

### Preventing cervical cancer - from bench to bedside and beyond

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### Cervical Cancer

- Second commonest cause of cancer in women worldwide
- 0.25m deaths/year
- >99.8% attributable to HPV infection
- Two HPV types (16 and 18) responsible for >70% of cancers
- HPV Infection is
  - very common (>30%)
  - only rarely leads to cancer (<2%)
- 15 year lag period between infection and cancer

### Cervical Cancer : the HPV connection

**Papillomaviruses**  
4 main groups:

Risk of cancer	Site of infection
High risk (Flat lesions)	Skin: HPV5, HPV8 Genital: HPV16, HPV18
Low risk (Warty lesions)	HPV1, HPV2 HPV6, HPV11

HPV Type	Percentage
16	57.6%
+ 18	71.7%
+ 45	77.4%
+ 31	81.3%
+ HPV X	85.0%
+ 33	87.9%
+ 52	90.1%
+ 58	91.8%
+ 35	93.3%
+ 59	94.6%
+ 56	95.7%

### New genital HPV infections are commonest amongst young adults

Incidence of New Genital Warts in Women by Age in US

Age (years)	Rate of New Genital Warts per 1000 Person-Years
<10	0.1
10-14	0.3
15-19	2.8
20-24	6.2
24-29	4.0
30-34	2.6
35-39	1.9
40-44	1.3
45-49	1.4
50+	0.8

Insinga RP. Clin Inf Dis. 2003;36:1397-1403.

### High risk HPVs and Tonsillar Cancer

HPV in tonsillar Cancer		
Age group	HPV+ve	HPV -ve
30-39	3	1
40-49	23	6
50-59	32	23
60-69	23	46
70-79	16	25
80-89	2	3

Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer  
Lalle Hammarstedt, David Lindquist, Hanna Dahlstrand, Mircea Romanitan, Liselotte Dahlgren, Jesenia Jonasson, Nomi Oreson, Johan Lindholm, Weimin Ye, Tina Dallanis and Eva Munck-Wikland  
Int. J. Cancer: 119, 2620-2623 (2006)

### Development of antibody to HPV capsids after HPV infection

Capsid specific antibody is:  
- not a diagnostic test for HPV  
- not a marker for likely regression

Carter JJ et al J Infect Dis 2000, 181, 1911-9

### Serum antibody to VLP conformational determinants conveys protection

Group	Immunogen	L1, µg per dose	Total protein, µg per dose	No. of dogs with warts
2	PBS	—	—	7/7
4	Crude COPV L1 VLPs	20	860	0/7
6	SDS-denatured COPV L1 VLPs	20	120	7/7
7	HPV-11 L1 VLPs	20	30	7/7


Serum from dogs from group 6 (control) and 4 (immunised),

- transferred to groups of naïve animals,
- challenged with COPV.

OUTCOME: Group 6: 4/4 with warts; Group 4: 0/4 with warts

J. A. Suzich, S. J. Ghim, F. J. Palmer-Hill, W. I. White, J. K. Tamura, J. A. Bell, J. A. Newsome, A. B. Jenson, and R. Schlegel. Proc.Natl.Acad.Sci.U.S.A 92 (25):11553-11557, 1995.


### Vaccines to prevent HPV infection



**Zur Hausen**

**Cancer associated Human Papillomaviruses (~1980)**

- Some HPVs cause cancer
- Virus can't be grown in the lab

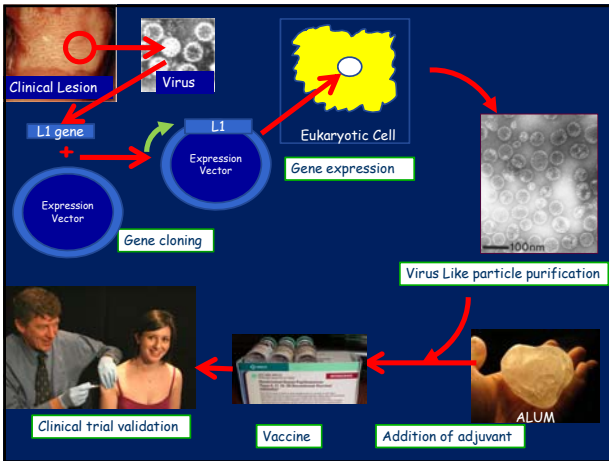


**Jian Zhou**


**Virus Like particles! (~1990)**

- L1 recombinant DNA
- Self assembly to VLPs
- VLPs highly immunogenic

1: J. Zhou, X. Y. Sun, D. J. Stenzel, and I. H. Frazer. Virology 185 (1):251-257, 1991.




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**HPV vaccines (~2005)**

- Conventional vaccines
- VLPs+ adjuvant
- Neutralising Antibody
- Protection > 5yrs
- Safe

1: J. Zhou, X. Y. Sun, D. J. Stenzel, and I. H. Frazer. Virology 185 (1):251-257, 1991.

### Disclosure of conflict of interest





Dr Ian Frazer and the University of Queensland benefit financially from commercial sale of the prophylactic HPV vaccines discussed in this talk

### HPV vaccines

#### One technology - two products

	Gardasil	Cervarix
Manufacturer	Merck (CSL)	GSK
HPV types	6,11,16,18	16,18
Adjuvant	Proprietary Alum	Alum OH +MPL (ASO4)
Administration	0,2,6 months	0,1,6 months
Manufacture	Yeast	SF9 cells/Baculovirus

### HPV 16/18-Related Cervical Cancer Vaccine Efficacy - Quadrivalent vaccine

Mean 36 Months of Follow-Up

- Subjects = Women, without prior infection with vaccine HPV types
- Efficacy = Prevention of disease caused by vaccine HPV types

Endpoint	Vaccine Cases (N=9342)	Placebo Cases (N=9400)	Efficacy 95% CI
High grade anogenital lesion (CIN, AIN)	1	73	99 (92, 100)

### HPV vaccine Phase III trial outcomes

Study <sup>1</sup>	Vaccine <sup>2</sup>	No of subjects		End-points	Vaccine efficacy % (confidence limits)
		Vaccine	Control		
Koutsky	6/11/16/18	6087	6080	CIN 2/3 AIS	98 (86-100)
Ault	6/11/16/18	10291	10292	CIN 2/3 AIS	99 (93-100)
Garland	6/11/16/18	2241 2261	2258 2279	CIN 2/3 AIS 6W VIN VAIN	100 (94-100) 100 (94-100)
Joura	6/11/16/18	7811	7785	VIN2/3 VAIN 2/3	100 (72-100)
Harper	16/18	481	470	CIN CIN2,3	100 (42-100) 100 (-8-100)
Parvonen	16/18	7788	7838	CIN CIN2,3	89 (59-99) 90 (53-99)

Adapted from J. A. Kahn and R. D. Burk. Papillomavirus vaccines in perspective. *Lancet* 369 (9580):2135-2137, 2007.

### Efficacy Against HPV 6/11/16/18-Related External Genital Lesions (Quadrivalent vaccine)

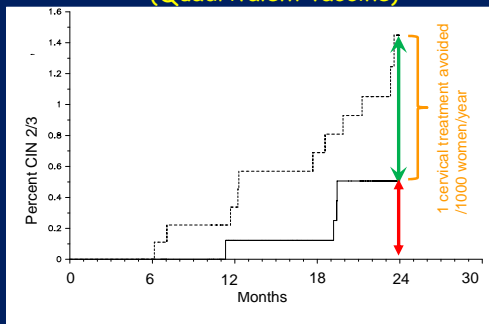
Mean 32 Months of Follow-Up

Endpoint	Vaccine Cases (N = 7899)	Placebo Cases (N = 7897)	Efficacy	CI
EGL	2	189	99	96, 100

### Cross protection against HPV associated CIN 2/3 (Quadrivalent vaccine)

Endpoint CIN 2/3 caused by	CASES Vaccine N= 4616	Placebo N= 4675	%Efficacy (95% CI)
any HPV	52	92	46 (24,62)
Vaccine types	0	52	100 (93,100)
Non vaccine types	38	62	38 (6, 60)
Non vaccine A9 (HPV16 like)	26	48	45 (10, 68)
Non vaccine A7 (HPV18 like)	8	15	46 (-35, 80)

### Protection over time against CIN2/3 -all HPV types (Quadrivalent vaccine)



A 70% reduction in cervical pre-cancer is observed with vaccination. Despite some cross protection there is still residual disease due to non vaccine HPV types.

### Efficacy Against HPV 6,11,16, 18-Related Disease by Baseline Serostatus and PCR Status

MITT-2 Analysis\* (Protocols 007, 013, and 015)

Endpoint	HPV Vaccine Cases (N = 8075)	Placebo Cases (N = 8075)	% Efficacy	95% CI
<b>Sero Negative &amp; PCR Negative</b>				
CIN (any grade)	16	309	95	(92, 97)
EGL	11	303	96	(94, 98)
<b>Sero Positive &amp; PCR Negative</b>				
CIN (any grade)	0	7	100	(29, 100)
EGL	0	8	100	(40, 100)
<b>Sero Negative &amp; PCR Positive</b>				
CIN (any grade)	83	101	22	(-6, 42)
EGL	46	43	-4	(-62, 33)
<b>Sero Positive &amp; PCR Positive</b>				
CIN (any grade)	105	113	5	(-25, 28)
EGL	14	16	12	(-93, 60)

Source : ACIP website 2008/03/30

## HPV VACCINE FAQs

### Are there vaccine specific side effects?

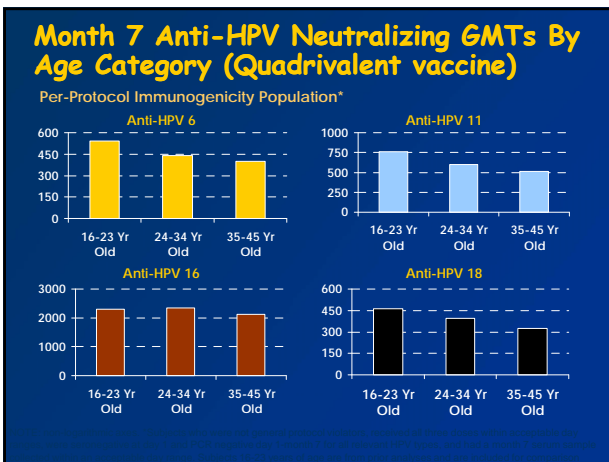
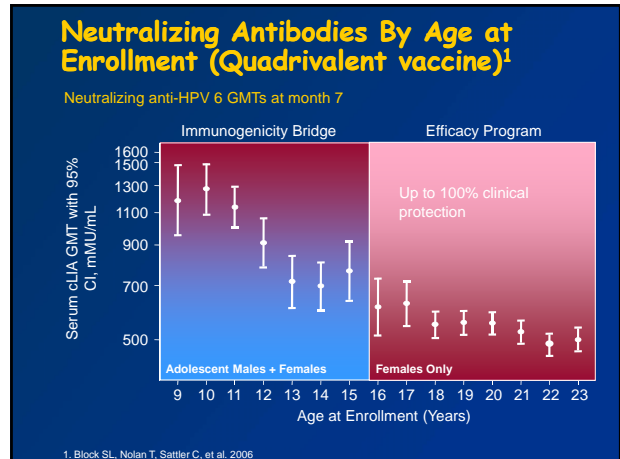
(Data for Quadrivalent vaccine)

- Placebo controlled trials
- Post Marketing Surveillance
  - 22,000,000 doses of vaccine administered
  - 7526 reported possibly associated events (June 08)

Injection Site (1 to 5 days Postvaccination)	Vaccine (N=5,088)	Placebo (Aluminum) (N=3,470)	Placebo (Saline) (N=320)
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.6%	0.6%
Systemic Allergic Reactions	0.1%	0.1%	0.0%

Mostly non-serious - fainting 1100 (one broken nose)  
 Urticaria (500) Anaphylaxis (28)  
 Some serious events - 2 cases Guillain-Barre - 7 expected for 7.5 million doses

- What about pregnancy safety?
  - 1244 Pregnancies in vaccine group
  - 1272 Pregnancies in placebo group
  - 3.6% adverse events in vaccine group and placebo group
  - 15 (vaccine) and 16 (placebo) congenital abnormalities

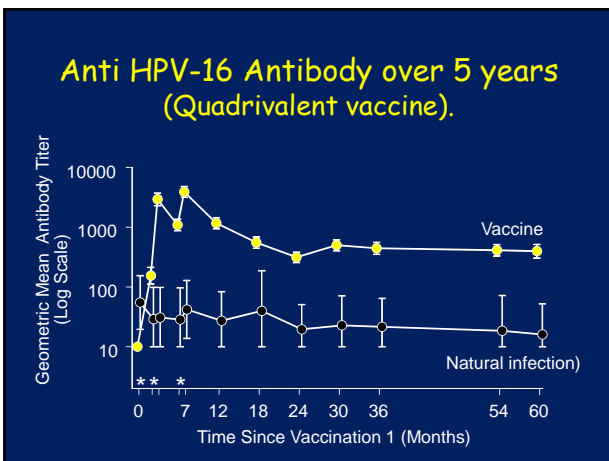


## Primary Efficacy Results (young and younger women)

Combined Incidence of HPV 6/11/16/18-Related Persistent Infection or Cervical/Vulvar/Vaginal Disease - Per Protocol Efficacy Population

Population	Vaccine	Placebo	Efficacy	95% CI	P-value
P019 Mid-Adult Women <sup>†</sup>	4	41	91%	74, 98	<0.001
P007 Young-Adult Women <sup>‡</sup>	1	26	96%	78, 100	<0.001

<sup>†</sup> P019: 24- to 45-Year-Old Women; mean of 1.65 years follow-up  
<sup>‡</sup> P007: 16- to 23-Year-Old Women; mean of 2.33 years follow-up\*



## Protection persists at 5 Years (Quadrivalent vaccine)

HPV 6, 11, 16, or 18-Related	Vaccine		Placebo		Efficacy (%)	95% CI
	N	Cases	N	Cases		
Persistent Infection	235	2*	233	45	96	83-100
Disease	235	0	233	6	100	12-100
CIN 1, 2, or 3	235	0	233	3	100	<0-100
Vulvar/vaginal neoplasias or genital warts	235	0	233	3	100	<0-100

Per Protocol efficacy against vaccine HPV types.

## Papillomavirus Prophylactic Vaccines - Where Next?

Determine from ongoing studies

- Duration of protection
  - Scandinavian Cohort study
- Efficacy in men
- Significance of cross protection
- Efficacy in older women
  - Studies underway

Consider broader spectrum vaccines

Challenge - how do you prove efficacy, if you need 250,000 subjects to do it, and have no approved surrogate marker

## Vaccine deployment

- Licenced in over 80 countries
  - Mostly for males and females 12-25
  - USA, Malaysia, Canada - females only
- Government sponsored univesal immunisation programs (routine + catch-up) in:
  - Australia (Quadrivalent)
  - (Girls 12 + 12-25) Commenced April 2007 through schools and GPs - 80% coverage in schools in most states
  - Germany, Italy, France (Q), Canada(Q), Great Britain (B) (Girls 11-13 + 13-18) - to commence in 2008
- Developing world initiatives
  - Gates Foundation, Merck/GSK, WHO collaborating on delivery to countries with GDP < US\$1000
  - Field trials - delivery strategies (eg Vanuatu) underway

## Deploying vaccines in the developing world



>10% of "healthy" Vanuatu Women over 30 have CIN3  
 No screening program feasible - one part time gynae for 0.2m people  
 >50% of 12 year old girls no longer attend school  
 Challenge - how to fund and how to deliver vaccine.

## Conclusions

- **Vaccines to prevent cervical cancer are here!**
  - They can prevent, with best results from early universal immunisation
    - Up to 70% of cervical cancer in an unscreened population
    - The majority of abnormal pap smears in screened populations
    - >90% of genital warts - quadrivalent vaccine only
      - (nb: no efficacy data for males yet)
  - They are not therapeutic for existing infection, therefore
    - full public health benefit requires universal administration to pre-teen girls
    - individual women of any age may benefit.
  - Vaccination should not alter participation in existing cervical cancer screening programs
  - We cannot claim a job well done till vaccine is delivered in the developing world.