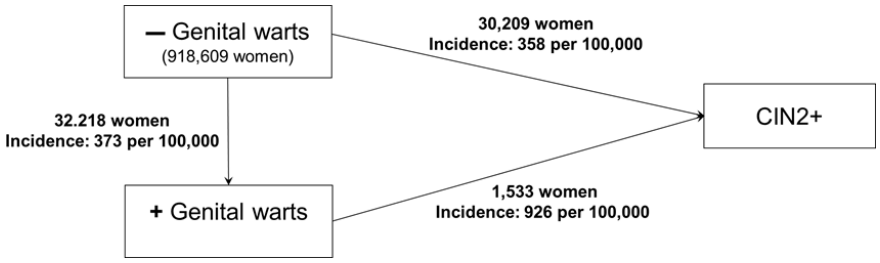
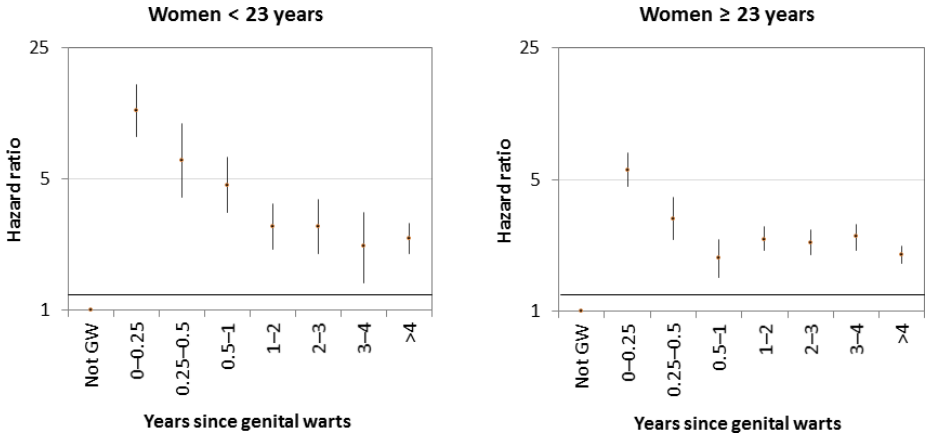
尖锐湿疣与宫颈HPV感染：
是否需要做宫颈HPV检测或细胞学检查？

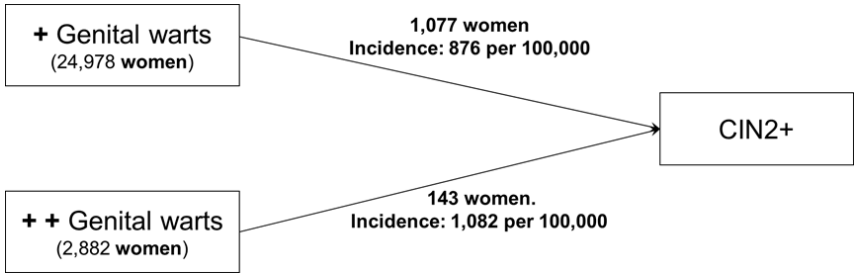
诊断尖锐湿疣后CIN2+的风险：

a nationwide cohort study



CIN 2 or CIN2+的发病率与尖锐湿疣的关系





CIN 2 orCIN2+发病与一过性或治疗抵抗的尖锐湿疣

CIN 2 orCIN2+的相对危险与尖锐湿疣发病时间

Blomberg M, et al. Sex Transm Infect 2019;0:1-5.

尖锐湿疣与宫颈HPV感染：
需要做宫颈HPV检测或细胞学检查吗？

尖锐湿疣是宫颈CIN2级或CIN2+的长期风险标志

▸▸这种风险在诊断尖锐湿疣后的一年内特别高：

小于23岁女性、尖锐湿疣难以治愈

▸▸一旦诊断生殖器疣，

就有足够理由及时进行宫颈筛查，TCT、HPV

尖锐湿疣治疗指南推荐：

治疗方式	美国CDC 2015[1]	中 国 2015[2]	加拿大 2014[3]	欧 洲 2012[4]	WHO 2003[5]
患者自用	• **咪喹莫特** • 鬼臼毒素 • 茶多酚	• **咪喹莫特** • 鬼臼毒素	• **咪喹莫特** • 鬼臼毒素/鬼臼树脂 • 茶多酚	• **咪喹莫特** • 鬼臼毒素 • 茶多酚	• **咪喹莫特** • 鬼臼毒素
医院治疗	• 液氮冷冻/冷冻 • 外科（剪除/切除/刮除/激光/电外科） • TCA/BCA	• CO2 激光 高频电治疗 液氮冷冻 光动力治疗 微波 • TCA/BCA • 外科手术切除	• 鬼臼树脂 • TCA • 冷冻 • 外科（CO2激光汽化疗法/ • 电外科/手术切除）	• 冷冻 • TCA • 电外科/切除/刮除/激光	• 鬼臼树脂 • TCA • 冷冻 • 电外科 • 外科手术

TCA：三氯乙酸；BCA：二氯乙酸

1.Workowski KA, et al. MMWR Recomm Rep. 2015,64(03)：1-137.
2.中华医学会皮肤性病学分会性病学组,中国医师协会皮肤科分会性病亚专业委员会.中国艾滋病性病,2015,21(2):172-174.
3. Canadian guidelines on sexually transmitted infections.Human Papillomavirus (HPV) Infections Chapter (2014).
4. Lacey CJ,et al. J Eur Acad Dermatol Venereol. 2013 Mar;27(3):e263-70.
5. World Health Organization.Switzerland:Geneva, 2003,51-53.

中国指南：重视治疗方法的选择

2014中国尖锐湿疣诊疗指南方案推荐

医院外治疗	• 鬼臼毒素酊、**5%咪喹莫特**
医院内治疗	• CO_2 激光或高频电治疗、液氮冷冻、微波、光动力、30%～50%三氯醋酸

- 单个疣体直径<0.5 cm 、疣体团块直径<1cm 、疣体数目<15 个：
  - 1cm的疣体已经很大， 15个以内的疣体已经很多，**外用药物治疗不如物理治疗及时**
  - 及早清除疣体**原则**，对减少复发尤为重要
- 疣体大小和数量均超过上述标准者：
  - 建议用物理方法治疗或联合氨基酮戊酸光动力疗法治疗

中华医学会皮肤性病学分会性病学组. 中华皮肤科杂志 2014; 47(8) : 598-599

尖锐湿疣的治疗选择

Table 3 Treatment options for AGW

Treatment	Mode of action	Schedule	Clearance rate (%)	Recurrence rate (%)	Advantages	Disadvantages	Refs
Ablative techniques							
Cryotherapy	Liquid nitrogen freezes and destroys lesions	Applied directly to lesions; repeat for two or three cycles	46–96	18–39	• Rapid results in some patients • Minimal training	• High recurrence rate • Repeat physician visits • Pain, necrosis, hypopigmentation	20,45–49
CO_2 and Nd: YAG laser	Laser vaporizes lesions	Under local anaesthesia, protocol depends on type of laser	23–95	2.5–77	• Rapid results • Effective for thick lesions	• High recurrence rate; in some cases even before healing of laser treatment • Repeat physician visits • Costly • Substantial training • Expertise required • Pain/scarring • Smoke evacuator needed	20,48,50
Electrocautery	High-frequency electrical currents cause thermal damage to infected tissue	Under local anaesthesia, base of lesion excised; repeat as required	35–94	20–25	• Rapid results	• High recurrence rate • Repeat physician visits • Expertise required • Smoke evacuator needed	18,20,49,51
Surgery	Scissor or scalpel excision	Under local or general anaesthesia; base of lesion excised	89–93	18–65	• Rapid results • Useful for large lesions	• High recurrence rate • Pain/scarring • Expertise required	52–54
Trichloroacetic acid (33–50%)	Acid induces a chemical burn	One to three times per week; repeat as necessary	70–100	18–36	• Rapid results • Suitable for a few small lesions	• High recurrence rate • Repeat physician visits • Intense burning sensation	20,45,47,55
Immunotherapies							
Imiquimod 5%	Immunomodulator: stimulates interferon and cytokine production	Three nights per week for up to 16 weeks or longer	35–75	6	• Efficacy • Simple regimen • Easy self-application • Preferred by patients • Lower recurrence rates than ablative techniques • Inflammatory reactions extending beyond treatment area can show the infected area	• Inflammatory reactions extending beyond treatment area • Response may be slow • Lower clearance rates than ablative techniques • Rare vitiligo-like depigmentation	20–26,41,56–62
Imiquimod 3.75%	Immunomodulator: stimulates interferon and cytokine production	Once daily before bedtime for up to 8 weeks	19–37	15–19	• Efficacy • Short treatment duration • Simple regimen • Easy self-application • Inflammatory reactions extending beyond treatment area can show the infected area	• Inflammatory reactions extending beyond treatment area • Response may be slow	20,27–29

O'Mahony et al. Position statement for the diagnosis and management of anogenital warts.JEADV 2019, 33, 1006–1019

尖锐湿疣的治疗选择

Table 3 *Continued*

Treatment	Mode of action	Schedule	Clearance rate (%)	Recurrence rate (%)	Advantages	Disadvantages	Refs
Sinecatechins 10% and 15%	Inflammatory response modulator	Three times daily for up to 16 weeks	40–81%	7–12	• Efficacy • Self-application • Lower recurrence rates than ablative techniques	• Intense application site reactions • Lower clearance rates than ablative techniques • Repeat 3 times daily administration may affect adherence • Need for sanitary pads	20,30–34
Other topical therapy							
Podophyllotoxin 0.5% (alcoholic solution) 0.15% (cream)	Antimitotic agent induces tissue necrosis	Twice-daily to affected areas for 3 consecutive days per week; discontinue for 4 days; repeat for up to 4 weeks	45–94	11–100	• Efficacy • Easy self-application	• High recurrence rate • Complicated regimen • Intense application site reactions	20,31,35–40, 42–44,63
Nitric–zinc complex topical solution	Induces a caustic effect on the wart through mummification and protein denaturation/ coagulation action	Once or up to four times; repeat at 2-week intervals if needed	90–99	Not evaluated	• Efficacy • Easy application	• Current evidence in AGW available from a limited number of patients only • Investigation of recurrence rate is required	64

AGW, anogenital warts.

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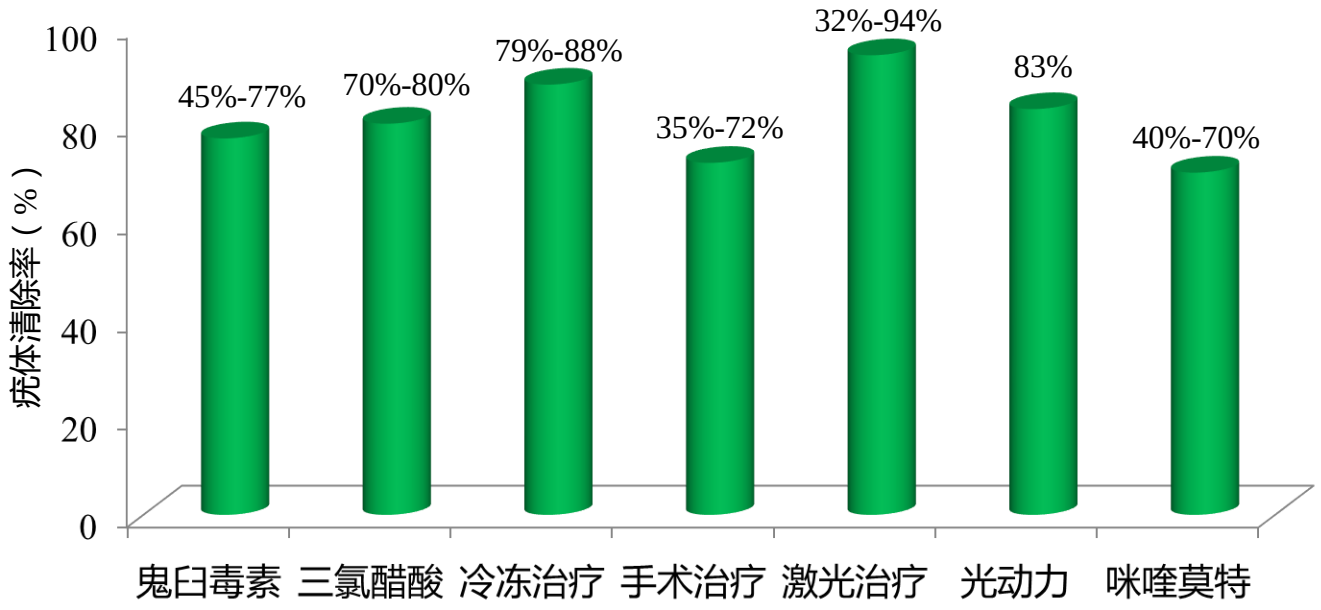
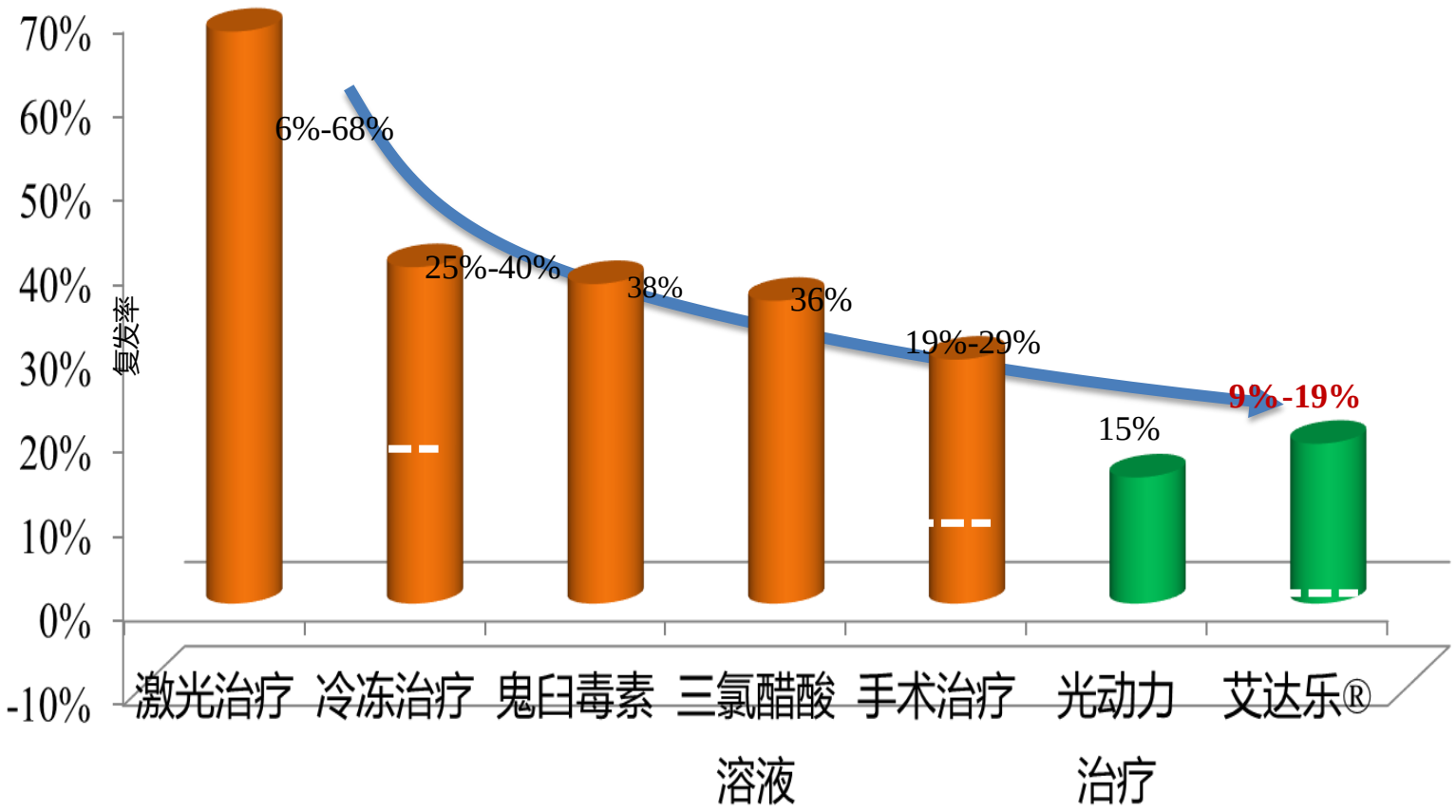
尖锐湿疣治疗难题-高复发率

- 常见治疗方案**疣体清除率差异不明显**



徐金华.中华皮肤科杂志,2015; 48(5) : 297-300

常用尖锐湿疣治疗手段复发率比较



徐金华.中华皮肤科杂志,2015; 48(5) : 297-300.

- 多数尖锐湿疣患者皮损去除后会再发
- 少数患者复发可持续数月乃至数年

复发的危害：

造成的心理影响比CA本身产生更大危害

复发者感染高危型HPV的概率较大

--致癌风险

生殖道HPV感染疾病的预防

全球共识：

1，健康宣教，安全套，健康的生活观念

2，筛查，性伴检查与

3，HPV疫苗

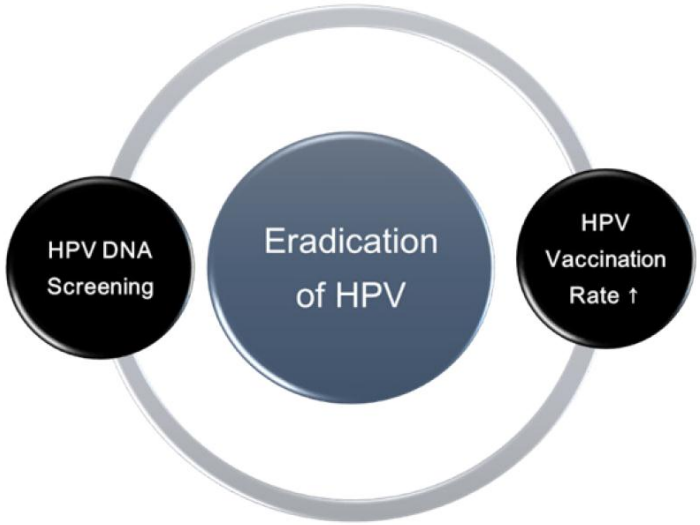


Fig. 1. Two different strategies against human papillomavirus (HPV) in the era of HPV vaccination.

宫颈癌筛查相关指南（2016）

- 应在21岁开始(A级证据)
- 年轻女性如出现HPV感染，几乎所有人1-2年内清除病毒
- 21～29岁女性不必联合检查，单独细胞学检查，每3年筛查一次，不必每年行宫颈癌筛查
- 2015年ASCCP和SGO发布临时指南：
  HPV检测作为25岁以上女性宫颈癌初筛可替代细胞学检查 (B级证据)
- 30～65岁女性每5年行细胞学和HPV联合检查，每3年单行细胞学检查也可行，不必每年筛查(A级证据)。
- 既往筛查结果阴性且无CIN2或更高级别病变，65岁后可停止各种筛查 (A级证据)
- 有CIN2、CIN3和宫颈原位腺癌病史女性，超过65岁，应治疗后持续筛查20年(B级证据)。

HPV疫苗：

- 被称为抗癌史上一次重大突破
- 多数发达国家开始推行女孩接种HPV疫苗项目
- 10余年数据：
  HPV疫苗结合宫颈癌筛查显著降低宫颈癌发病率
- 2014年WHO发布指南：
  9-13岁女孩需注射两剂HPV疫苗，预防HPV病毒感染

Zur Hausen

Ian Frazer

周健

HPV疫苗上市史

- **2006年，四价疫苗佳达修（Gardasil，MSD）FDA批准上市**

  预防6、11、16、18四种HPV病毒亚型所致疾病

  预防宫颈癌发生有效率可达70%

- **2007年，二价疫苗“卉妍康”（Cervarix，GSK）欧盟上市**

  （我国称希瑞适）

  主要针对HPV-16、18型病毒

- **2014年，佳达修9价（Gardasil-9，MSD）**

  四价基础上新增31、33、45、52 和58五种亚型病毒

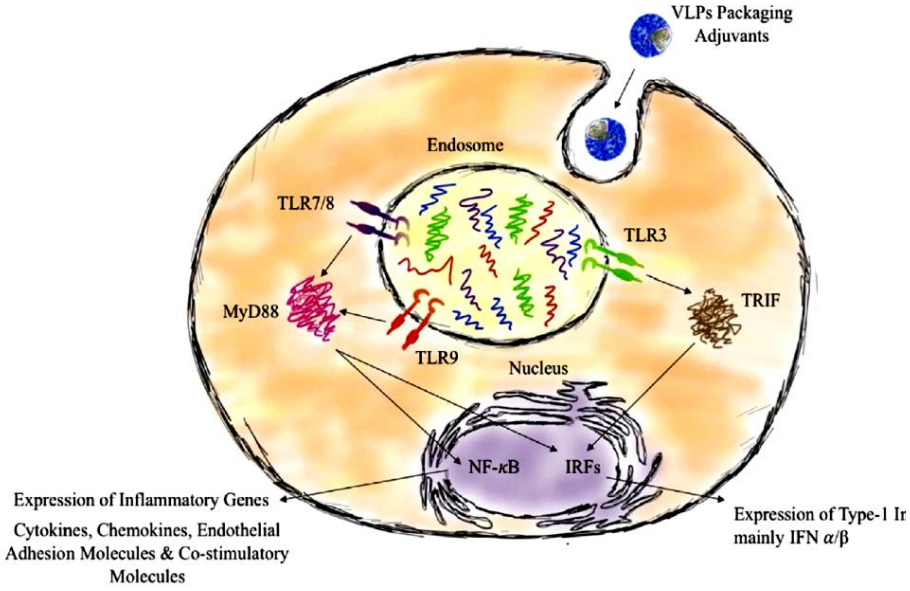
  对宫颈癌的预防率达90%

Table 1 Vaccine compositions of Cervarix, Gardasil-4 and Gardasil-9 (Harper and Demars 2017)

Type (ml)	Manufacturer	Vaccine antigen for preventing cervical cancer (μg)	Vaccine antigen for preventing genital warts (μg)	Cross protection ability suggested[a]	Expression system used for antigen production	Adjuvant (μg)
Cervarix (0.5 ml)	GSK	HPV16 (20) HPV18 (20)		HPV31 HPV33 HPV45	Insect cell *Trichoplusia ni*	3-*O*-desacyl-4′-monophosphryl lipid (MPL, 50) Aluminum hydroxide salt (500)
Gardasil-4 (0.5 ml)	MSD	HPV16 (40) HPV18 (20)	HPV6 (20) HPV11 (40)	HPV31 HPV33 HPV45	*S. cerevisiae*	Amorphous aluminum hydroxyphosphate sulfate (225)
Gardasil-9 (0.5 ml)	MSD	HPV16 (60) HPV18 (40) HPV31 (20) HPV33 (20) HPV45 (20) HPV52 (20) HPV58 (20)	HPV6 (30) HPV11 (40)	Not determined	*S. cerevisiae*	Amorphous aluminum hydroxyphosphate sulfate (500)

[a] Malagon et al. (2012): cervarix may have more efficacious cross protection against HPV31, 33 and 45 than Gardasil-4

病毒样颗粒VLP为基础的预防性疫苗作用机制



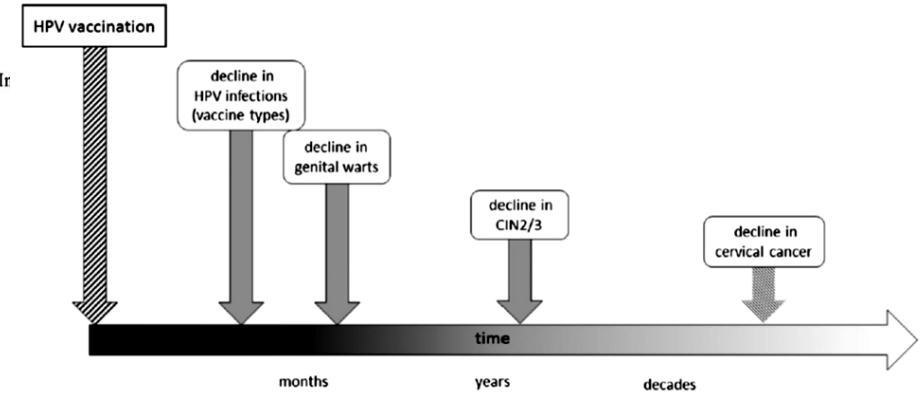
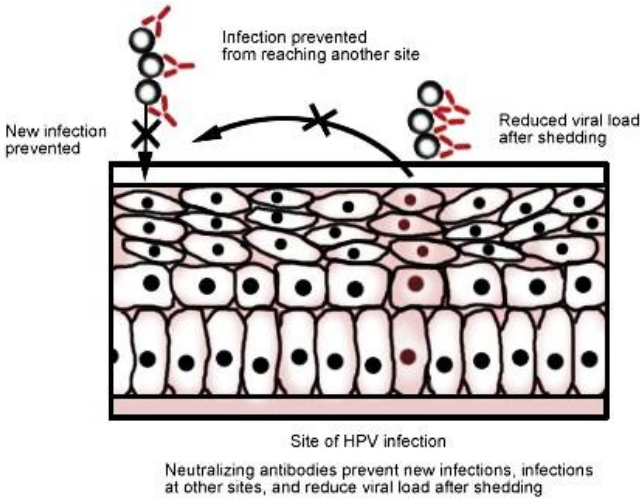
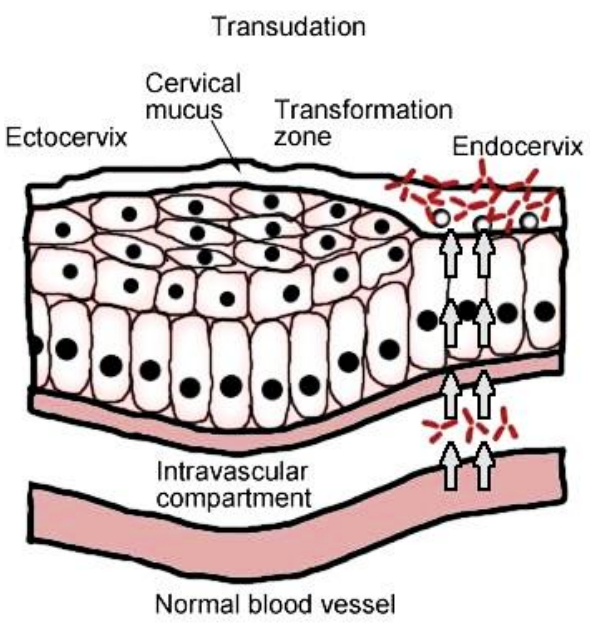
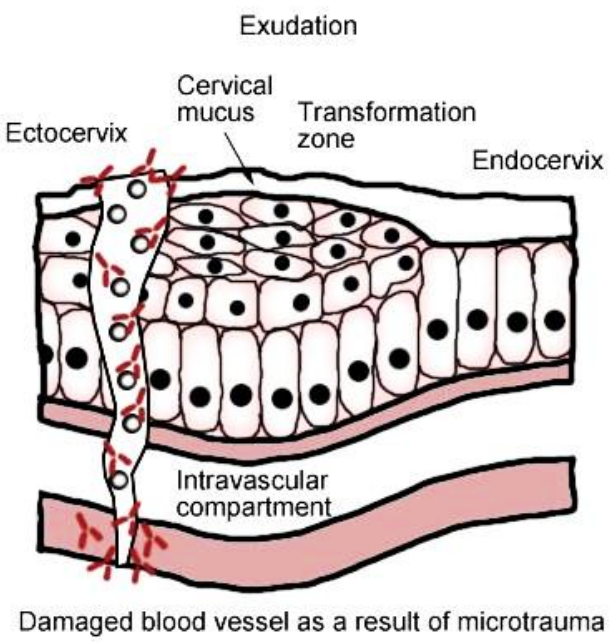


Fig. 1. Timeline of expected population-based vaccine impact on different endpoints.

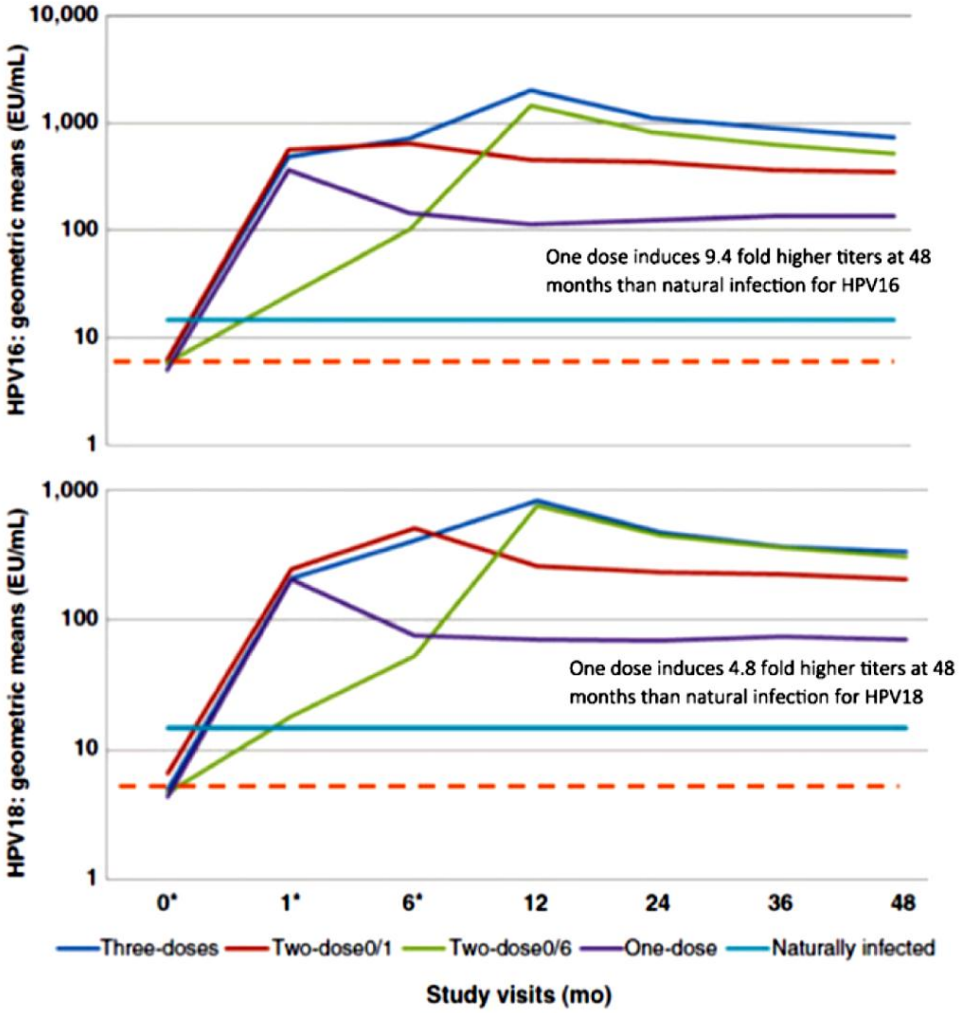
预防性HPV疫苗产生中和抗体保护感染







预防性HPV疫苗的免疫学反应



HPV疫苗对宫颈癌前病变的预防作用

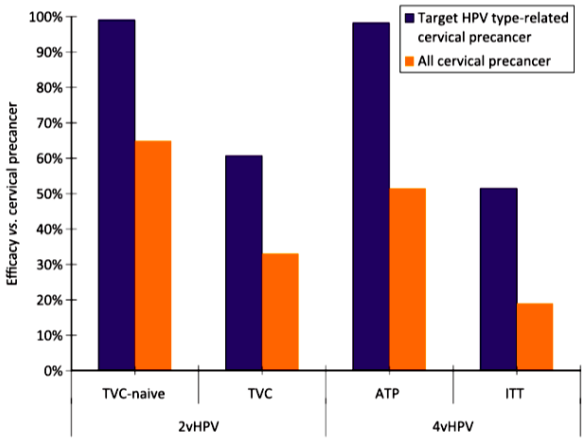


Fig. 1. A comparison of vaccine efficacy against targeted HPV type-related (purple bars) and all cervical precancer (CIN2, CIN3, or AIS) (orange bars) by 2vHPV [29] and 4vHPV [28], for the HPV-naive populations (TVC-naive and ATP, respectively) and the entire vaccinated cohort (TVC and ITT, respectively). TVC, total vaccine cohort; ATP, attention to protocol; ITT, intention to treat.

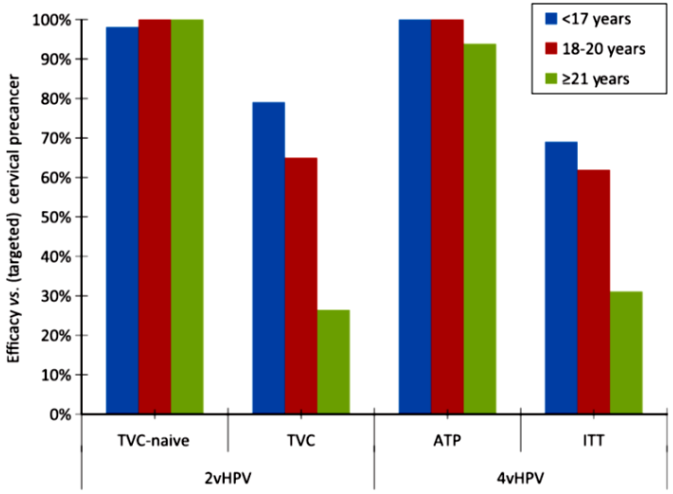


Fig. 2. A comparison of efficacy against targeted HPV type-related cervical precancer (CIN2, CIN3, or AIS) by 2vHPV [30] and 4vHPV [27] for the HPV-naive populations (TVC-naive and ATP, respectively) and the entire vaccinated cohort (TVC and ITT, respectively), stratified by age group [<17 years (blue bars), 18–20 years (red bars), and ⩾21 years (green bars)]. TVC, total vaccine cohort; ATP, attention to protocol; ITT, intention to treat.

HPV疫苗对宫颈HPV感染和相关病变的预防作用

Table 2
Summary table of vaccine efficacies against cervical HPV infection and disease endpoints [34–50].

	Gardasil	Gardasil9	Cervarix
Among women 15/16–26 years			
4–6 months HPV 16/18 infection	96% (83, 100)	na	94% (92, 96)
6 month HPV 31/33/45/52/58 infection	18% (5, 29)	96% (94, 98)	na
6 month HPV 31 infection	46% (15, 66)	96% (91, 98)	77% (69, 83)
6 month HPV 33 infection	NS	99% (95, 100)	45% (25, 60)
6 month HPV 45 infection	NS	97% (92, 99)	74% (58, 84)
6 month HPV 51 infection	na	na	17% (4, 28)
6 month HPV 52 infection	NS	97% (95, 99)	na
6 month HPV 58 infection	NS	95% (91, 97)	na
CIN 2+ related to HPV 16/18	98% (94, 100)	na	98% (88, 100)
CIN 2+ related to HPV 31	70% (32, 88)	100% (40, 100)	88% (68, 96)
CIN 2+ related to HPV 33	NS	100% (33, 100)	68% (40, 84)
CIN 2+ related to HPV 39	NS	na	75% (22, 94)
CIN 2+ related to HPV 45	NS	NS	82% (17, 98)
CIN 2+ related to HPV 51	NS	na	54% (22, 74)
CIN 2+ related to HPV 52	NS	100% (67, 100)	na
CIN 2+ related to HPV 58	NS	NS	na
CIN 2+ caused by any HPV type	**22% (3, 38)**	**63% (35, 79)**	**62% (47, 73)**
CIN 3+ caused by any HPV type	**43% (24, 57)**	**na**	**93% (79, 99)**
AIS caused by any HPV type	na	na	100% (31, 100)
Among women older than 25 years			
6 month infection or disease related to HPV 16/18	85% (68, 94)	na	91% (79, 97)
6 month HPV 31 infection	na	na	66% (25, 86)
6 month HPV 45 infection	na	na	71% (34, 88)

Vaccine efficacies are presented with 95% confidence intervals.
NS means not significant; na means not applicable/available.
Bold signifies the clinically important outcomes.

HPV疫苗接种后对HPV流行病学的影响

英国

- 2008 始实施国家免疫接种计划，二价HPV疫苗
- **收集16- 24岁女性外阴阴道试纸剩余标本，15459 样**
- 2010/2011- 2016间HPV16/18感染率下降：
  16-18岁：8.2% to 1.6%
  19-21岁：14.0% to 1.6%
- HPV31/33/45也下降：
  16-18 岁：6.5% to 0.6%
  19-21 岁：8.6% to 2.6%
- 接种有效率：
  HPV16/18 为 82.0% (95% CI, 60.6%-91.8%)
  HPV31/33/45 为 48.7% (95% CI, 20.8%-66.8%).

J Infect Dis. 2018 Jun 18.

北欧地区

Decline of HPV infections in Scandinavian cervical screening populations after introduction of HPV vaccination programs.

- 开始qHPV 疫苗接种时间：
  Denmark 2008, Norway 2009, Sweden 2012
- **液基细胞学标本6538例，2006-2008**
  6332 相同入组妇女 2012-2013.
- 结果
  *总体HPV 阳性率下降轻微：2006-2008的36.5% 到 2012-2013的34.5%
  *HPV感染主要下降的妇女年龄 18-26岁:从 54.4% to 48.1% (P < 0.001)
  27-50 岁妇女, 改变不明显：22.5% and 21.6%
  *疫苗覆盖的 HPV 型下降明显：
  HPV6/11/16/18: 从 22.3% to 16.6%; P < 0.001
  两个低危型HPV6/11，从 5.0%下降到 2.5%
  高危型HPV16/18， 从18.9%下降到 14.9%
- **结论:**
  四价疫苗2008-2009开始在该地区接种后HPV感染显著下降

Vaccine. 2018 Jun 18;36(26):3820-3829.

疫苗接种对HPV基因型分布的影响

- 德国，一个队列研究，2价疫苗接种
  结果：年龄≤22岁的妇女HPV16,18,31感染显著下降
  疫苗未覆盖HPV51,53,56在接种妇女的感染比例增高

- 苏格兰，2008年始国家接种计划，12-13岁女孩接种二价疫苗
  结果：HPV 16，18感染显著下降75%
  HPV 31, 33,和45 交叉保护
  HPV 51，56感染上升为最常见感染型
  接种的女孩HPV感染比未接种妇女下降23% - 32%
  其它高危性HPV感染率未见差别

Obstet Gynecol Sci 2018;61(3):298-308

HPV疫苗接种对尖锐湿疣发病的影响

Human Papillomavirus Vaccination and Anogenital Warts: A Systematic Review of Impact and Effectiveness in the United States

Anthony E. Yakely, BA*, Lital Avni-Singer, BA†, Carlos R. Oliveira, MD‡, and Linda M. Niccolai, PhD*

Sex Transm Dis. 2019 April ; 46(4): 213–220

Results:

Eight eligible studies published through March 2018 were included.

Population-based impact studies examining trends in diagnoses reported consistent declines in females ages 25 years and younger after 2006 when routine female vaccination began in the United States. Declines in males ages 25 years and younger were also seen; however, these declines were lower than those in females and more evident after routine male vaccination began in 2011.

Among females and males older than 25 years, little to no change has been seen in the trends of anogenital warts since 2006.

Studies that included the pre-vaccine era (before 2006) reported increasing trends during this period. After vaccine introduction, a reversal in these trends was observed.

Effectiveness studies that included individual-level vaccination histories consistently demonstrated a lower risk of anogenital warts for those receiving at least one dose of the vaccine compared to those unvaccinated.

Conclusions:

the degree of HPV vaccine impact has varied substantially by age and sex. Achieving the full prevention potential of HPV vaccines will likely require greater coverage among both females and males. Post-licensure estimates of effectiveness demonstrate the real-world benefit of the vaccine

Declines in anogenital warts diagnoses since the change in 2012 to use the quadrivalent HPV vaccine in England: data to end 2017

Marta Checchi, David Mesher, Hamish Mohammed, Kate Soldan

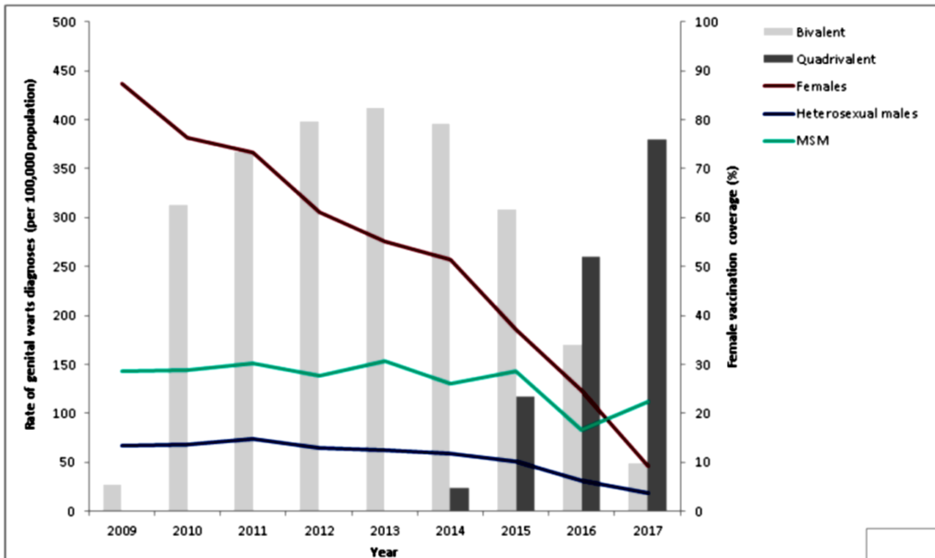
Table 1 Rate of AGW diagnoses and declines in SHC in England over 2009–2013 and 2014–2017 time periods

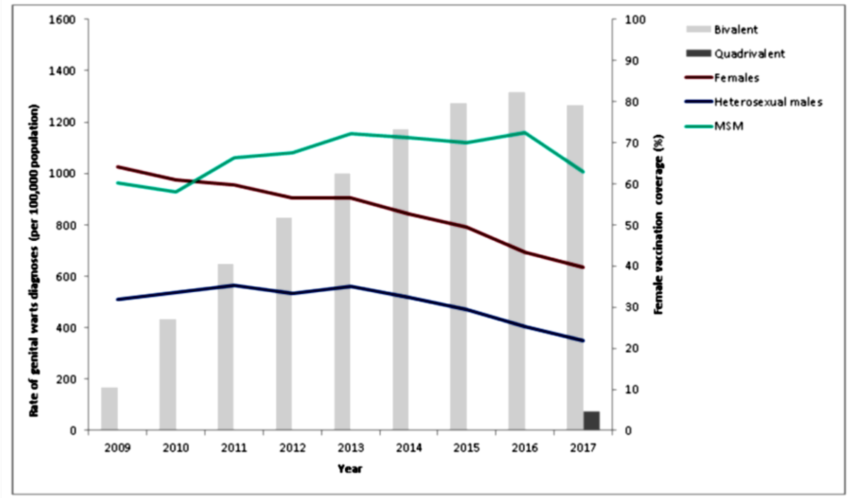
	Bivalent years: 2009–2013						Quadrivalent years: 2014–2017					
	Number of AGW diagnoses and rate of AGW per 100 000 individuals						Number of AGW diagnoses and rate of AGW per 100 000 individuals					
Age group (years)	2009		2013		% decline in rates	P value for trend	2014		2017		% decline in rates	P value for trend
	n	Rate	n	Rate			n	Rate	n	Rate		
Females												
15–17	4230	436.5	2584	275.6	36.9	<0.001	2403	257.5	413	45.7	82.3	<0.001
18–20	10 385	1027.5	8895	905.6	11.9	<0.001	8202	841.5	6165	634.2	24.6	<0.001
21–24	8816	627.9	8889	617.9	1.6	0.207	8368	583.8	6592	468.6	19.7	<0.001
Heterosexual males												
15–17	654	66.7	604	62.8	5.8	0.162	564	59.1	177	19.1	67.7	<0.001
18–20	5172	512.0	5626	562.8	−9.9	<0.001	5165	516.7	3503	350.3	32.2	<0.001
21–24	8781	652.1	11 013	766.2	−17.5	0.004	10 252	711.2	7921	553.9	22.1	<0.001
MSM												
15–17	42	143.4	44	153.2	−6.8	0.847	37	129.9	31	112.2	13.6	0.219
18–20	291	964.5	345	1155.5	−19.8	<0.001	340	1138.7	301	1007.7	11.5	0.193
21–24	525	1305.4	698	1626.1	−24.6	<0.001	793	1842.0	735	1720.8	6.6	0.232

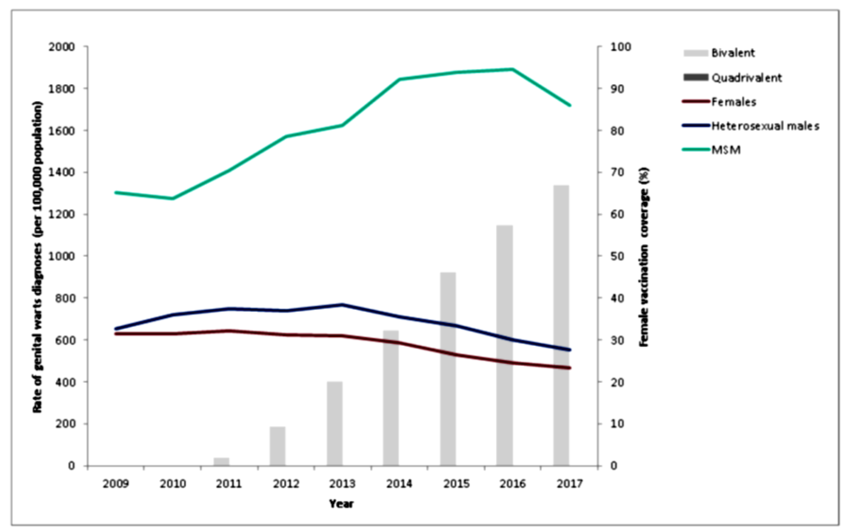
AGW, anogenital wart; MSM, men who have sex with men; SHC, sexual health clinic.

Checchi M, et al. Sex Transm Infect 2019;0:1－6.

英国AGW诊断率与女性HPV疫苗接种（2009 to 2017）



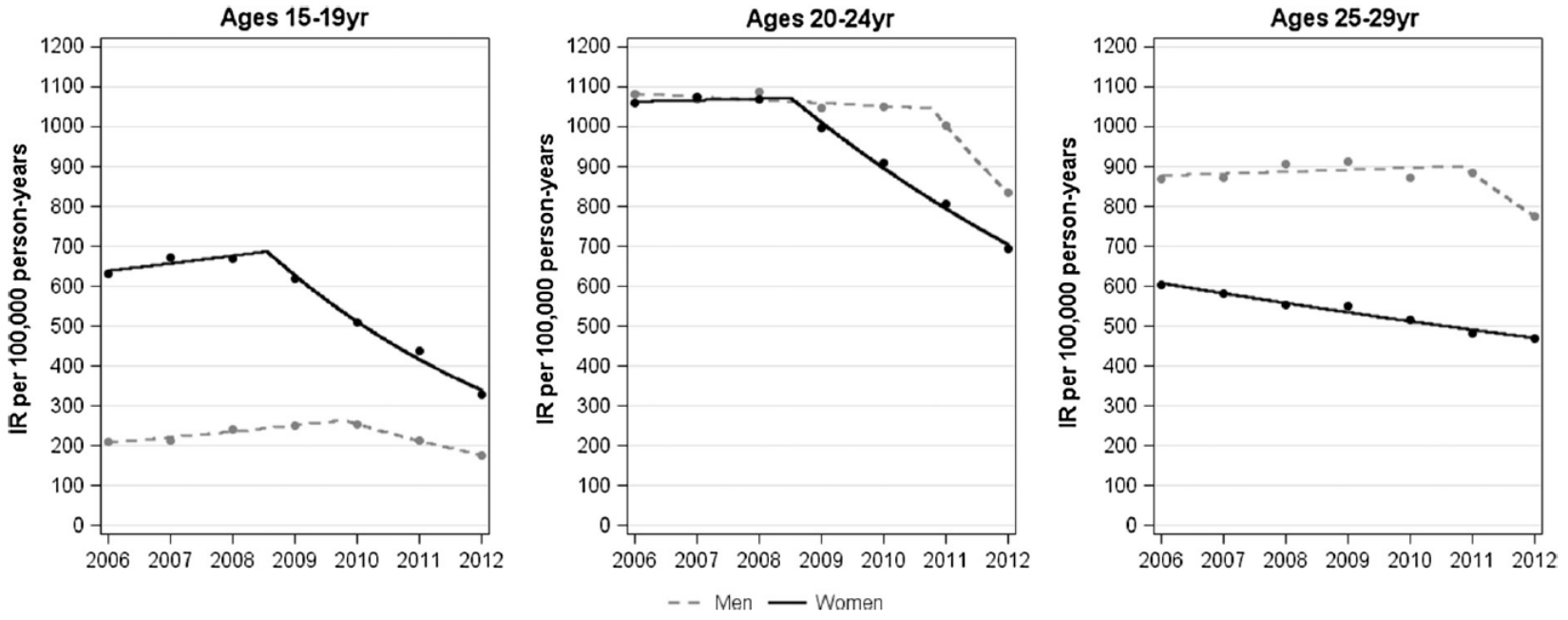




(A) in subjects 15－17 years old.
(B) in subjects 18－20 years old.
(C) in subjects 21－24 years old.

Checchi M, et al. Sex Transm Infect 2019;**0**:1－6.

Substantially reduced incidence of genital warts in women and men six years after HPV vaccine availability in Sweden



Incidence of condyloma by sex, age, and calendar year.

E. Herweijer et al. / Vaccine 36 (2018) 1917 – 1920

各指南的推荐历程

Table 1
Timeline of FDA approvals and ACIP recommendations for the HPV vaccine in the United States.

Year	Month	Agency	Vaccine	Recommendation/Approval
2006	June	FDA	**4vHPV**	Approved vaccine for use in females 9–26 years of age
	June	ACIP	**4vHPV**	Recommended routine vaccine for females 11–12 years; catch-up 13–26 years; can be started at age 9
2009	October	FDA	**2vHPV**	Approved vaccine for use in females 10–25 years of age
	October	ACIP	**2vHPV**	Recommended vaccination for females 11–12 years; catch-up 13–26 years; can be started at age 9
	October	FDA	**4vHPV**	Approved vaccine for use males 9–26 years of age
	October	ACIP	**4vHPV**	Recommended vaccination may be given to males age 9–26 years – did not recommend routine vaccination
2011	October	ACIP	**4vHPV**	Recommended routine vaccination for males 11–12 years; catch-up 13–21 years and catch-up 22–26 years for men who have sex with men (MSM) or are immunocompromised; can be started at age 9
2014	December	FDA	**9vHPV**	Approved use in females 9–26 years of age
			9vHPV	Approved use in males 9–15 years of age
2015	February	ACIP	**9vHPV**	Recommended routine vaccination for females 11–12 years; catch-up 13–26 years; can be started at age 9
			9vHPV	Recommended routine vaccination for males 11–12 years; catch-up 13–21 years and catch-up 22–26 years for MSM and men who are immunocompromised; can be started at age 9
	December	FDA	**9vHPV**	Approved use in males 16–26 years of age
2016	October	FDA	**9vHPV**	Approved use of a two-dose option for males and females 9–14 years
	December	ACIP	**9vHPV**	Recommended two-dose option for males and females 9–14 years

预防性HPV疫苗接种的推荐

WHO有关HPV预防性疫苗的建议：

- 具备下述条件的国家应将HPV疫苗纳入国家免疫规划：
  - 预防宫颈癌和/或其他HPV相关疾病是公共卫生领域的一项重点任务
  - 引进HPV疫苗在规划方面是可行的、持续的资金能得到保障
  - 考虑本国或本区域HPV疫苗接种策略的成本效果问题

- 主要目标年龄人群：
  发生首次性行为前的女孩，年龄范围 9-13岁

- 以下情况下推荐年龄较大女性接种HPV疫苗：
  能负担疫苗费用
  符合成本效果
  不会转移主要目标人群疫苗接种资源和宫颈癌筛查资源

。

HPV疫苗女性免疫接种的推荐：

- **美国免疫接种实践咨询委员会(ACIP)**
  推荐**11～12岁**女孩接种HPV疫苗，接种年龄可低至**9岁**
  推荐4价或9价HPV疫苗
  未接种或未完成系列接种的13～26岁女性可补接种
  推荐用9价疫苗
  已完成一种HPV疫苗接种的个体不需要重复接种9价疫苗

- **其它学会的推荐与ACIP指南基本一致：**
  美国儿科学会(AAP)、美国家庭医师学会(AAFP)、美国CDC
  美国妇产科医师学会(ACOG)、美国癌症学会(ACS)指南
  推荐未接种或未完成系列接种的13～18岁女性须追加接种
  无足够证据推荐或反对**19～26岁**女性接种疫苗

HPV疫苗接种年龄的推荐：

- 全球范围内9-45岁
- HPV疫苗接种对未感染HPV的个体最有效，预防效果100%

  接种最佳时间为首次性行为前，戏称“处女疫苗”
- 接种年龄放宽：

  ---大于26岁仍有HPV感染风险，预防再受感染

  --减低因持续感染演变成子宫颈癌的机会
- “HPV-FASTER”计划

  女孩和妇女的接种年龄放宽：9岁～45岁

  配合30岁以后的HPV检测筛查

  已在11个欧洲国家实施

男孩接种HPV疫苗的意义

- HPV病毒对男性影响趋势增加：
  男性患HPV相关口咽癌概率比女性高至少3倍
  多数国家推行宫颈癌筛查，但无口咽癌和肛门癌检查
- 澳大利亚、奥地利、巴西、加拿大、德国、以色列、意大利、瑞士及美国都开始对男孩接种HPV疫苗
- 男孩接种HPV疫苗为临床、经济、伦理带来优势和益处：
  为与未接种HPV疫苗的女性发生关系的男性提供保护
  为女性提供更多一层防护
  为高危人群例如男男性行为者（MSM）提供保护
  降低HPV相关疾病的治疗成本
  减轻对“群体免疫”的依赖

男性HPV疫苗免疫接种的推荐

- 2009年ACIP建议：

  男性可接种4价HPV疫苗预防生殖器疣—

  间接进一步降低女性HPV感染和宫颈癌风险

- 2011年ACIP更新建议：

  男性11-12岁应常规接种，13-21岁男性可追加接种

  22至26岁的男性高危人群：MSM、免疫受损(如HIV)男性

  更推荐接种9价疫苗

  女性疫苗接种率低--男性疫苗接种的成本-效益可能更高

  AIN史、生殖器疣史或HPV感染病史均非接种禁忌证

特殊人群的免疫接种

- **妊娠与哺乳期女性：**
  不推荐妊娠期使用
  已开始接种尚未完成3次注射的孕妇，产后继续接种。
  不影响母乳喂养婴儿安全，哺乳期可接受免疫接种

- **已有宫颈HPV感染或异常或生殖器疣的女性：**
  疫苗接种仍能防护未感染HPV型
  ACIP推荐进行免疫接种
  对已存HPV感染或CIN作用有限

- **免疫抑制或免疫功能受损的宿主：**
  ACIP推荐对免疫功能受损的26岁及以下患者进行接种

HPV疫苗的选择

- 二价疫苗和四价疫苗均具备极佳的安全性和效果
- 选择HPV疫苗时应基于：
  - *当地相关数据评估
  - *主要HPV相关公共卫生问题（宫颈癌、其他肛门与生殖器癌或尖锐湿疣）的影响程度
  - *所批准的疫苗接种的目标人群
  - *疫苗产品特点，如价格、供应和规划性方面的问题

2价疫苗已在全球132国家及地区获批上市（包括中国大陆）
已有超过6千9百万剂供应全球市场
全球已有70个国家将HPV疫苗纳入国家计划免疫项目

www.who.int/immunization/documents/positionpapers

预防性HPV疫苗的展望

- **第二代HPV L1 VLP 疫苗**
  提高疫苗生产效力的研究--
  HPV L1 VLP疫苗表达体系的改良
  进入临床前研究、或I-III期临床研究
- **L2为基础的HPV疫苗**
  以HPV病毒结构蛋白L2为基础的HPV疫苗有较大潜力
  *如将L2 蛋白抗原表位表现在一个携带蛋白如肽多聚体上--
  再结合融合分子，以提高L2免疫原性
  *构建一个嵌合HPV16 L1 VLP 疫苗提呈HPV16 RG1 L2表位--
  显示有效保护阴道粘膜感染多个型别HPV
  高危型假病毒HPV16,18,45, 31,33, 52,58, 35, 39, 51, 59, 68,56, 73, 26, 53, 66, 34
  低危型HPV6、43、和44
  --降低疫苗价格
- **亚单位疫苗**


谢谢