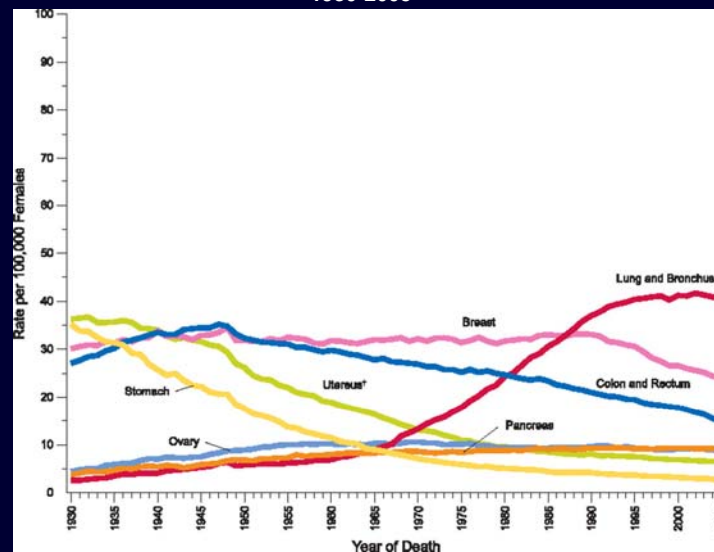


## HPV Testing and Vaccines and Your Patients

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Annual age-adjusted cancer death rates among females for selected cancers, US, 1930-2005



From Jemal, A. et al.  
CA Cancer J Clin 2009;59:225-249.

CA  
A Cancer Journal for Clinicians

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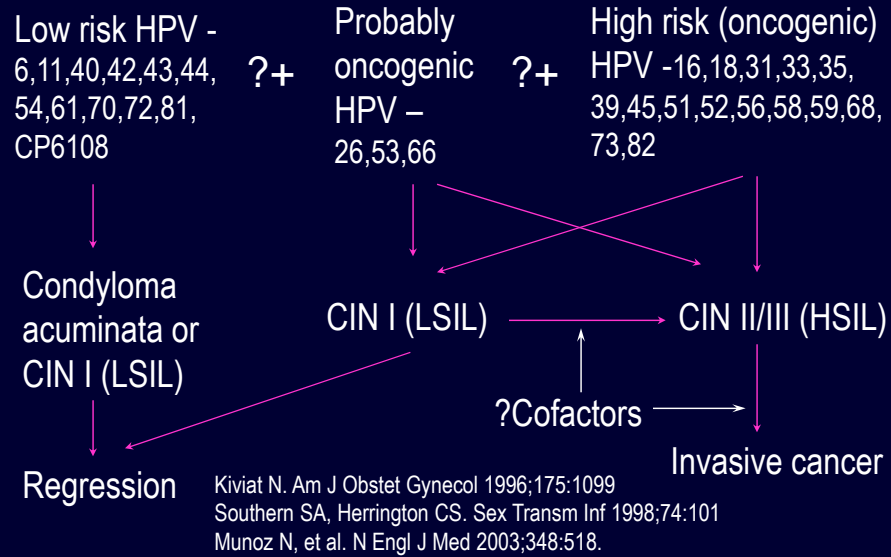
## **Cervical Cancer and Human Papilloma Virus**

- Prototype of success in cancer screening
- Best-studied model of viral carcinogenesis in human malignancies
- The success of screening preceded our understanding of the carcinogenesis by decades

## **Cervical Screening Programs**

- Endorsed by the American Cancer Society in 1945
- No prospective randomized trials to test efficacy, BUT
- Rates of cervical cancer decrease 75% in N America and Europe after widespread adoption
- Cervical cancer still common in low-resource regions of the world

## HPV in Cervical Carcinogenesis (New Model)



## Performance of Cytology versus HPV Testing in Detecting HSIL

	Cytology	HPV testing
Sensitivity (%)	53 (19-77)	96 (85-100)
Specificity (%)	96 (84-100)	91 (77-96)

Cuzick J, et al. Int J Cancer 2006;119:1095.

Pap was then.

HPV is now.

for you, your physician customers and their patients is simple: greater assurance that you're not missing cervical disease or cancer, and better risk-assessment for women 30 and over than the Pap alone.

Digene's he2 High-Risk HPV DNA Test.<sup>™</sup>  
The DNAtestPAP Test. Rewriting the future of women's health.

**DNAtestPAP**

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DIGENE CORPORATION - 1201 CLOPPER ROAD - GAITHERSBURG, MD 20878 - 800-DIGENE1 - WWW.DIGENE.COM

### Cost-effectiveness of Alternative Approaches to Manage ASC with Biennial Screening

Strategy	Reduction in cancer incidence	\$/year-life saved
No screening	-	-
LBC - Ignore ASC-US	84.0%	13,700
Reflex HPV	90.4%	44,400
Repeat Pap	90.2%	>44,400
Immed. colpo.	90.5%	905,300
Smear- Ignore ASC-US	78.9%	11,900
Reflex HPV*	86.4%	33,600
2-visit HPV	86.4%	>33,600
Repeat Pap	85.0%	>33,600
Immed. colpo.	86.6%	570,900

\* Assumes co-collection of a second specimen at the time of the initial Pap test for HPV tests.

Kim JJ, et al. JAMA 2002;287:2382.

## Cost-effectiveness of Cervical Cancer Screening Strategies

Strategy	Death/ 100,000	Increment \$/ QALY
No screening	1822	-
Pap/2 years till 75 years	185	29,781
Pap/2 years till 100 years	124	56,440
HPV/2 years till 75 years	177	-288,780
HPV/2years till 100 years	113	1,810,900
Pap+HPV/2 years till 75 years	113	70,347
Pap+HPV/2 years till 100 years	51	76,183

\* Assumptions: lab fee: Pap = \$10, HPV = \$30. HPV testing would be more effective and less costly than Paps at \$5/HPV test.

Mandelblatt JS, et al. JAMA 2002;287:2372.

## Statement on HPV DNA Test Utilization

Solomon D, et al. for the Members of the Cytopathology Education and Technology Consortium

Age	Routine Screening	Initial Triage				
		ASC-US	LSIL	ASC-H	AGC*	HSIL
≤20	2.1	2.3	2.3	2.3	2.3	2.3
21-29	2.1	1.2	2.4	2.5	2.5	2.5
≥30	1.1 <sup>#</sup>	1.2	2.4	2.5	2.5	2.5
Post-Menopausal	1.1 <sup>#</sup>	1.2	1.3	2.5	2.5	2.5

In addition, postcolposcopy management of women with discrepant biopsy and cytology results; posttreatment surveillance.

### Lifetime Costs and Reduction in Cancer Risk with Alternative Cervical Cancer Screening Strategies

Strategy	Test interval	Lifetime costs (US\$)	Reduction lifetime risk
Conventional Pap, lifetime	1	2,457	89.5%
Liquid Pap with reflex HPV testing, lifetime	1	2,653	92.3%
Liquid Pap until age 30, HPV and Pap after age 30	1	3,575	93.4%
Liquid Pap with reflex HPV testing, lifetime	2	1,707	91.4%
Liquid Pap until age 30, HPV and Pap after age 30	3	1,647	91.9%

Goldie SJ, et al. Obstet Gynecol 2004;103:619.

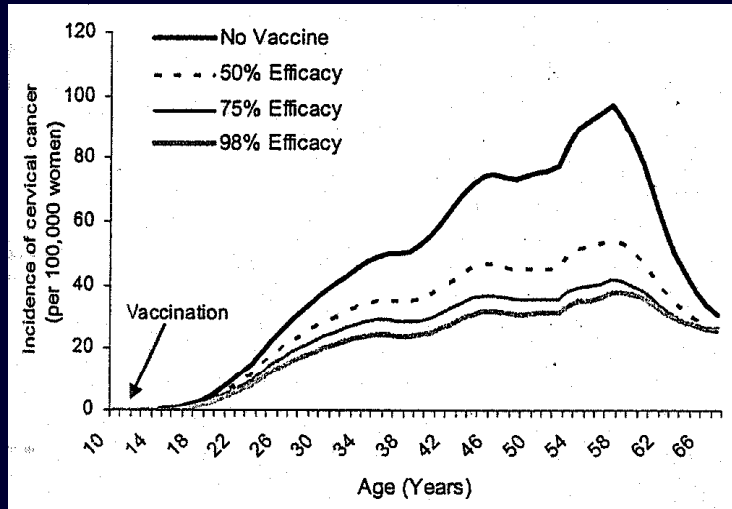
### Human Papilloma L1 Virus-Like-Particle Vaccine

Sponsor	Genotype	Efficacy (against persistent infection)	Efficacy (against abnormal cytology)
GlaxoSmithKline (Cervarix, approved by FDA in October, 2009)	16 and 18	95%	93%
Merck (Gardasil, approved by FDA in June, 2006)	16, 18, 6, 11	89%	100%

Harper DM et al. Lancet 2004;364:1757.

Villa LL et al. Lancet Oncol 2005;6:271.

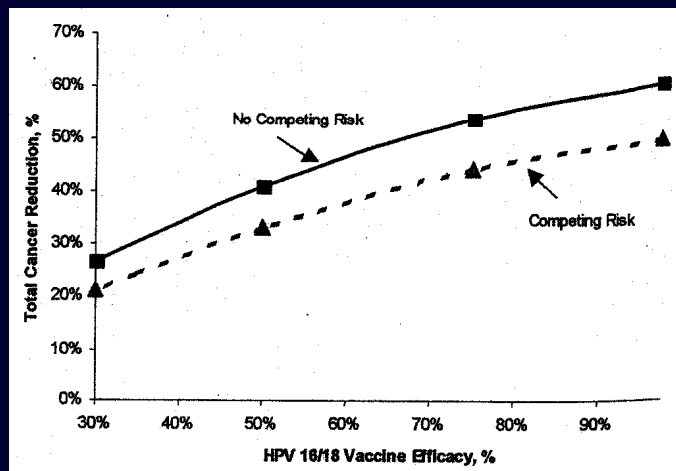
## Impact of HPV-16/18 Vaccines on Incidence of Cervical Cancer



HPV 16+18 cause ~ 70% of cervical cancers worldwide.

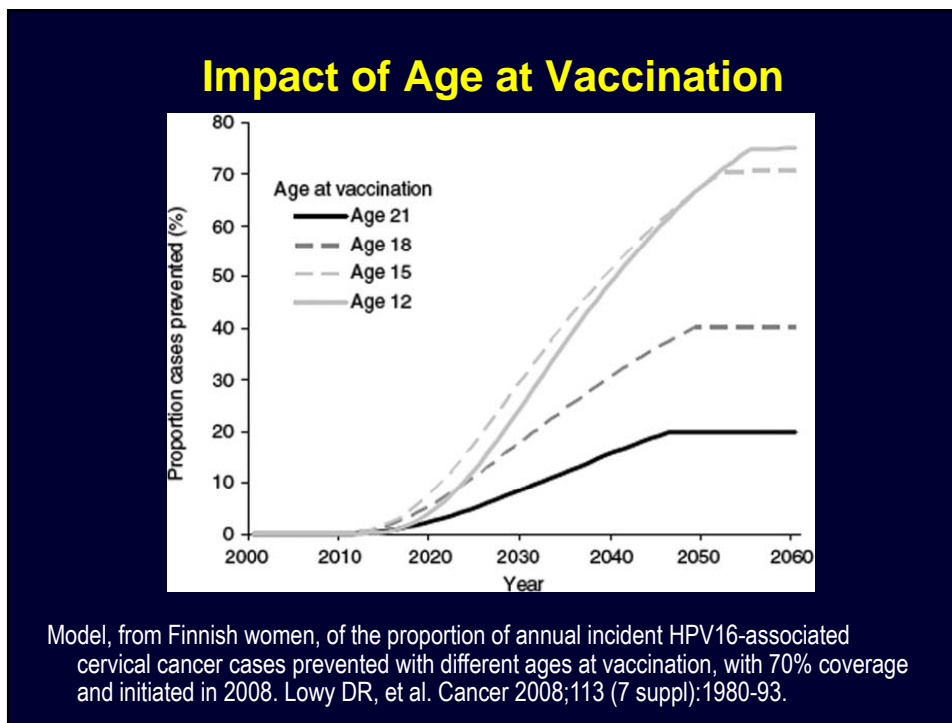
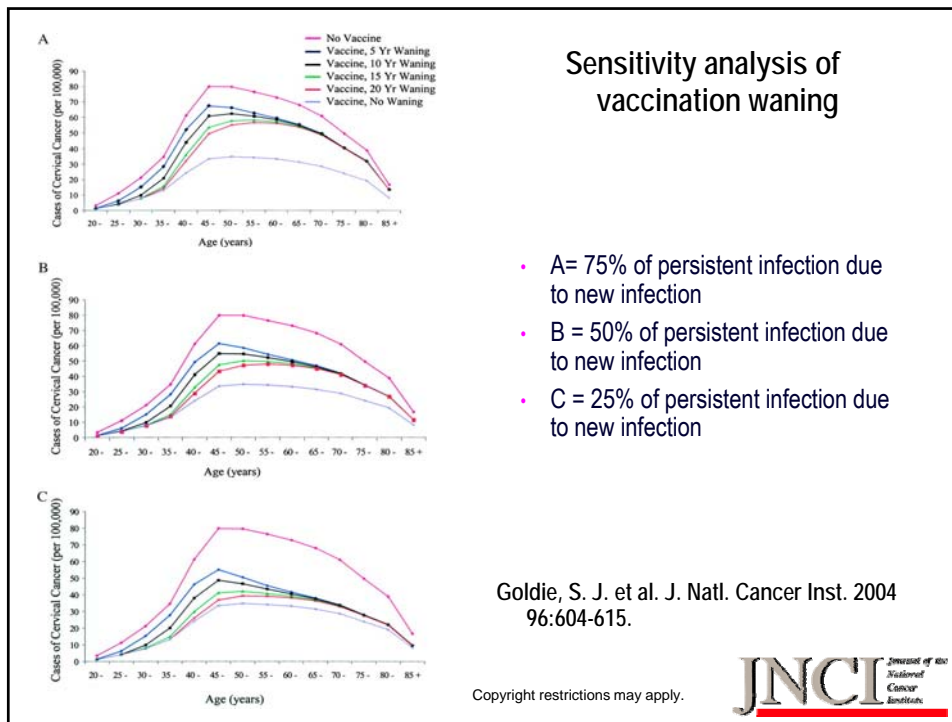
Goldie SJ, et al. Int J Cancer 2003;106:896

## Impact of HPV-16/18 Vaccines on Incidence of Cervical Cancer



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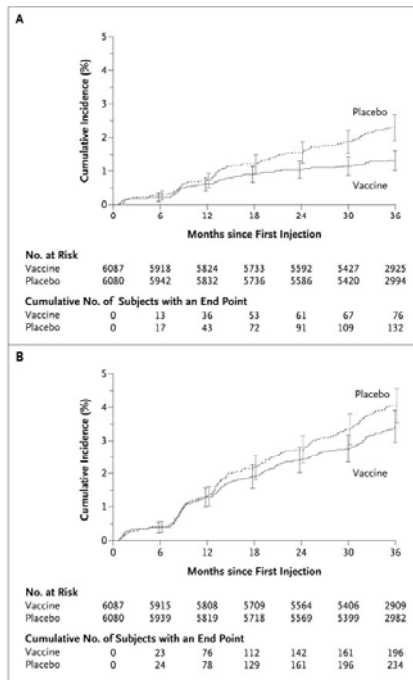


## Prophylactic Efficacy of HPV Vaccines

Outcome	Vaccine	Efficacy (95% CI)
CIN2+ (HSIL)		
MITT <sup>a</sup>	GSK <sup>1</sup>	90 (53-99) (mean f/u: 15 mo)
MITT	Merck <sup>2</sup>	95 (85-99) (mean f/u: 3 yr)
ATP <sup>b</sup>	Merck <sup>2</sup>	98 (86-100)
CIN1+		
MITT	GSK <sup>1</sup>	89 (59-99)
ATP	Merck <sup>3</sup>	100 (94-100)
Persistent HPV		
MITT, 12 mo	GSK <sup>1</sup>	76 (48-90)
MITT, 4 mo	Merck <sup>4</sup>	94 (83-96)

a – modified intention to treat (unrestricted susceptible); b – according to protocol

1 – Paavonen J, et al. Lancet 2007;369:2161-70; 2 – FUTURE II Study Group. N Engl J Med 2007; 356:1915-27; 3 – Garland SM, et al. N Engl J Med 2007;356:1928-43; 4 – Villa LL, et al. Br J Cancer 2006;95:1459-66.

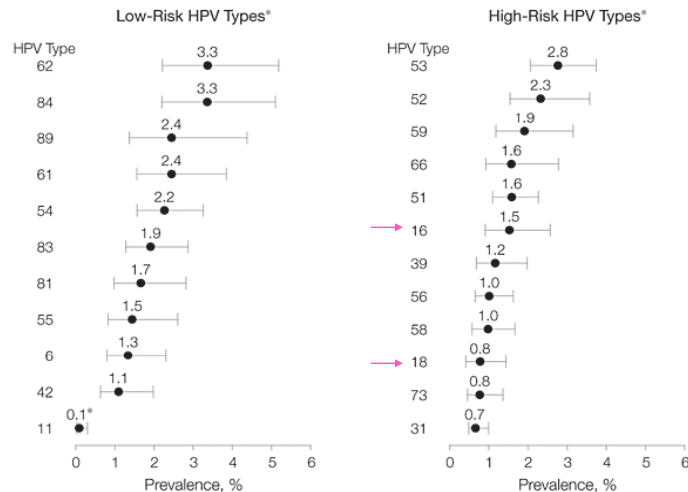


Time until the Development of High-Grade Cervical Disease Associated with HPV-16, HPV-18 (panel A), or Any HPV Type (panel B) (Intention-to-Treat Population- all who had randomization regardless of baseline status with respect to HPV and SIL status and who received at least one dose of vaccine or placebo)

The FUTURE II Study Group. N Engl J Med 2007;356:1915-1927



### Prevalence of HPV Types Among Females Aged 14 to 59 Years, NHANES 2003-2004



Dunne, E. F. et al. JAMA 2007;297:813-819.

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JAMA

### Risk of SCC according to HPV type

Type	Odds Ratio	Type	Odds Ratio
16	435	6	4.3
18	248	11	11
45	198	16 & 18	327
31	124	16 & other HR	617
52	200	16 & other LR	131
58	115	18 & other HR	187
59	419	Triple infections	65
33	374	≥ 4 infections	33

Muñoz N et al. N Engl J Med 2003;348:518.

## Relative Risk of CIS/AIS and ICC for HPV Type Relative to HPV 16

HPV type	CIS/AIS RR (95%CI)	Invasive cervical ca (ICC) RR (95%CI)
16	100 (referent)	100 (referent)
18	14 (9-21)	68 (47-100)
31	43 (31-60)	8 (5-14)
33	101 (62-163)	57 (13-107)
35	41 (24-72)	22 (11-47)
45	7 (4-13)	32 (20-53)
58	15 (9-22)	2 (1-5)

Wheeler CM, et al. J Natl Cancer Inst 2009;101:475-87.

## Clinical Management Guidelines for Obstetrician-Gynecologist

ACOG Practice Bulletin. Number 109, Dec 2009

- .....
- The US FDA has approved a DNA test specific for HPV-16 and HPV-18, which can be used as an adjunct in women with negative Pap test results, but who have tested positive for HR HPV by an assay testing for 13 or 14 HR types.
- ..... based primarily on consensus and expert opinion (C)
- .....
- Women who have been immunized against HPV-16 and HPV-18 should be screened by the same regimen as nonimmunized women.

## Furthermore

.... “Little difference in the cumulative incidence of CIN II+ between testing positive twice for any carcinogenic HPV genotype (same genotype or different genotype) versus testing positive twice for the same carcinogenic genotype (17% versus 21%, respectively).”

Castle PE, et al. BMJ 2009;339:b2569

## Cost-Effectiveness of Different Cervical Cancer Prevention Policies

Strategy	Cytology type	Age at screening initiation, y	Interval, y	Lifetime cost	Reduction in lifetime cancer risk, %	\$US/ QALY saved
Screening	CS	25	5	526	74	12,100
Screen/Vaccine	CS	25	5	828	90	31,200
Screen/Vaccine	CS	25	3	1030	94	58,500
Screen/Vaccine	CS	18	2	1581	97	280,200
Screen/Vaccine	LB	18	2	2314	98	617,900
Screen/Vaccine	LB	18	1	3992	99	3,867,500

\*Vaccination at age 12 with 90% efficacy  
Goldie SJ, et al. J Natl Cancer Inst 2004;96:604

QALY = quality-adjusted life-year

## **Impact of Reducing HPV-16 and HPV-18 on Screening and Management**

- Reduce predictive values of cytology
- Reduce predictive values of colposcopic impression
- Later initiation of screening and longer intervals
- Reduce predictive values of a pooled-probe HPV test
- HPV typing in addition to testing

Schiffman M. Cancer Cytopathol 2007;111:145-53.

## **Anal Neoplasia**

- Anal carcinoma is uncommon: annual incidence: 0.7/100,000 in men and 0.9/100,000 in women.
- Risk factors:
  - HPV – HRHPV detected in 84-100% of AIN III and anal carcinoma
  - HIV – independent (of sexual exposure) risk factor, and not influenced by antiretroviral therapy
  - iatrogenic immunosuppression – 10 – 100x than in general population, with women trice as affected as men.

## Screening for AIN and Anal Cancer

- Similar management principle to cervical cancers and their precursors.
- It was estimated that to provide cost effective life expectancy benefits comparable to those of other accepted preventive health measures requires annual cytology screening in the HIV (+) group and every two or three years in the HIV (-) group.

Abbasakoor F and Boulos PB. Br J Surg 2005;92:277-90.

## Screening for AIN and Anal Cancer in HIV(+) Homosexual and Bisexual Men

initial screening when CD4 of  $0.2-0.5 \times 10^9/L$

Screening strategy by anal cytology	Lifetime cost (\$)	Incremental life expectancy (months)	Cost-effectiveness (\$ per year of life saved)
No screening	71,640	-	-
Every 3 years	73,360	0.96	*
Every 2 years	73,630	0.18	21,000
Every year	73,920	0.17	21,100
Every 6 months	74,160	0.06	48,500

\* Strategy has a higher incremental cost-effectiveness ratio than a more ineffective alternate strategy.

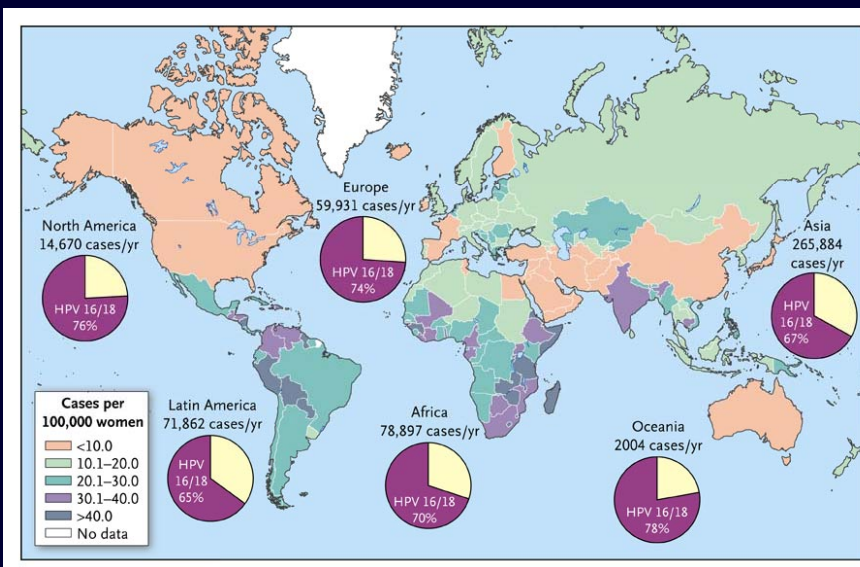
Goldie SJ, et al. Am J Med 2000;108:634-41.

## Screening for AIN and Anal Cancer in HIV(-) Homosexual and Bisexual Men

Screening strategy by anal cytology	Lifetime cost (\$)	Incremental life expectancy (months)	Cost-effectiveness (\$ per year of life saved)
No screening	4,130	-	-
Every 3 years	5,178	1.61	7,800
Every 2 years	5,583	0.29	16,700
Every year	6,676	0.34	38,700
Every 6 months	8,744	0.15	159,600

Goldie SJ, et al. Am J Med 2000;108:634-41.

Age-Standardized Rates of New Cases of Cervical Cancer per 100,000 Women, 2002



Agosti J and Goldie S. N Engl J Med 2007;356:1908-1910

The NEW ENGLAND JOURNAL of MEDICINE

## Cost-Effectiveness of Cervical-Cancer Screening in Developing Countries

Strategy (single screening at age 35 years)	Method	Lifetime cancer reduction, %
1- or 2-visit	Visual inspection	25 - 31
1- or 2-visit	HPV DNA testing	30 - 36
2- or 3-visit	Cytology	18 - 22

1-visit = same day screening & treatment

2-visit = separate screening & treatment

3-visit = screening, colposcopy with biopsy, and then treatment.

Goldie SJ et al. N Engl J Med 2005;353:2158.

## Incidence of Cervical Cancer and Rates of Death (within 7 years after one round of screening in rural India)

Hazard ratio (95% CI)	HPV testing	Cytology	VIA	Control
Incidence of all cancer	1.1 (0.8-1.4)	1.3 (0.99-1.8)	1.3 (0.95-1.8)	1.0
Incidence of stage II or higher cancer	0.47 (0.32-0.69)	0.75 (0.51-1.1)	1.0 (0.72-1.5)	1.0
Death	0.52 (0.33-0.83)	0.89 (0.62-1.3)	0.86 (0.60-1.3)	1.0

Sankaranarayanan R, et al. N Engl J Med 2009;360:1385-94.



## **Challenges of HPV Vaccine**

- Unknown duration
- Uncertain acceptance
- Uncommitted funding