

STI Screening – Have We Got It Right?

HPV Prevention & Treatment – More Choices?

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No conflict of interest

***Neisseria gonorrhoeae / Chlamydia trachomatis* Hurdles and Challenges**

- **many infections are asymptomatic:**
 - **up to 80% of females; 10-20% of males**
- **even more likely to be asymptomatic if infected at rectal or pharyngeal sites**
- **quinolone and cephalosporin resistant gonorrhea increasing in Canada**

Urethritis/Cervicitis

- **inflammation of the urethra or cervix with a mucoid, mucopurulent, or purulent discharge**
- or (for urethritis only)**
- **increased number of PMNs in urethral secretions (≥ 4 PMN/HPF in a mean of 5 fields)**

Urethritis/Cervicitis Laboratory Investigations

- **urine (first-void) / urethral / endocervical samples for *N. gonorrhoeae* & *C. trachomatis* (culture, NAAT, PCR*)**
 - **NAAT does not allow for susceptibility testing**
- **consider Pap smear**
- **serology for syphilis, HIV & HBV**

* Amplicor PCR

Sensitivity and Specificity of NAAT for Female Genital Samples

Specimen	Symptom status	<i>C trachomatis</i>		<i>N gonorrhoeae</i>	
		Sens	Spec	Sens	Spec
Swab	Symptomatic	92.4%	96.7%	100%	98.1%
	Asymptomatic	98.4%	98.8%	96.9%	99.6%
Urine	Symptomatic	93.8%	98.8%	92.6%	99.1%
	Asymptomatic	96.8%	99.0%	87.5%	99.5%

Swabs were tested by the APTIMA COMBO 2 Assay, two commercially-available NAATs for CT, one commercially-available NAAT for GC, and GC culture

Urine was tested by the APTIMA COMBO 2 Assay, two commercially-available NAATs for CT, and one commercially-available amplified assay for GC

CT infected status, any two positive reference NAAT results by any combination of swab and urine
GC infected status, a positive culture, or positive swab and urine results by the amplified reference assay

Reference: Package insert GEN-PROBE® APTIMA COMBO 2® Assay

Sensitivity and Specificity of NAAT for Male Genital Samples

Specimen	Symptom status	<i>C trachomatis</i>		<i>N gonorrhoeae</i>	
		Sens	Spec	Sens	Spec
Swab	Symptomatic	96.4%	96.9%	99.0%	98.8%
	Asymptomatic	94.6%	98.4%	100%	96.7%
Urine	Symptomatic	98.5%	98.4%	98.4%	99.8%
	Asymptomatic	96.3%	98.8%	100%	99.5%

Swabs were tested by the APTIMA COMBO 2 Assay, a commercially-available NAAT for CT and GC testing and GC culture

Urine was tested by the APTIMA COMBO 2 Assay, two commercially-available NAATs for CT, and one commercially-available amplified assay for GC

CT infected status, any two positive reference NAAT results by any combination of swab and urine
GC infected status, a positive culture, or positive swab and urine results by the amplified reference assay

Reference: Package insert GEN-PROBE® APTIMA COMBO 2® Assay

Who should be screened?

- sexually active youth / adult under 25
- all symptomatic individuals
- all pregnant women
- for sexually active males and other females, screen if risk factors present:
 - sexual contact with infected partner
 - new sexual partner or more than 2 partners in the past year
 - history of STI
 - at risk populations i.e. IDU, inmates, sex trade workers, street youth

Repeat screening of individuals infected with chlamydia or gonorrhea after 6 months is recommended

Treatment of Urethritis and Cervicitis 2011

Do not treat without lab samples obtained first

- treat for both gonorrhea and chlamydia unless negative test result available
- cefixime 400 mg po given as a single dose (ciprofloxacin 500 mg / ofloxacin 400 mg MUST only be used if cefixime is absolutely contra-indicated and if used, a test of cure MUST be arranged)

FOLLOWED BY

- azithromycin 1 gm po single dose OR doxycycline 100 mg bid x 7 days

Treatment of Urethritis and Cervicitis 2012

- **changes required due to increasing GC antimicrobial resistance, especially among MSM**
 - **treat for both gonorrhea and chlamydia**
 - **cefixime 800 mg po, ceftriaxone 250 mg IM or azithromycin 2 gm po all given as a single dose**
- FOLLOWED BY (unless azithro given as GC Rx)***
- **azithromycin 1 gm po single dose OR doxycycline 100 mg bid x 7 days**

Chlamydia in pregnancy and neonate

- **screening recommended for all pregnant women**
- **topical treatment for neonatal conjunctivitis is NOT adequate**
- **neonates born to infected mothers should be tested for *C. trachomatis* and treated if positive test results**
- **prophylaxis is not routinely recommended unless follow up cannot be guaranteed**

Chlamydia trachomatis: Pregnancy

Treatment

- Amoxicillin 500 mg PO tid x 7 days

OR

- Erythromycin base 500 mg PO qid x 7 days

OR

- Azithromycin 1 gm PO x one dose, if poor compliance expected

Test of cure for N gonorrhoeae

CULTURE preferred

- not routinely required if recommended Rx taken & symptoms / signs disappear and no re-exposure except:
 - suboptimal compliance
 - antimicrobial resistance is documented
 - treatment failure has previously occurred
 - alternate Rx agent used
 - all prepubertal children and pregnant women
 - pharyngeal, PID or disseminated infection is diagnosed
- timing of TOC: 4-5 days after completion of Rx if culture used and 3-4 weeks if NAAT used

Test of cure for *C trachomatis*

Drug resistance is rare

- **not routinely required if recommended Rx taken & symptoms / signs disappear and no re-exposure except:**
 - **suboptimal compliance**
 - **antimicrobial resistance is documented**
 - **alternate Rx agent used**
 - **all prepubertal children and pregnant women**
 - **PID or disseminated infection is diagnosed**
- **timing of TOC: 3-4 weeks with NAAT or PCR**

Preventing STI Choices!

- **education**
- **delaying sexual activity**
- **abstinence**
- **mutually monogamous partners**
- **reducing number of partners**
- **non-insertive sexual practices – not effective for HPV**
- **barrier methods**
 - **male and female condoms**

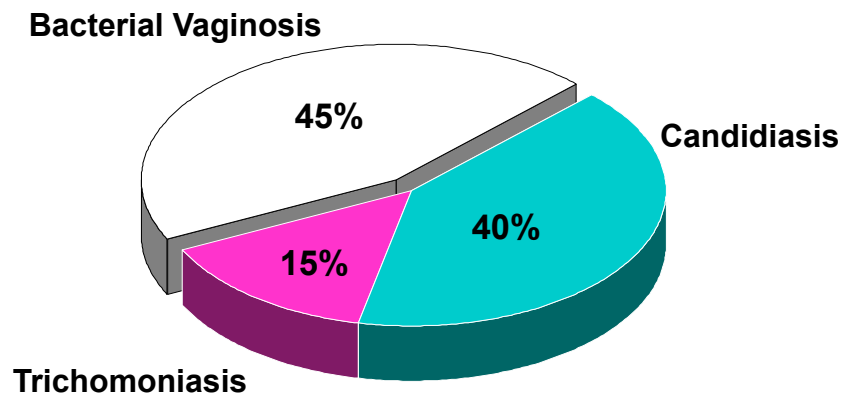
Vaginal Discharge

- cervicitis versus vaginitis
- physiologic versus infectious
- etiology of infectious vaginitis
 - bacterial vaginosis
 - candida
 - *Trichomonas vaginalis*

Infectious Vaginal Discharge

	Candida	Trichomonas	Bacterial Vaginosis
Clinical	curdy pruritis+++ white-yellow	odour+++ pruritis++ yellow-green	odour+++ pruritis+/- thin-gray
pH	<4.5	>5.0	>5.0
KOH Whiff	-ve	+ve	+ve
Microscopy	hyphae spores	polys motile trich	clue cells ↓ lactobacilli ↑ gm -ve

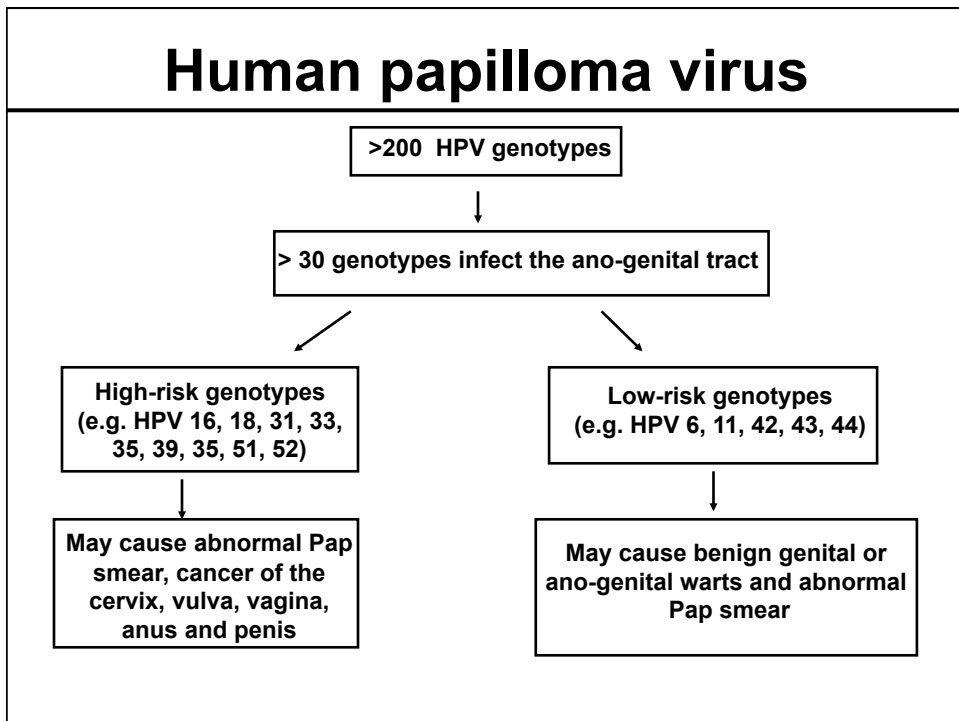
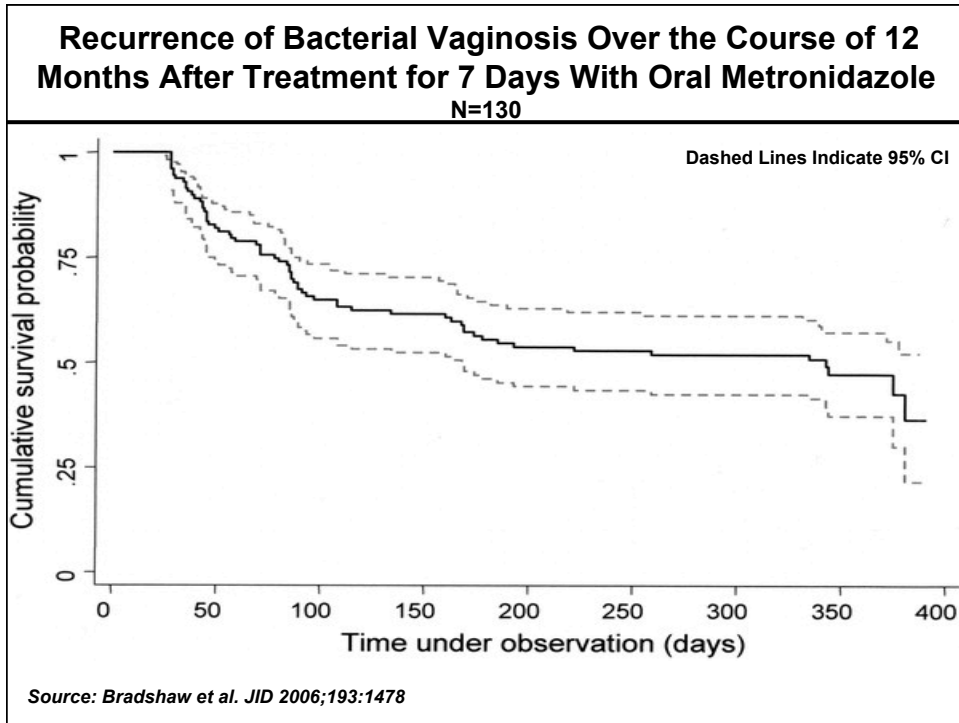
Relative Incidence of Vaginitis/Vaginosis



Bacterial Vaginosis

- a polymicrobial condition
- *G. vaginalis* can be found in up to 40-50% of healthy, asymptomatic women
- associated with
 - preterm labour & delivery
 - postpartum maternal & neonatal infections
 - PID
- not considered sexually transmitted but related to sexually activity

Source: Hay et al. *Br J ObGyn* 1992;99:63, Mazzulli et al. *J Clin Micro* 1990;28:1506



Association of HPV with anogenital and oropharyngeal cancers

Site	% HPV related	% HPV 16	% HPV 18
Cervix	100	52.4	18.3
<i>Squamous cell</i>		64.4	18.1
<i>Adenoca</i>		40.9	44.7
Anus	93.8	79.7	9.4
Vulva	89	71.2	5.9
Vagina	90.7	63	5.6
Penis	81.8	69.7	3
Oro-pharynx	14-57	78	?

Source: WHO IARC

Oncogenic HPV persists longer than low-risk HPV

Study (country)	N	Average follow-up, years	Median duration of infection, months		
			Type 16	Type 18	Type 6
Ho, 1998 (USA) ¹	608	2.2	11	12	6
Muñoz, 2004 (Columbia) ²	1,610	4.1	14	12	-
Richardson, 2003 (Canada) ³	621	1.8	19	9	6
Woodman 2001 (UK) ⁴	1,075	2.4	10	8	9*

*Type 6 or 11

1. Ho et al *N Engl J Med* 1998; 338:423 2. Muñoz et al *J Infect Dis* 2004; 190:2077 3. Richardson et al *Cancer Epidemiol Biomarkers Prevent* 2003; 12:485 4. Woodman et al *Lancet* 2001; 357:1831

Recommended Treatments: Provider-Administered vs Patient-Applied

No therapy guarantees eradication of HPV and recurrences are common

Provider-Administered Treatments	Patient-Applied Treatments
<ul style="list-style-type: none"> ▪ Surgical removal* ▪ Cryotherapy ▪ Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80%-90% 	<ul style="list-style-type: none"> ▪ imiquimod cream ▪ Podophyllotoxin 0.5% solution or gel ▪ Sinecatechins 15% ointment

Given the limitations of current individual treatments, some providers use multiple treatment options

*Includes tangential scissor or shave excision, curettage, or electrosurgery

Imiquimod 3.75% cream (Zyclara)

- **for the treatment of external genital warts**
- **same mechanism of action as imiquimod 5%**
- **intended for daily application**
- **fewer local side effects than imiquimod 5% cream**

Imiquimod 3.75% cream Anatomic Site-Specific Clearance Rates*

Women	Placebo N = 87	Imiquimod 3.75% N = 153
Anatomic site complete clearance		
Vulvar	14/51 (27.5)	53/104 (51.0)¶
Inguinal	2/9 (22.2)	9/20 (45.0)
Perineal	11/43 (25.6)	48/74 (64.9)¶
Perianal	10/40 (25.0)	51/65 (78.5)¶
Overall clearance of all EGW	16.1%	43.1%
# with no recurrence at 12 wk follow up	9/9 (100%)	47/72 (65.3%)

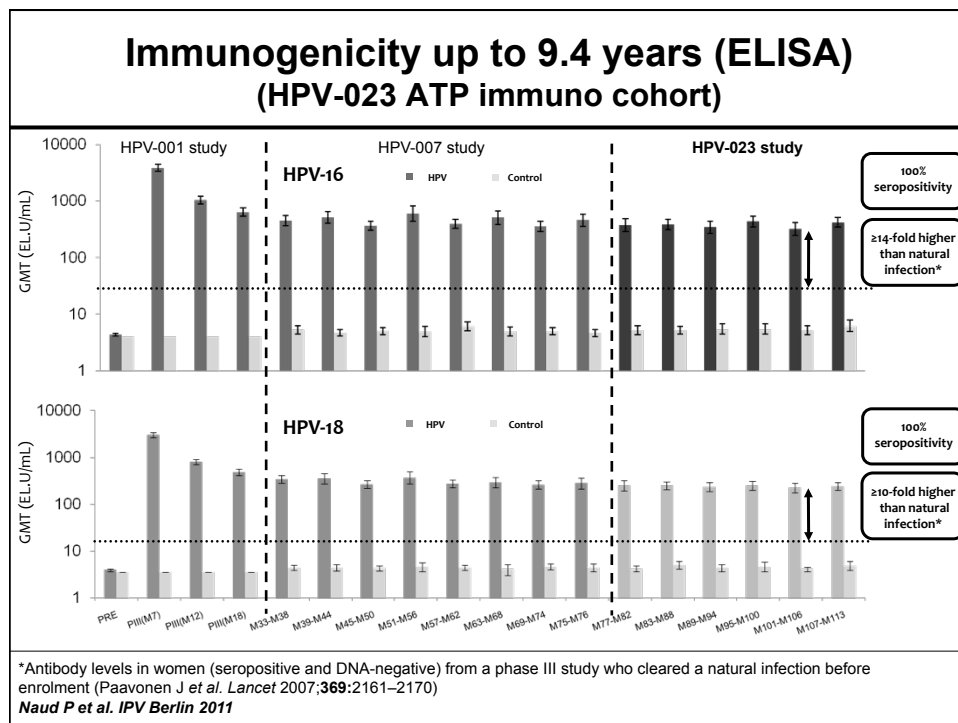
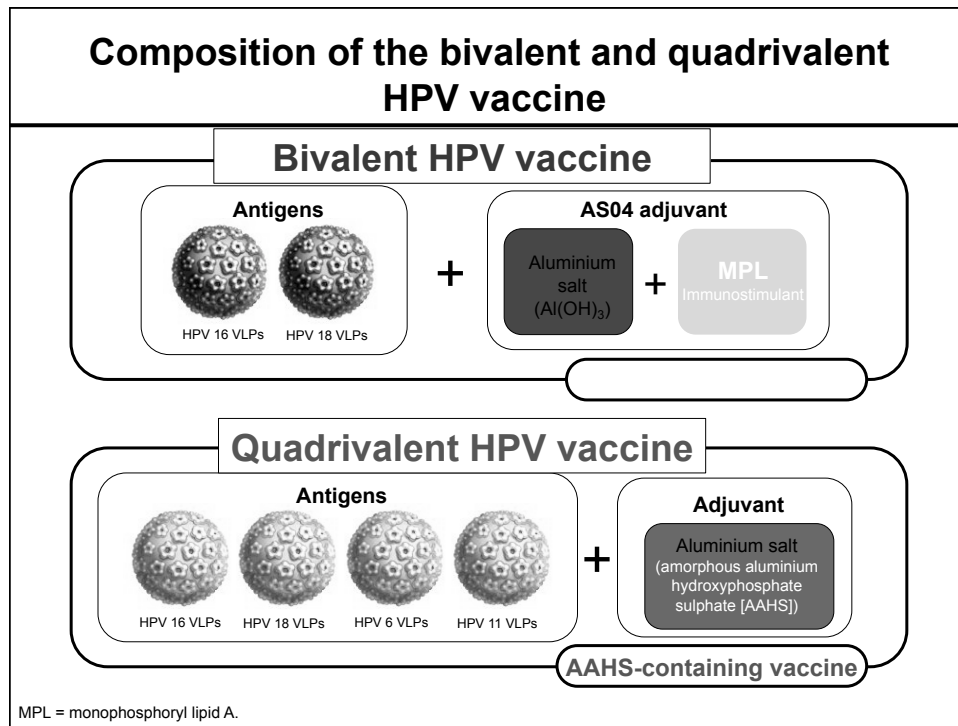
Source: Baker et al. *Inf Dis Obstet Gyne* 2011

* per protocol population
¶ p<0.05

Indication and Safety: imiquimod 3.75% cream (Zyclara)

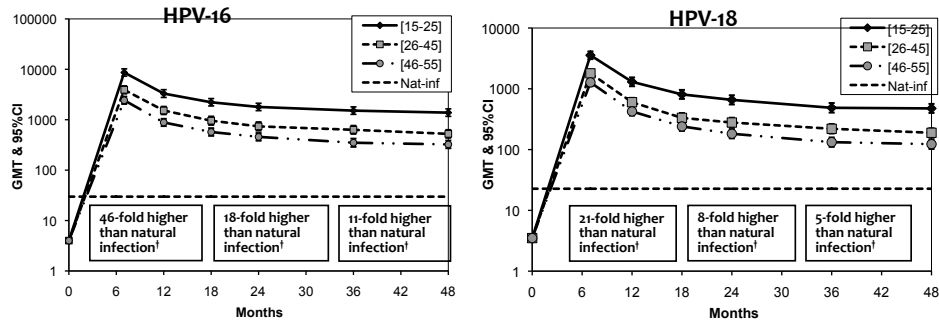
- Zyclara is indicated for the treatment of external genital/perianal warts in patients 12 years or older.
- In clinical studies, the most frequently reported adverse reactions were local skin reactions including erythema, edema, erosion or ulceration, and exudate at the genital wart site. Most local skin reactions were mild to moderate. Intense local inflammatory reactions and/or flu-like symptoms and signs can also occur. Dosing interruptions may be required.
- Zyclara is not recommended for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal warts as it has not been studied.
- The effect of Zyclara on the transmission of HPV is unknown. Zyclara may weaken condoms and diaphragms. Sexual contact should be avoided while the cream is on the skin.

¹ Zyclara product monogram 2011



Bivalent vaccine immunogenicity in females 15 - 55 years

- Peak response at Month 7 then gradual decline towards a plateau in all age groups
- GMTs at Month 48 at least 5-fold higher than natural infection levels



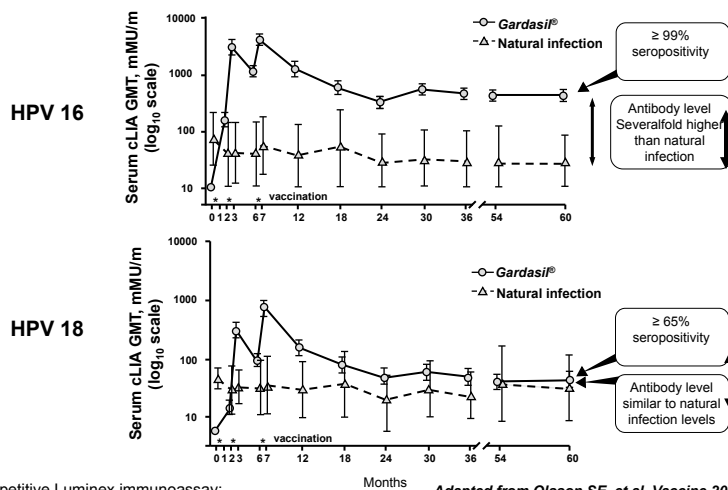
[†]IgG antibody level in women from the phase III PATRICIA study who had cleared a natural infection before enrolment (Paavonen J *et al. Lancet* 2007; 369: 2161–70)

GMTs, geometric mean antibody titres; ATP, according-to-protocol

Schwarz TF *et al. AOGIN, Dehli, 2010*

Quadrivalent vaccine : HPV 16 and 18 neutralizing antibody responses up to 5 years

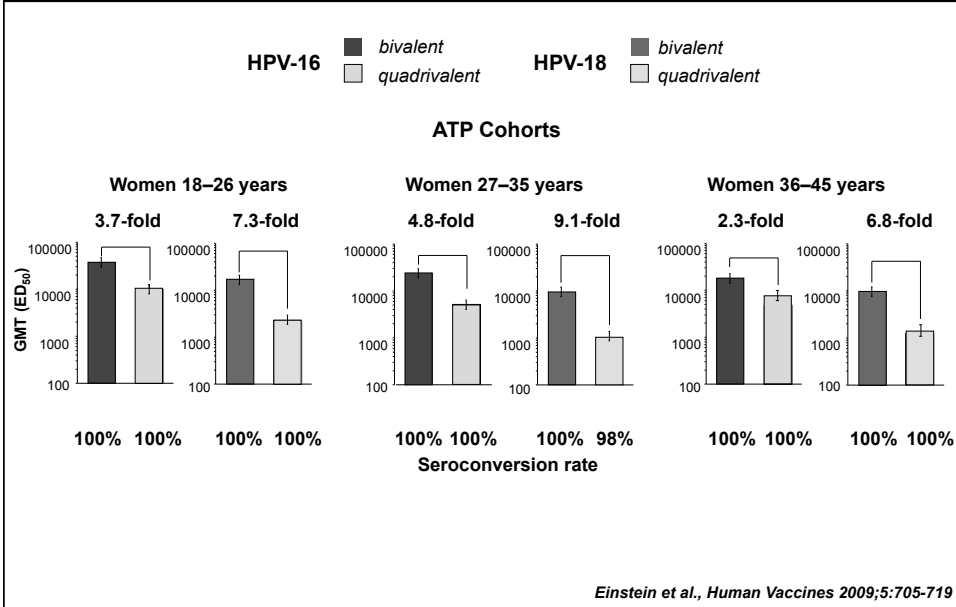
Phase II study up to 5 years



cLIA = competitive Luminex immunoassay;
GMT = geometric mean titre.

Adapted from Olsson SE, *et al. Vaccine* 2007; 25:4931–4939;
Villa LL, *et al. Vaccine* 2006; 24:5571–5583.

“Head to head study” HPV 16 and 18 neutralizing antibody responses: GMTs, GMT ratio and seroconversion rate



HPV Vaccine Efficacy

Overall vaccine efficacy

Efficacy against HPV 16/18

+

Efficacy against non-vaccine oncogenic types

Efficacy of HPV vaccines in “naïve” women

Vaccine	Bivalent ^{1,2}	Quadrivalent ^{3,4}
Study Population	DNA naïve to 14 HR HPV + 16/18 sero-negative	“Generally naïve”
N	11,641	9,296
	Vaccine efficacy (%)	
CIN 2+ HPV 16/18	99.0 (94.2,100; p<.0001)	98 (93,100)
CIN 2+ HPV 16,18,31,33,45 no type assignment	93.2 (84.1,97.7; p<.0001)	Not reported
CIN 2+ HPV 31,33,45,52,58	68.2 (40.5,84.1; p<.0001)	32.5 (-0.3,55)

1. Paavonen et al. *Lancet* 2009;374:301 2. Naud et al. *IDSA* 2010 3. Brown et al. *JID* 2009;199:926
4. Future II Study Group *NEJM* 2007;356:1915

Bivalent HPV vaccine: cross-protective efficacy data against incident infection with HPV 45 and 31 up to 6.4 years (Phase II study)

Combined analysis of initial efficacy study and extended follow-up

HPV type	Bivalent HPV vaccine	Control	Vaccine efficacy	
	n	n	%	95% CI
HPV 45	5	21	78	39–93
HPV 31	13	30	60	21–81

ATP cohort.
n = number of subjects reporting at least one event in each group.

Romanowski B et al. *Lancet* 2009;374: 1975

Overall efficacy against CIN2+ due to any HPV type

Bivalent – TVC Naive¹

Endpoint	Cohort	VE %	96.1% CI
CIN2+ irrespective of HPV type in lesion,	TVC naïve	64.9%	52.7, 74.2
CIN3+ irrespective of HPV type in lesion,	TVC naïve	93.2%	78.9, 98.7

Quadrivalent – Generally naïve¹

Endpoint	Cohort	VE %	95% CI
CIN 2/3 or AIS Due to Any HPV Type	Generally naïve	42.7%	23.7, 57.3
CIN 3 or AIS Due to Any HPV Type	Generally naïve	NA	NA

Not head-to-head studies

Paavonen J *et al.* 25th International Papillomavirus Conference (Abstract O-29.06), 2009
 EMEA Product Information* 28/05/2009 Gardasil-H-C-703-II-22 (p 20)

Efficacy of HPV vaccines in entire study cohort

Vaccine	Bivalent ¹	Quadrivalent ^{2,3}
Study Population	ATP-E Excluded if high grade cytology at month 0	Per protocol Excluded if past history HPV or abnormal Pap
N	14,656	12,167
	Vaccine efficacy (%)	
CIN 2+ HPV 16/18 no type assignment	92.9 (79.9,98.3; p<.0001)	98 (86,100)
CIN 2+ HPV 16/18 with type assignment	98.1 (88.4,100; p<.0001)	98.2 (93.5,99.8)
CIN 2+ HPV 31,33,45,52,58	53 (24.7,71.3; p<.0004)	14.6 ITT (-2.9,29.1)

1. Paavonen *et al.* *Lancet* 2009;374:301 2. Future II Study Group *NEJM* 2007;356:1915

3. Wheeler *et al.* *JID* 2009;199:936

Bivalent VE against persistent infection &/or CIN1+ lesions associated with HPV-16/18 in women ≥ 26 yrs

Cohort	HPV group (n)	Control group (n)	VE (%)	97.7% CI	P-value
6-month PI and/or CIN1+ lesions associated with HPV-16/18					
ATP-E seronegative	7	36	81.1	52.1, 94.0	<0.0001
ATP-E irrespective of serostatus	9	51	82.8	61.2, 93.5	<0.0001
TVC	90	158	43.9	23.9, 59.0	<0.0001

ATP-E, according-to-protocol cohort for efficacy; CIN, cervical intraepithelial neoplasia; control, subjects who received aluminium hydroxide; HPV, subjects who received the HPV-16/18 AS04-adjuvanted vaccine; n, number of cases; PI, persistent infection; TAA, type assignment algorithm; TVC, total vaccinated cohort; VE, vaccine efficacy

4 year follow-up

Skinner R et al. IPV, Berlin, 2011

Quadrivalent VE against persistent infection &/or CIN1+ lesions associated with HPV-16/18 in women ≥ 24 yrs

Cohort	HPV group (n)	Control group (n)	VE (%)	95% CI
PPE 6 month PI	7	50	86.2	69.4,94.7
CIN 1+	1	13	92.4	49.1,99.8
ITT	95	160	41.6	24.3,55.2

PPE – per protocol for efficacy; ITT – intention to treat

4 year follow-up

Castellsague X et al. Br J Cancer 2011

qHPV Vaccine Efficacy against Genital Warts

**Prophylactic not therapeutic vaccine – not
indicated for treatment of genital warts**

	Follow-up	Vaccine Efficacy (%)	95% CI
Women	3 - 4 yrs		
16 – 26 yrs (naïve)		99	96.2,99.9
24 – 45 yrs		100	30.8,100
Men	2 - 3yrs		
16 – 26 yrs (naïve)		89.3	65.3,97.9