Update on Clinical Trials for Bivalent HPV Vaccine

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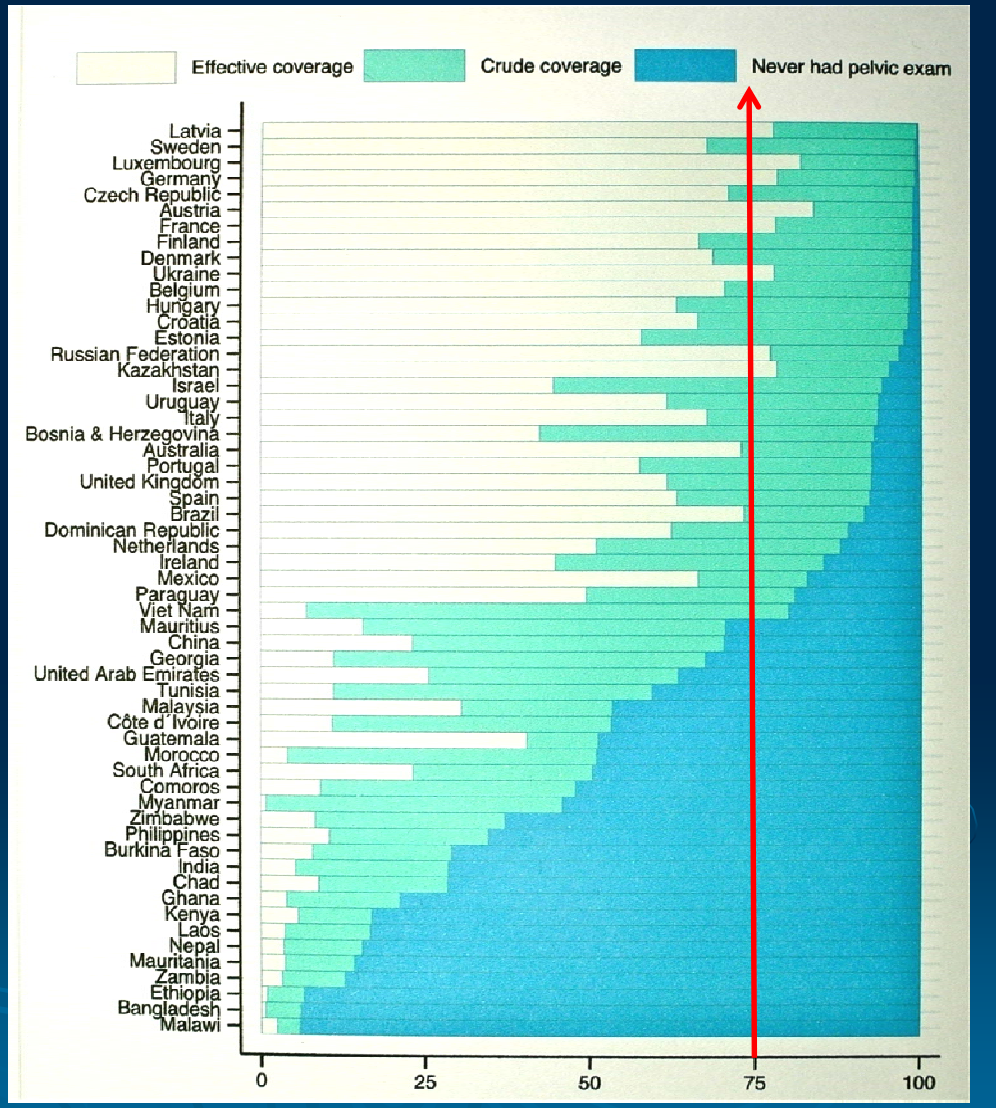
Disclosure of interest

- Swee Chong Quek has received honoraria from GSK and Merck as an investigator in clinical vaccine trials, member of advisory boards & lecturer

World estimates of crude & effective screening in women aged 25–64

- One of the most important factors for screening success is coverage of the population at risk
- Necessary to achieve at least 70% coverage to make an impact on cervical cancer incidence rates
- Quality of the screening test is also important



Adapted from Gakidou E et al. PLoS Med 2008;5:e132. World Health Surveys. Geneva: World Health Organization (WHO); 2003.

Adenocarcinoma of Cervix

- Incidence increasing (≈20% of all cervical cancers), pre-cancerous glandular lesions not easily detected with traditional pap screening[1,2]
- More aggressive and occurs in younger women[3]
- The top 3 HPV types that cause ~ 90% of adenocarcinomas are 16, 18 & 45[4]
- HPV 18 confers the highest risk (RR=410), HPV 16 (RR=164)[5]

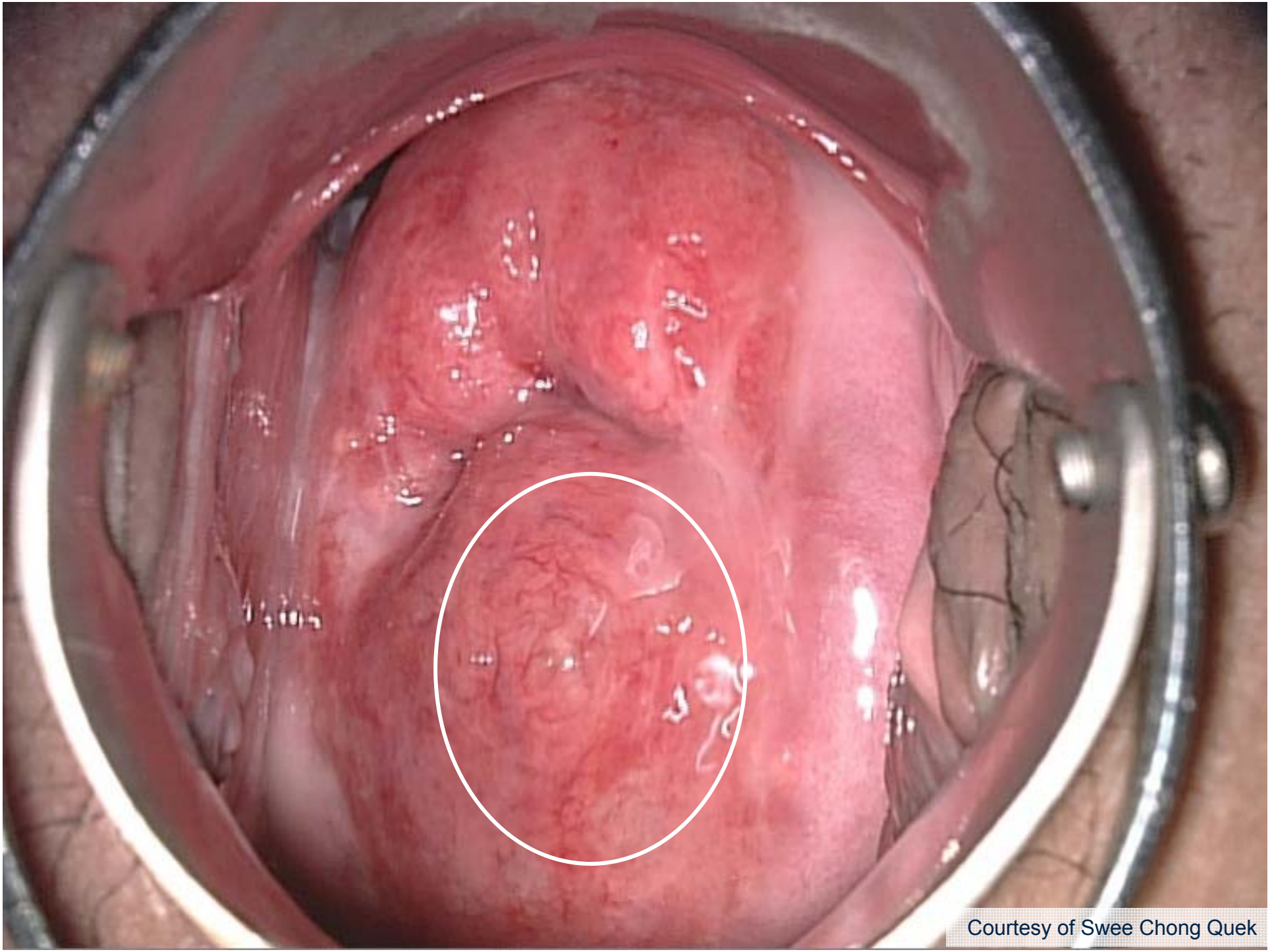
1. Parkin DM, *et al. Vaccine* 2006; **24(Suppl 3):**11-25; 2. Vinh-Hung V, *et al. BMC Cancer* 2007; **7:**164–176; 3. Hildesheim A, *et al. Am J Obstet Gynecol* 1999; **180:**571–577; 4. Bosch FX, *et al. Vaccine* 2008; **26S:**K1–K16; 5. Castellsague X, *et al. JNCI* 2006; **98:**303–315.

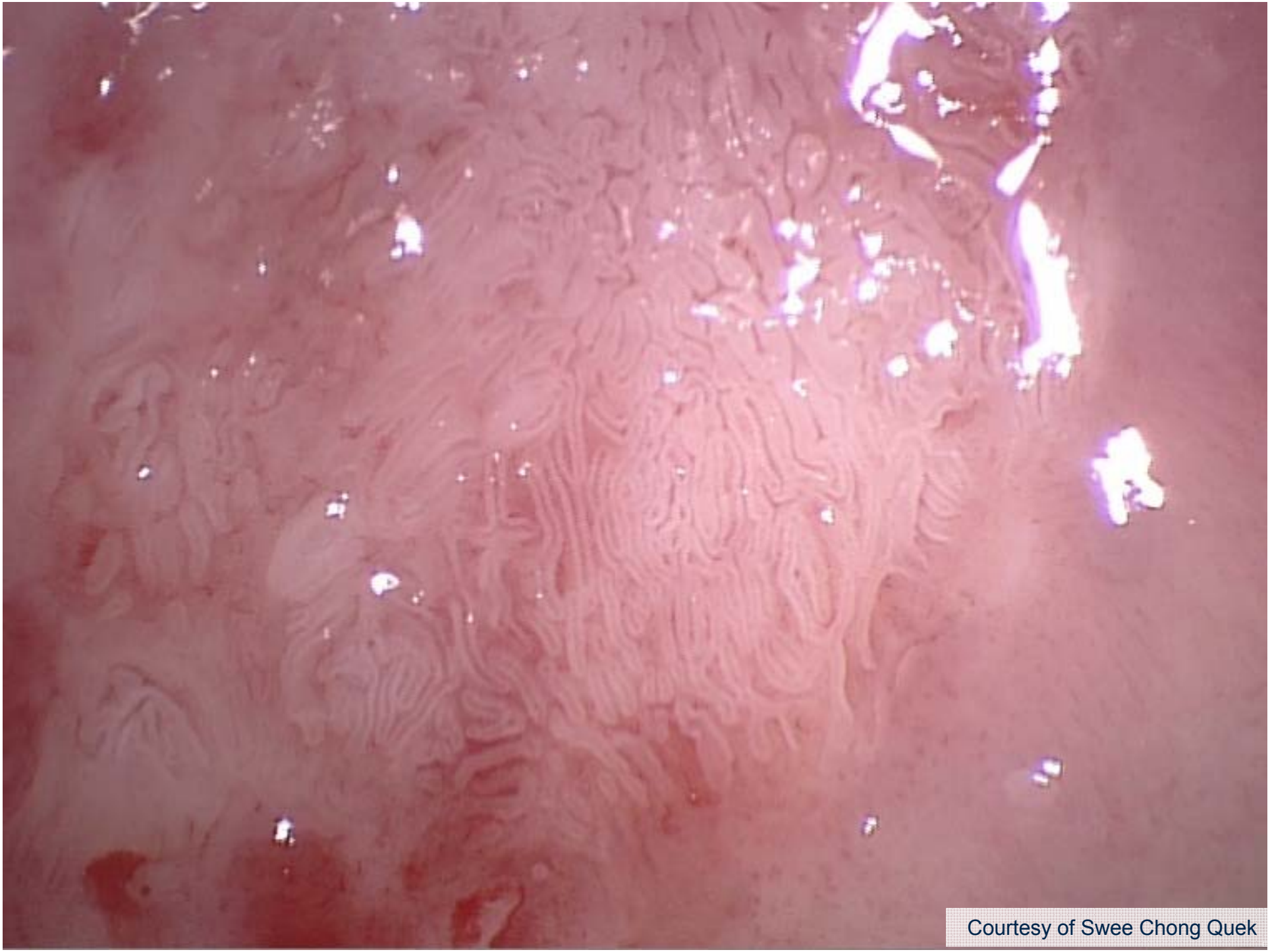
Mrs K

- 45 year old secretary
- 2 children - 18 year old daughter and 16 year old son
- Last pap smear 3 years ago negative
- Referred with pap smear showing "Atypical Glandular cells"[1]

Courtesy of Swee Chong Quek.

National Advisory Committee on Immunization. *Can Commun Dis Rep* 2007; **33:**1–31.


Courtesy of Swee Chong Quek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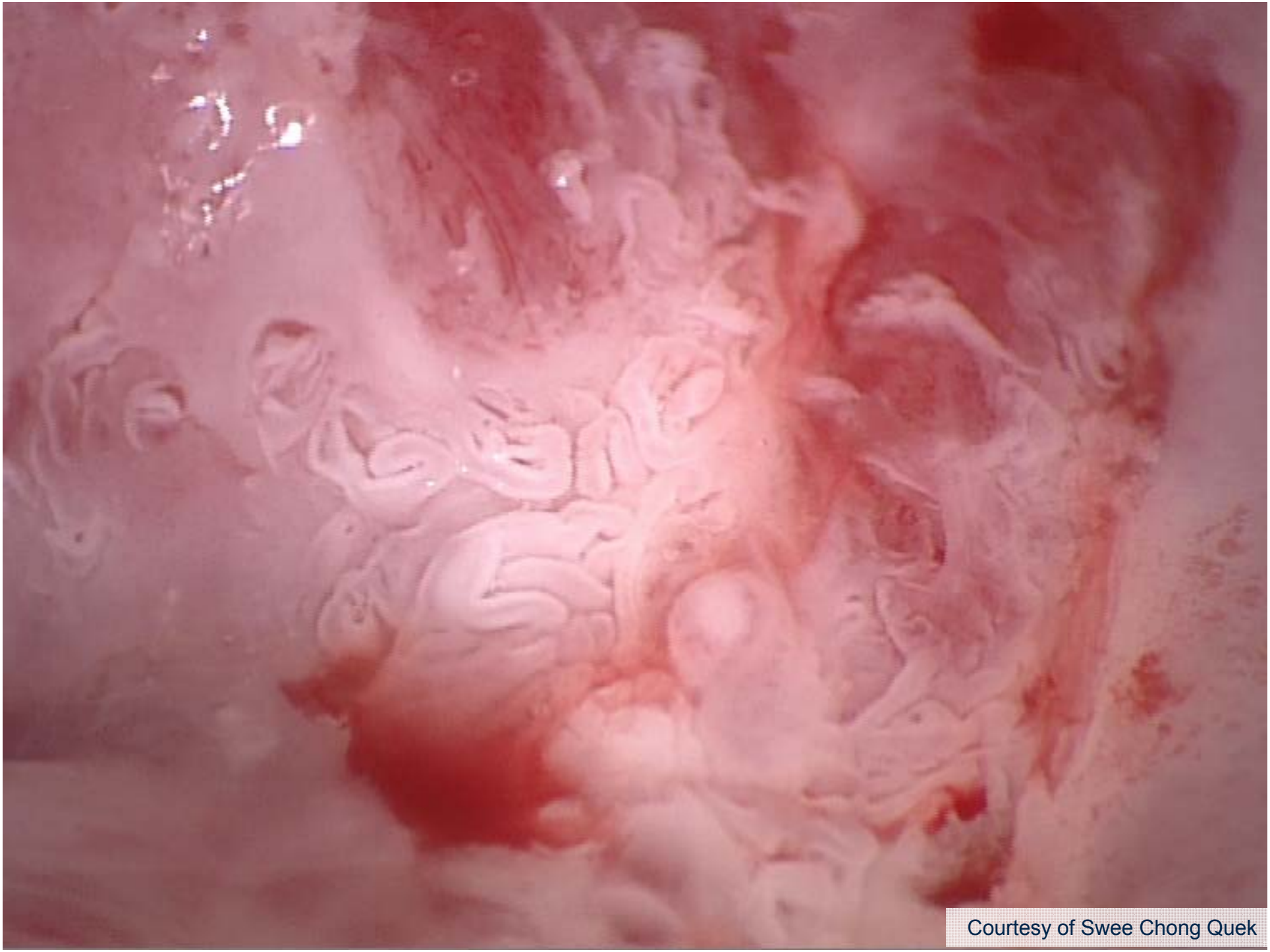
Courtesy of Swee Chong Quek

Treatment

Laser Cone Biopsy

- Adenocarcinoma-in-situ with features suspicious of stromal invasion
- Superficially invasive squamous cell carcinoma, 1.3 mm wide and 1.5mm from surface.
- Resection margins clear of disease

Laparoscopic Hysterectomy 6 weeks later

- No residual disease

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  WAS THIS A FALSE NEGATIVE?
- Referred with pap smear showing "Atypical Glandular cells"[1]

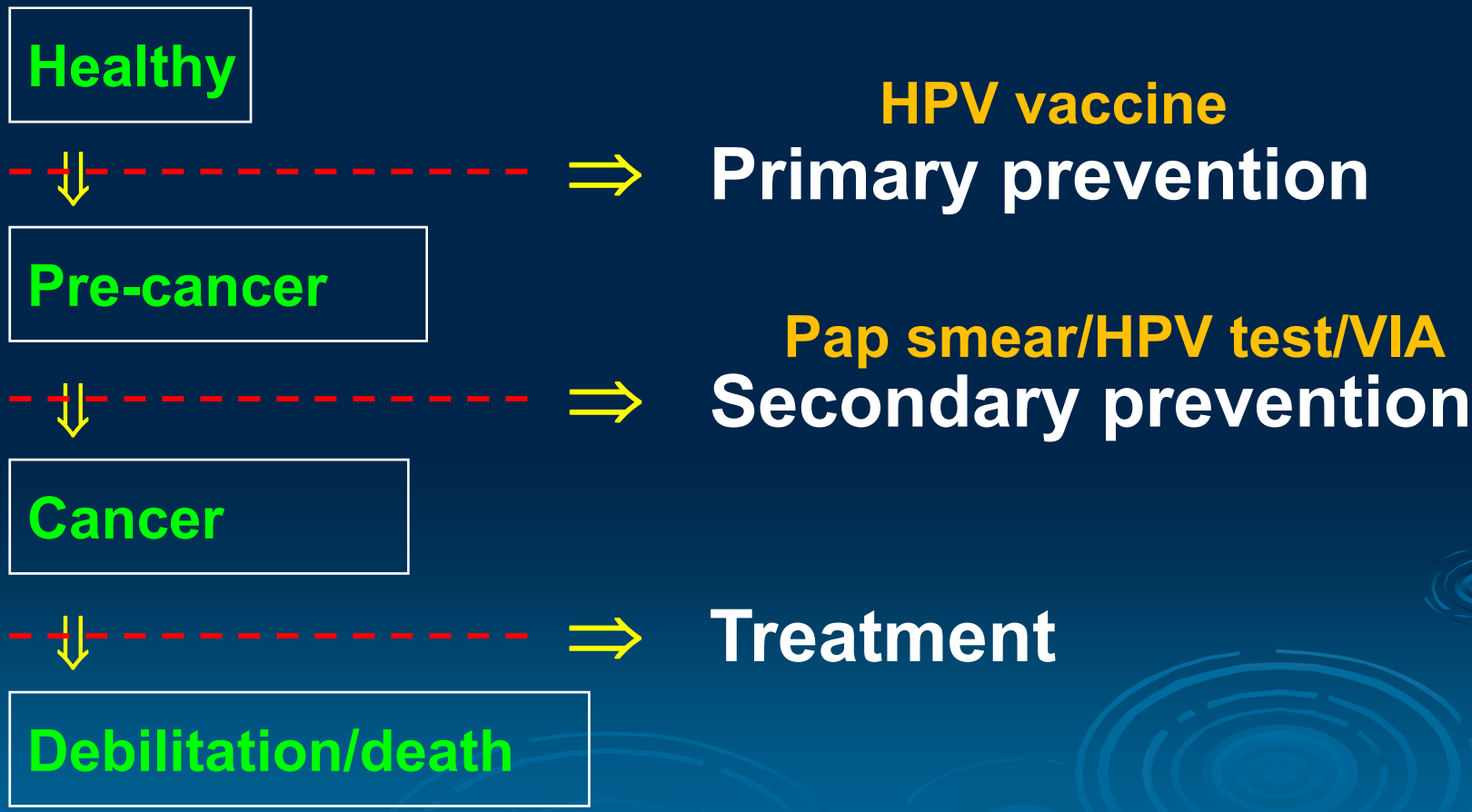
Courtesy of Swee Chong Quek.

National Advisory Committee on Immunization. *Can Commun Dis Rep* 2007; **33:**1–31.

Twin-strategy approach

Screening identifies existing pre-cancerous lesions

Vaccination potentially prevents them occurring in the first place



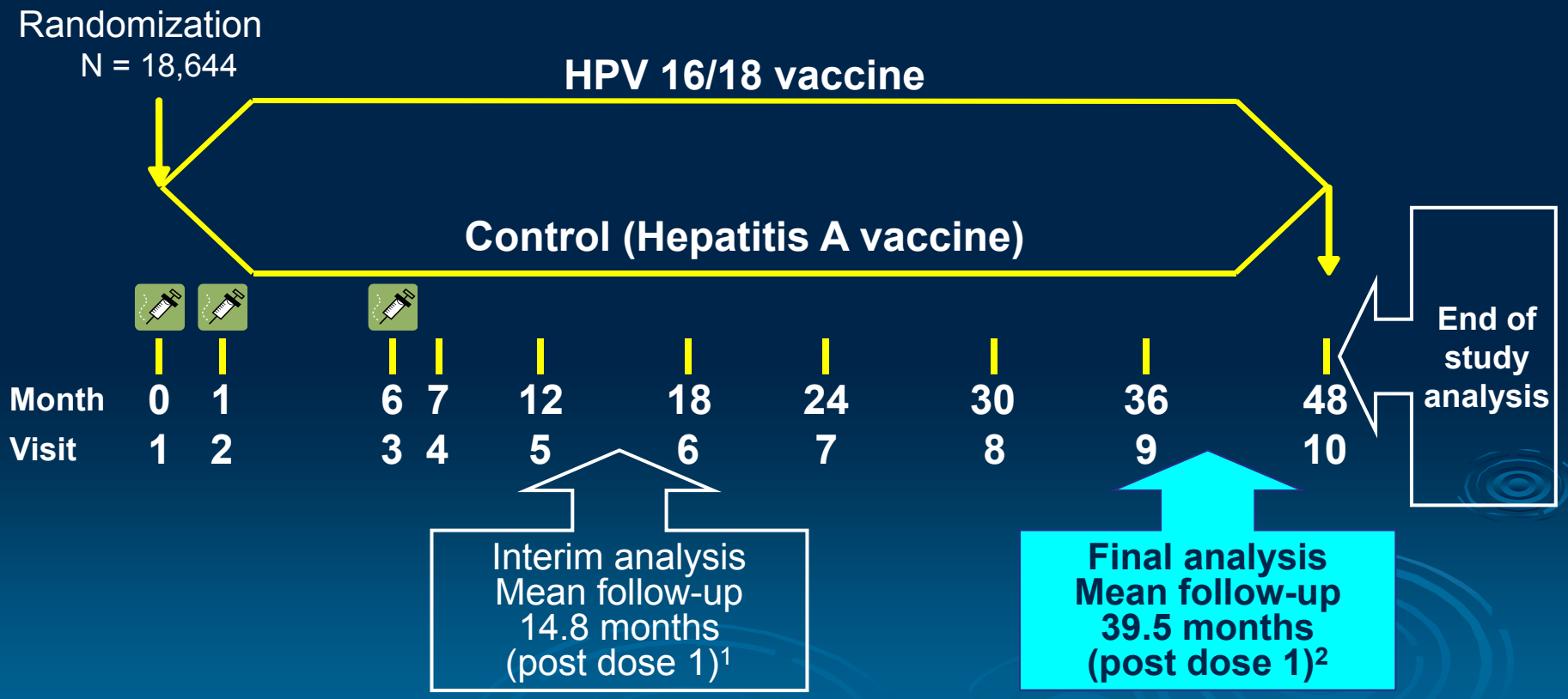
VIA = Visual inspection with acetic acid

Cervarix™

- Does it work?
  - In which age groups?
- Is it safe?
- How long will protection last?

PATRICIA Phase III Trial (Cervarix™)

18,644 women enrolled (15–25 years); Double-blind; randomized 1:1; *Vaccine* vs control (Hep A vaccine); Event triggered interim and final efficacy analyses

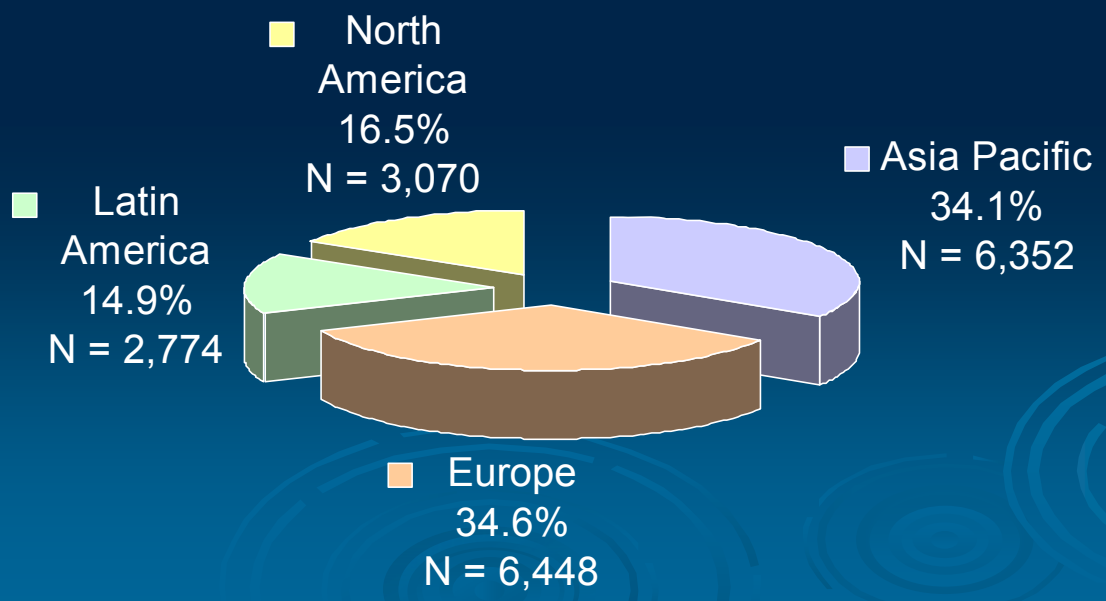


1. Paavonen J, *et al. Lancet* 2007; **369:**2161–2170; 2. Paavonen J, *et al. Lancet* 2009; **374:**301–304.

PATRICIA (HPV-008) demographics

Total Vaccinated Cohort (TVC): 18,644 subjects

- Average age: 20.0 years
- ≤ 6 sexual partners
- 92% of subjects received 3 doses of study vaccine
- 26% current/past infection with HPV 16/18



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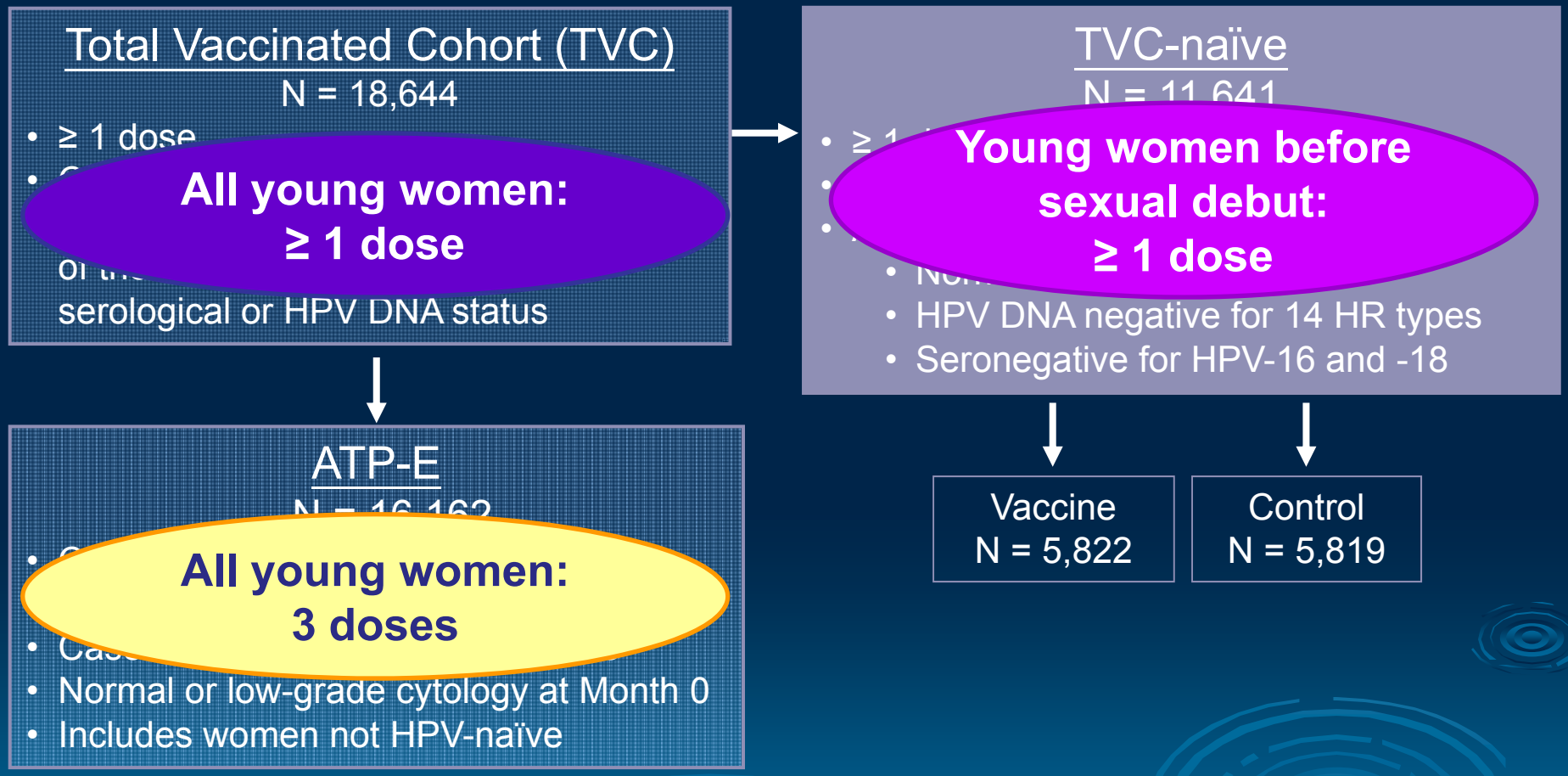
PATRICIA (HPV-008) Study Cohorts



According to Protocol Primary Analysis

ATP-E: According-to-protocol for efficacy; TVC: Total vaccinated cohort; TVC-naïve: Total vaccinated cohort of HPV-naïve women

Paavonen J, *et al. Lancet* 2009; **374:**301–304.

Vaccine efficacy against HPV 16/18 CIN2+

ATP-E

All young women: 3 doses

End-of-study Analysis:

HPV 16/18 Endpoint	Vaccine cases N = 7,338	Control cases N = 7,305	Efficacy %	95% CI	*p*-value
CIN2+ (Pre-specified analysis)	**5**	**97**	**94.9**[3]	87.7–98.4	< 0.0001

1. Paavonen J, *et al. Lancet* 2009; **374**:301–314;
2. GlaxoSmithKline Inc. Canadian Product Monograph for *Cervarix*™. March 2010; 3. Paavonen J, *et al. IPvC* 2010; Poster P-689.

HPV type-assignment algorithm (TAA)
Which HPV Type caused the lesion?

- At final analysis, many lesions containing HPV 16/18 also contained other oncogenic HPV types, therefore, a TAA was applied

- This algorithm assigned the HPV type most likely to be responsible for each lesion
  - HPV type had to be detected in at least 1 of the 2 preceding cytological samples, in addition to detection in the lesion

GlaxoSmithKline Inc. Canadian Product Monograph for *Cervarix*™. March 2010.

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CIN2+ (TAA)	**1**	**92**	**98.9[3]**	93.8–100	< 0.0001

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Vaccine efficacy against HPV 16/18 CIN2+

TVC-naïve

Young women before sexual debut: ≥ 1 dose

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CIN2+ (TAA)	**1**	**93**	**98.9[2]**	93.9–100	< 0.0001

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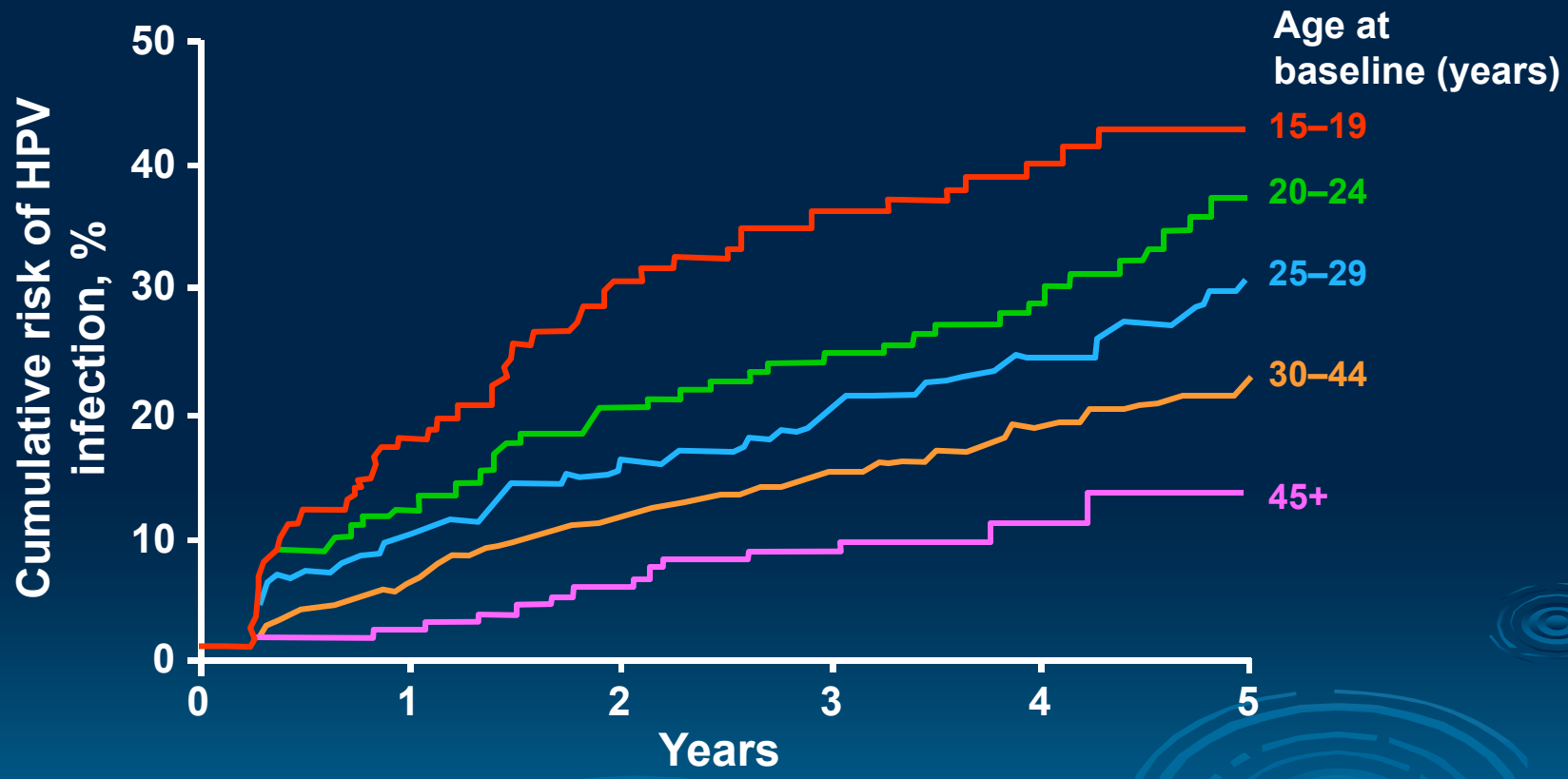
Women continue to acquire new HPV infections



Cohort study, Bogota, Colombia, N = 1,610

Bosch FX, *et al. Vaccine* 2008; **26S:**K1–K16.

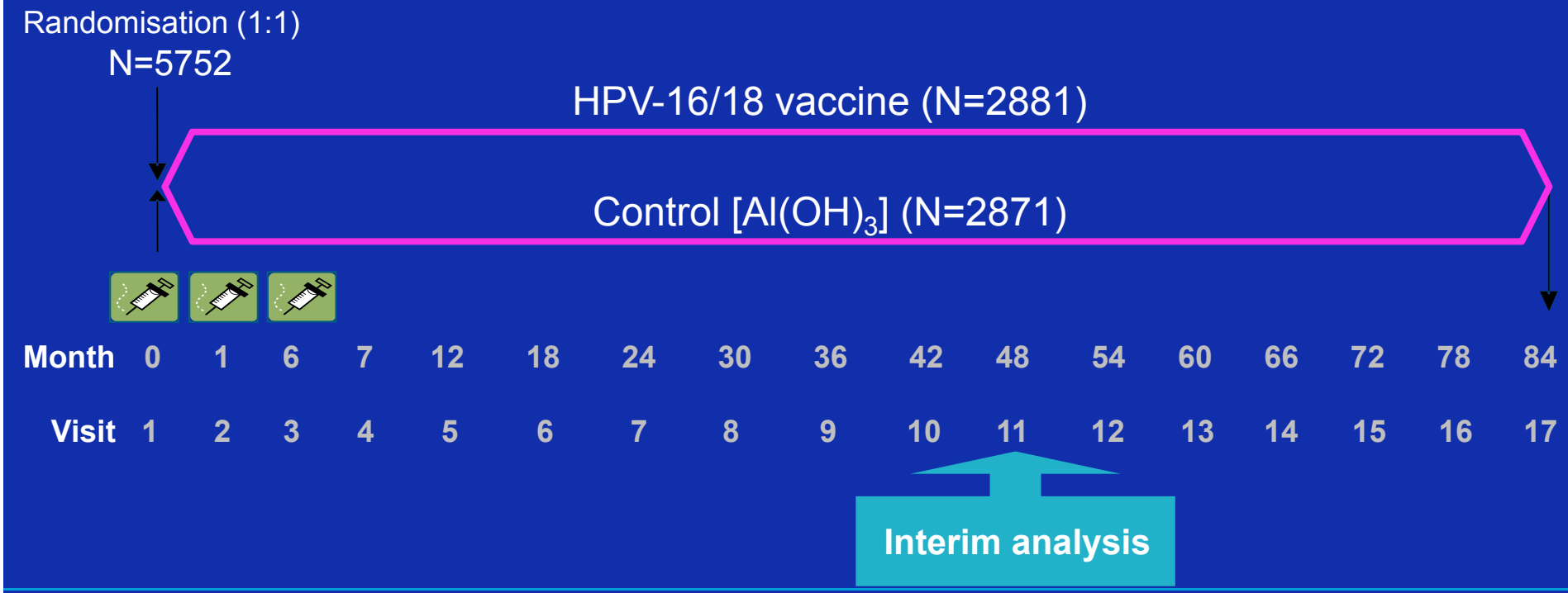
VIVIANE*

- Human PapillomaVIrus: Vaccine Immunogenicity And Efficacy study (HPV015)
- Phase III double-blind, randomised, placebo-controlled, multinational (Asia Pacific, Europe, Latin America and North America) study in women ≥26 years old (N=5752)
- Subjects vaccinated with HPV-16/18 AS04-adjuvanted vaccine or control [$Al(OH)_3$] at Months 0, 1 and 6
- We present results after four years of follow-up

*Study HPV-015; NCT00294047

HPV-015 – Study design
Study design

- Enrolment stratified by
  (1) age: 26–35 years (~45%), 36–45 years (~45%), ≥46 years (~10%)
  (2) previous HPV history (each age stratum included ~15% of women with a history of HPV infection/treatment*)



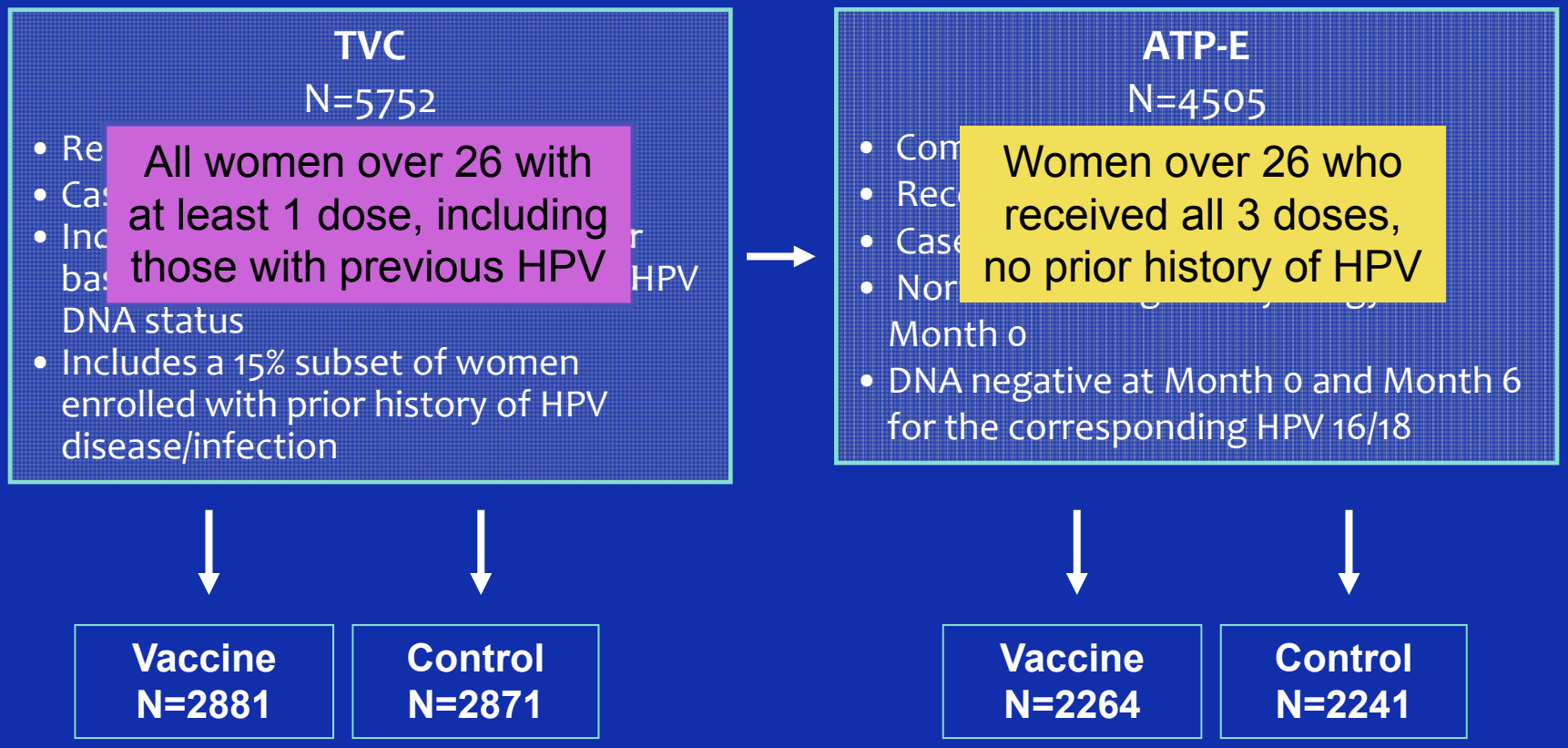
* HPV infection/treatment : two or more abnormal smears in follow-up sequence (approximately 2 to 3 years) or abnormal colposcopy or biopsy/treatment of the cervix

Study objectives

- Co-primary objectives (sequentially evaluated)
  - VE against 6-month persistent infection (PI) and/or CIN1+ lesions associated with HPV-16/18
    - Detection of HPV-16/18 DNA in the lesion only
    - Detection of HPV-16/18 DNA in lesion and preceding cytology samples (HPV type assignment algorithm [TAA])
- Secondary objectives included
  - VE against CIN1+ lesions associated with HPV-16/18
  - VE against 6-month PI associated with any oncogenic HPV
  - VE against ASCUS or greater associated with HPV-16/18
  - Incidences of adverse events

Study population

- Efficacy analyses were performed in the ATP-E and TVC
- Safety was assessed in the TVC



ATP-E, according-to-protocol cohort for efficacy; control, subjects who received aluminium hydroxide; HPV, subjects who received the HPV-16/18 AS04-adjuvanted vaccine; TVC, total vaccinated cohort

VE against persistent infection and/or CIN1+ lesions associated with HPV-16/18

Cohort	Vaccine 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

***Results using the HPV TAA were similar**

ATP-E, according-to-protocol cohort for efficacy; CIN, cervical intraepithelial neoplasia; control, subjects who received aluminium hydroxide; Vaccine, 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

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TVC	90	158	43.9	23.9, 59.0	<0.0001

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TVC	90	158	43.9	23.9, 59.0	<0.0001
6-month PI associated with HPV-16/18					
ATP-E seronegative	6	34	82.9	53.8, 95.1	<0.0001
ATP-E irrespective of serostatus	8	45	82.6	58.9, 93.9	<0.0001

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ATP-E irrespective of serostatus	8	45	82.6	58.9, 93.9	<0.0001
TVC	71	132	47.0	25.4, 62.7	<0.0001

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VE against CIN1+ lesions associated with HPV-16/18

Cohort	Vaccine group (n)	Control group (n)	VE (%)	97.7% CI	P-value
CIN1+ lesions associated with HPV-16/18*					
ATP-E seronegative	1	7	86.1	-35.4, 99.9	0.0368
ATP-E irrespective of serostatus	1	11	91.1	25.4, 99.9	0.0032
TVC	35	56	37.8	-3.2, 63.1	0.0267

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

VE against ASCUS+ associated with HPV-16/18

Cohort	Vaccine group (n)	Control group (n)	VE (%)	97.7% CI	P-value
ATP-E seronegative	2	31	93.7	71.5, 99.5	<0.0001
TVC	38	88	57.2	32.9, 73.3	<0.0001

ASCUS, atypical squamous cells of undetermined significance; ATP-E, according-to-protocol cohort for efficacy; control, subjects who received aluminium hydroxide; Vaccine, subjects who received the HPV-16/18 AS04-adjuvanted vaccine; n, number of cases; TVC, total vaccinated cohort; VE, vaccine efficacy

VE against persistent infection and/or CIN1+ associated with any oncogenic HPV type

Cohort	Vaccine group (n)	Control group (n)	VE (%)	97.7% CI	P-value
6-month PI, any oncogenic HPV type*					
ATP-E DNA- for type analysed	170	217	23.8	3.4, 40.0	0.0090
TVC	441	514	16.0	2.4, 27.7	0.0115

*HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

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

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TVC	56	98	43.6	16.7, 62.2	0.0008

*HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

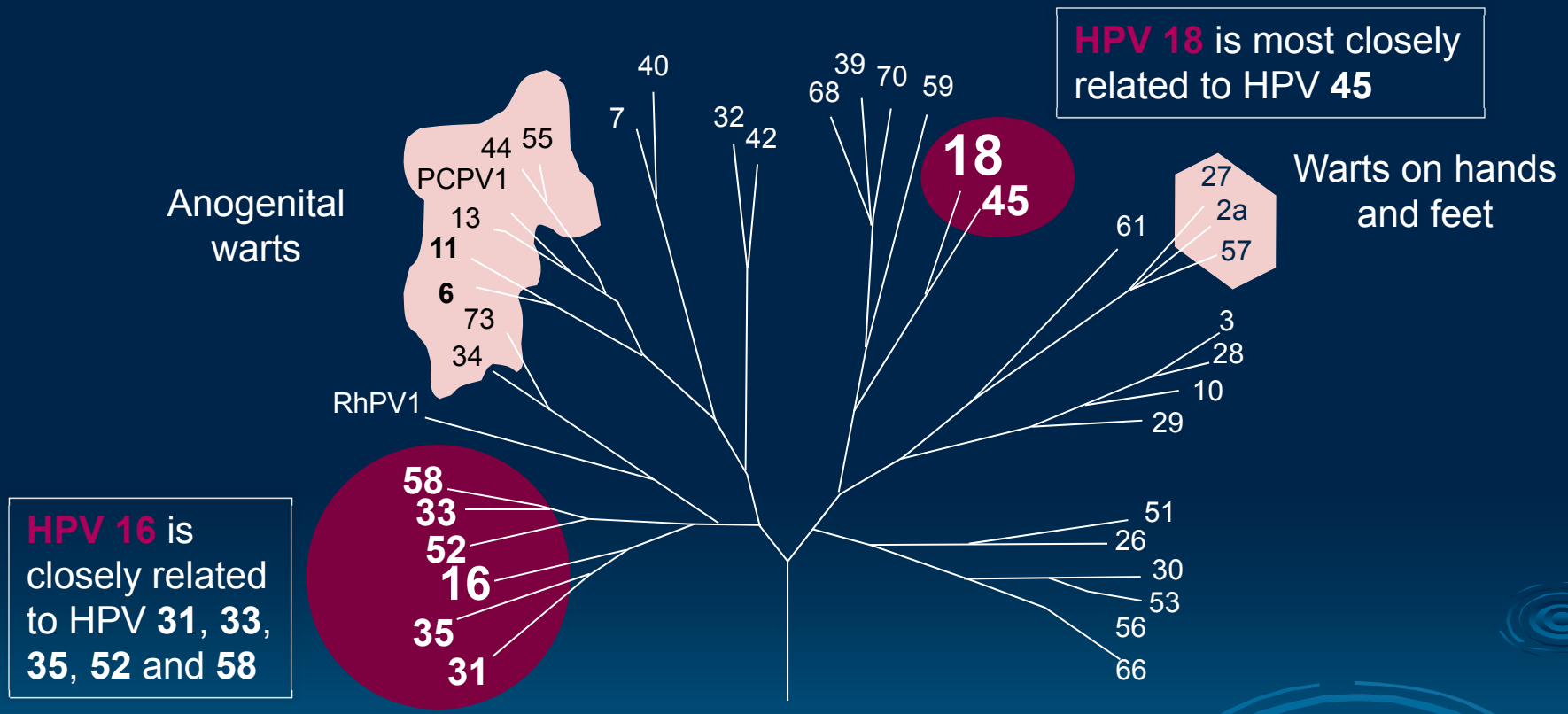
ATP-E, according-to-protocol cohort for efficacy; CIN, cervical intraepithelial neoplasia; control, subjects who received aluminium hydroxide; Vaccine, subjects who received the HPV-16/18 AS04-adjuvanted vaccine; n, number of cases; PI, persistent infection; TVC, total vaccinated cohort; VE, vaccine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

Conclusions of HPV015

- The HPV-16/18 AS04-adjuvanted vaccine showed high efficacy against CIN1+ and/or 6-month PI associated with HPV-16/18 in women aged ≥26 years
- The vaccine was also highly efficacious in preventing cytological abnormalities (ASCUS+) associated with HPV-16/18
- The vaccine showed evidence of cross-protection against 6-month persistent infection associated with HPV-31/45
- The vaccine demonstrated a clinically acceptable safety profile

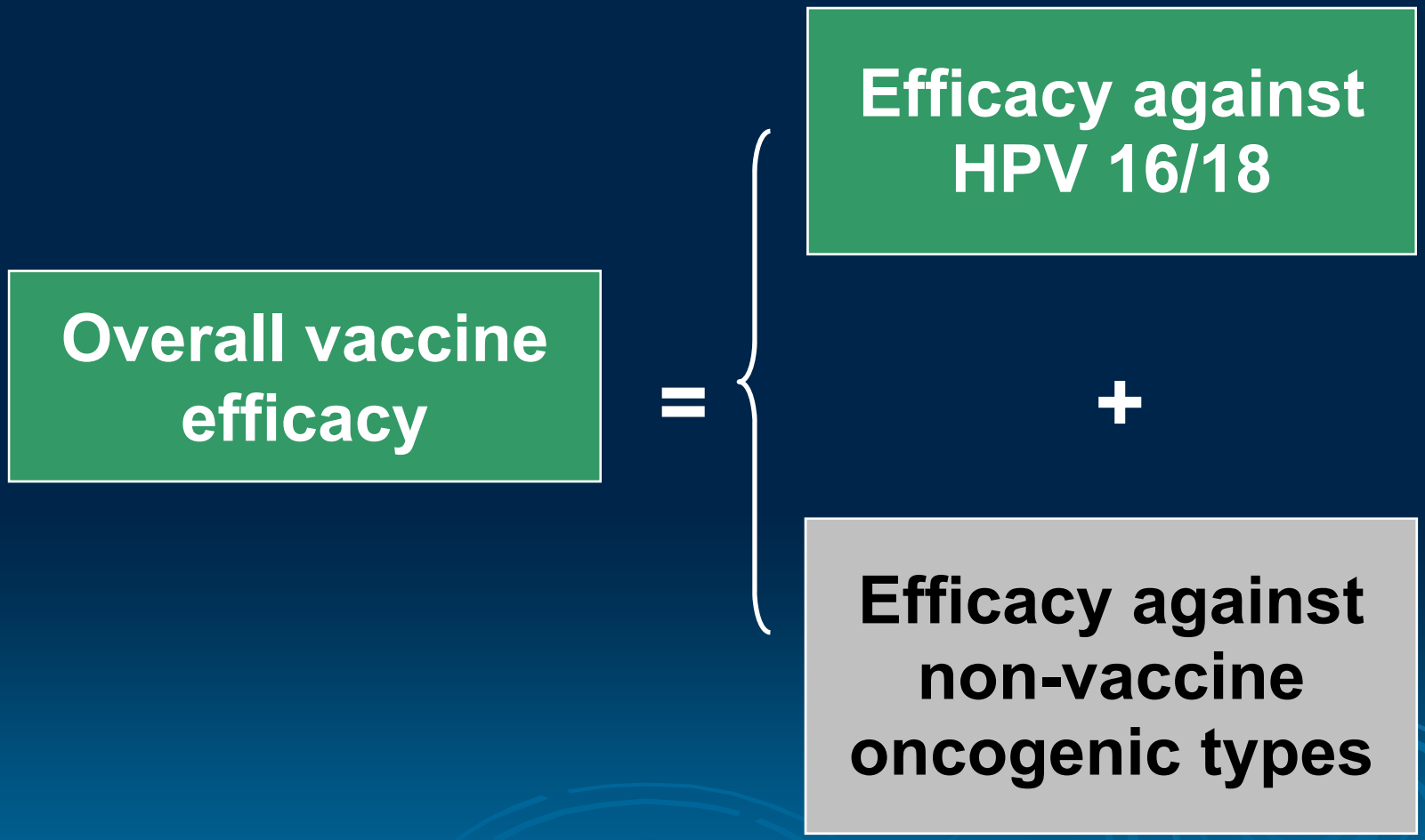
Cross Protection
Efficacy beyond HPV types 16 and 18

Papillomavirus phylogenetics: the reason behind cross-protection



Adapted from de Villiers EM, *et al. Virology* 2004; **324:**17–27.

Efficacy of HPV Vaccines



PATRICIA : Overall Efficacy of *Cervarix*™ Against CIN2+ Irrespective of HPV Type in a Lesion

Young women before sexual debut: ≥ 1 dose

- Total vaccinated cohort-naïve (TVC-naïve)
- Estimated worldwide prevalence of HPV 16/18 in high-grade lesions (CIN2/3) is 52%[1]

Final Analysis

Endpoint	Vaccine efficacy	
	%	96.1% CI
CIN2+ irrespective of HPV type in lesion, DNA negative for all high-risk HPV types at baseline	70.2[2]	54.7–80.9

1. Smith JS, *et al. Int J Cancer* 2007; **121:**621–632;
2. Paavonen J, *et al. Lancet* 2009; **374:**301–304.

Overall vaccine efficacy against CIN3+ irrespective of HPV type in the lesion

TVC-naïve

Young women before sexual debut: ≥ 1 dose

- Up to 70% of CIN3 is caused by HPV16/18

End-of-study Analysis:

Endpoint	Vaccine cases N = 5,466	Control cases N = 5,452	Efficacy %	96.1% CI	*p*-value
CIN3+	**3**	**44**	**93.2**	78.9–98.7	< 0.0001

Paavonen J, *et al. IPvC* 2010; Poster P-689.

Vaccine efficacy against CIN2+ due to oncogenic non-vaccine HPV types (PATRICIA)

TVC-naïve

Young women before sexual debut: ≥ 1 dose

End-of-study Analysis:

HPV type	CIN2+ (pre-specified analysis)		
	Vaccine cases N = 5,466	Control cases N = 5,452	Vaccine efficacy, % (95% CI)
HPV 31	3	28	89.4 (65.5–97.9)
HPV 33	5	28	82.3 (53.4–94.7)
HPV 45	0	8	100 (41.7–100)

Romanowski B. *IPvC* 2010; Abstract 416.

Potential Impact of Cross Protection

- Protection against HPV 16/18: up to 52% of CIN2+[1] and up to 71% of cervical cancer could be prevented[2]
- The cross-protection observed could result in an additional 11% to 16% of cervical cancer protection[3]
- HPV 16, 18, 31 and 45 account for > 90% of adenocarcinoma[2]
- Impact on CIN2/3 observed within 5–10 years[4]
- Impact on cervical cancers observed within 10–20 years[4]

1. Smith JS, *et al. Int J Cancer* 2007; **121:**621–632.
2. De Sanjose, *et al. Lancet Oncol* 2010; **11:**1048–1056;
3. Paavonen J, *et al. Lancet* 2009; **374:**301–314;
4. Cuzick J, *et al. BJC* 2010; **102:**933−939.

Cervarix™

- Does it work?
- Is it safe?
- How long will protection last?

BBC NEWS

1 October, 2009

Cancer jab girl 'died of tumour'

A girl who was vaccinated against cervical cancer died from a malignant tumour of the chest and not from a reaction to the jab, it has emerged.

Natalie Morton, 14, died after being given the injection at the Blue Coat Church of England School in Coventry.

Deputy coroner for Coventry Louise Hunt said the vaccine was not thought to have been a contributing factor. A pathologist said her undiagnosed condition was "so severe that death could have arisen at any point".

Natalie collapsed less than two hours after being given the *Cervarix* vaccine on Monday and was pronounced dead at Coventry's University Hospital.

The deputy coroner, who opened and adjourned the hearing at Coventry Magistrates' Court, said: "It appears that Natalie died from a tumour in her chest involving her heart and her lungs." The inquest was told that the tumour had "heavily infiltrated" her heart and extended into her left lung.

Safety issues

- Important to distinguish “temporality” from “causality”
- Take into account the “background rates” of diseases when assessing individual reports of adverse events[1]

Siegcrist CA *et al, Pediatr Infect Dis J* 2007; **26:**979-984.

Cervarix™ Vaccine: UK post-marketing surveillance

- UK MHRA 2-year safety report, October 2010:
  - "Following administration of at least 4.5 million doses across the UK, the balance of risks and benefits of AS04-adjuvanted bivalent HPV vaccine remains positive"[1]
  - "The vast majority of suspected adverse reactions reported continue to be either recognized side effects listed in the product information or symptoms related to the injection process (i.e. 'psychogenic' in nature such as faints)"[1]

Worldwide distribution of doses to date:
> 25 million doses

1. MHRA. 2010. Available at: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Productspecificinformationandadvice/Product-specificinformationandadvice%E2%80%93G%E2%80%93L/HumanpapillomavirusHPVvaccine/index.htm. Accessed October 2010

Safety (PATRICIA)

TVC

All young women: ≥ 1 dose

End-of-study Analysis

Outcome	Vaccine (N = 9,319) % (n)	Control (N = 9,325) % (n)
Serious adverse events	**9.0** (835)	**8.9** (829)
Medically significant conditions	**35.4** (3,298)	**36.2** (3,378)
New-onset autoimmune disease	**1.1** (99)	**1.0** (95)
Pregnancy*		
Congenital anomalies	**1.2** (26)	**1.0** (22)
Spontaneous abortion	**9.1** (205)	**8.6** (195)

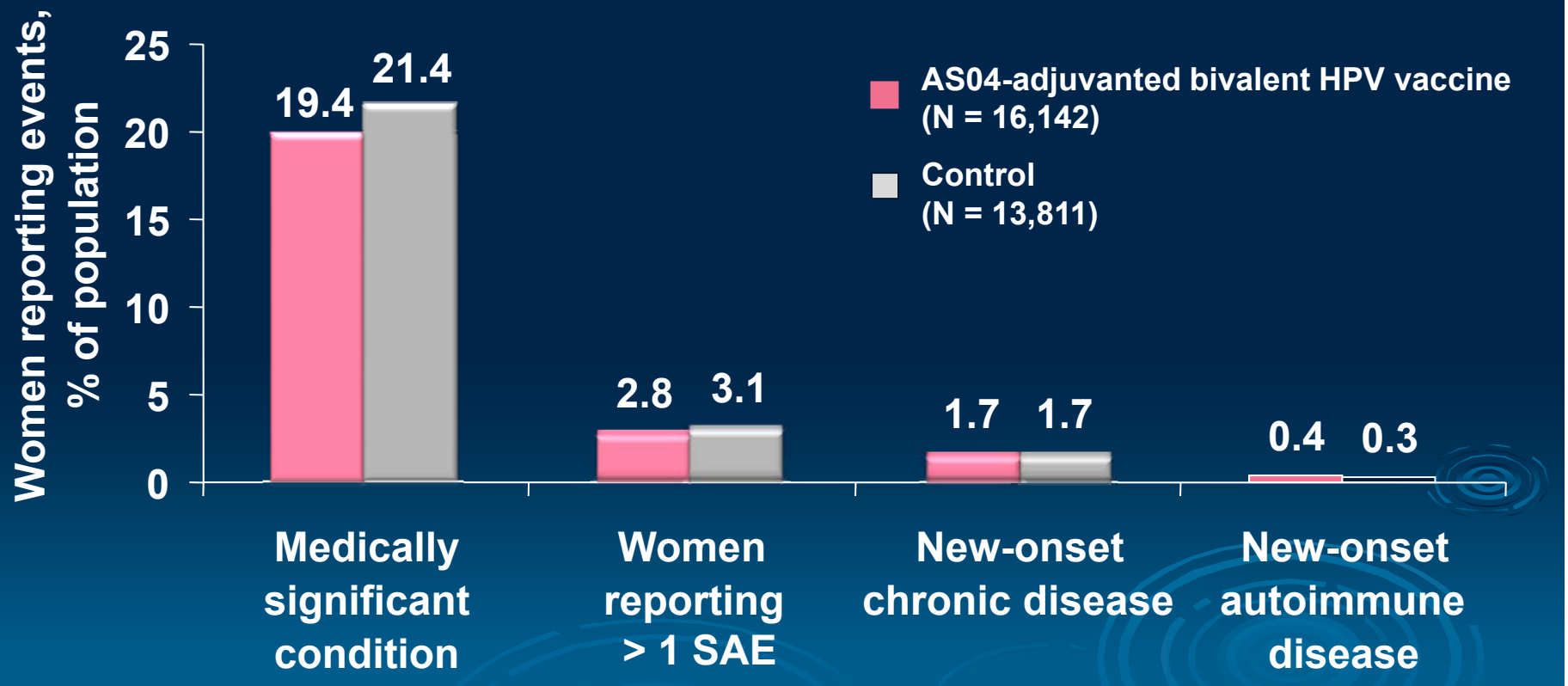
- The most common adverse events were due to local reactogenicity

* The data are insufficient to recommend use of AS04-adjuvanted bivalent HPV vaccine during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

Paavonen J, *et al. IPvC* 2010; Poster P-689.

Cervarix™ Vaccine Pooled Studies: Safety Analysis

Eleven studies with same vaccination schedule and similar methodology of safety assessment



SAE = severe adverse event.

Descamps D, *et al. Hum Vaccin* 2009; **5**:1–9.

HPV vaccines: safety and approval

- WHO's Global Advisory Committee on Vaccine Safety (GACVS) concluded that both *Cervarix*™ and *Gardasil*® had good safety profiles[1]
- U.S. Food and Drug Administration (FDA) approved *Cervarix*™ for use in girls and women aged 10–25 years on 16 October 2009[2]

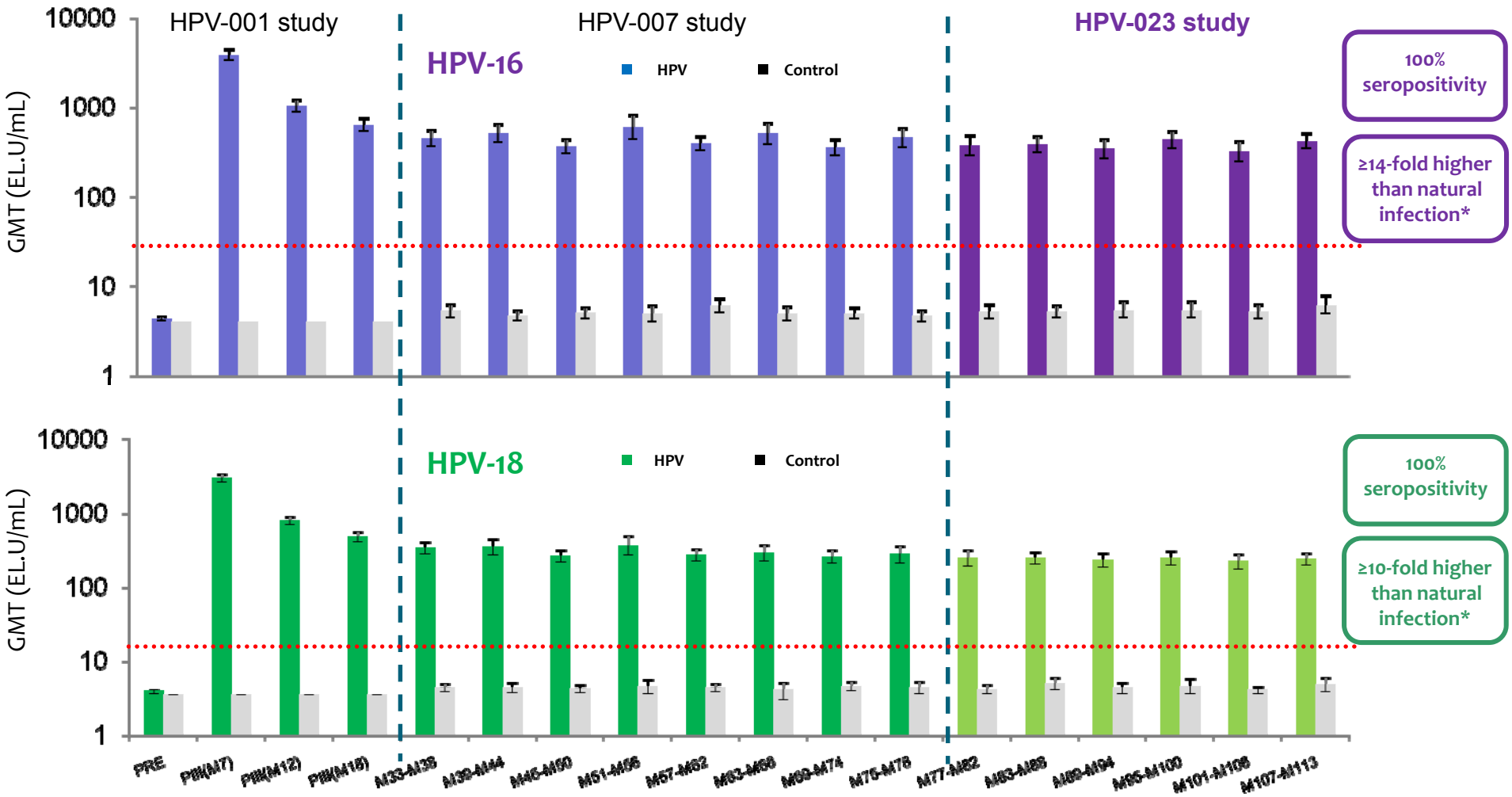
Gardasil is a registered trade mark of Merck & Co., Inc.

1. http://www.who.int/wer/2009/wer8415.pdf. Accessed Feb 2010;
2. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186959.htm. Accessed Feb 2010.

Cervarix™

- Does it work?
- Is it safe?
- How long will protection last?

Immunogenicity up to 9.4 years (ELISA)
(HPV-023 ATP immuno cohort)



Red line indicates natural infection levels

*Antibody levels in women (seropositive and DNA-negative) from a phase III study who cleared a natural infection before enrolment (Paavonen J *et al. Lancet* 2007;**369:**2161–2170)

HPV010 “Head to Head Trial”

Comparing the immunogenicity and safety of *Cervarix*™ and *Gardasil*® in women aged 18–45 years

Multicenter, Observer Blind, Randomized Phase IIIb Trial Comparing the Immunogenicity of *Cervarix*™ and *Gardasil*® (HPV-010 Study) Using Pseudovirion-based Neutralization Assay

Study design and methodology

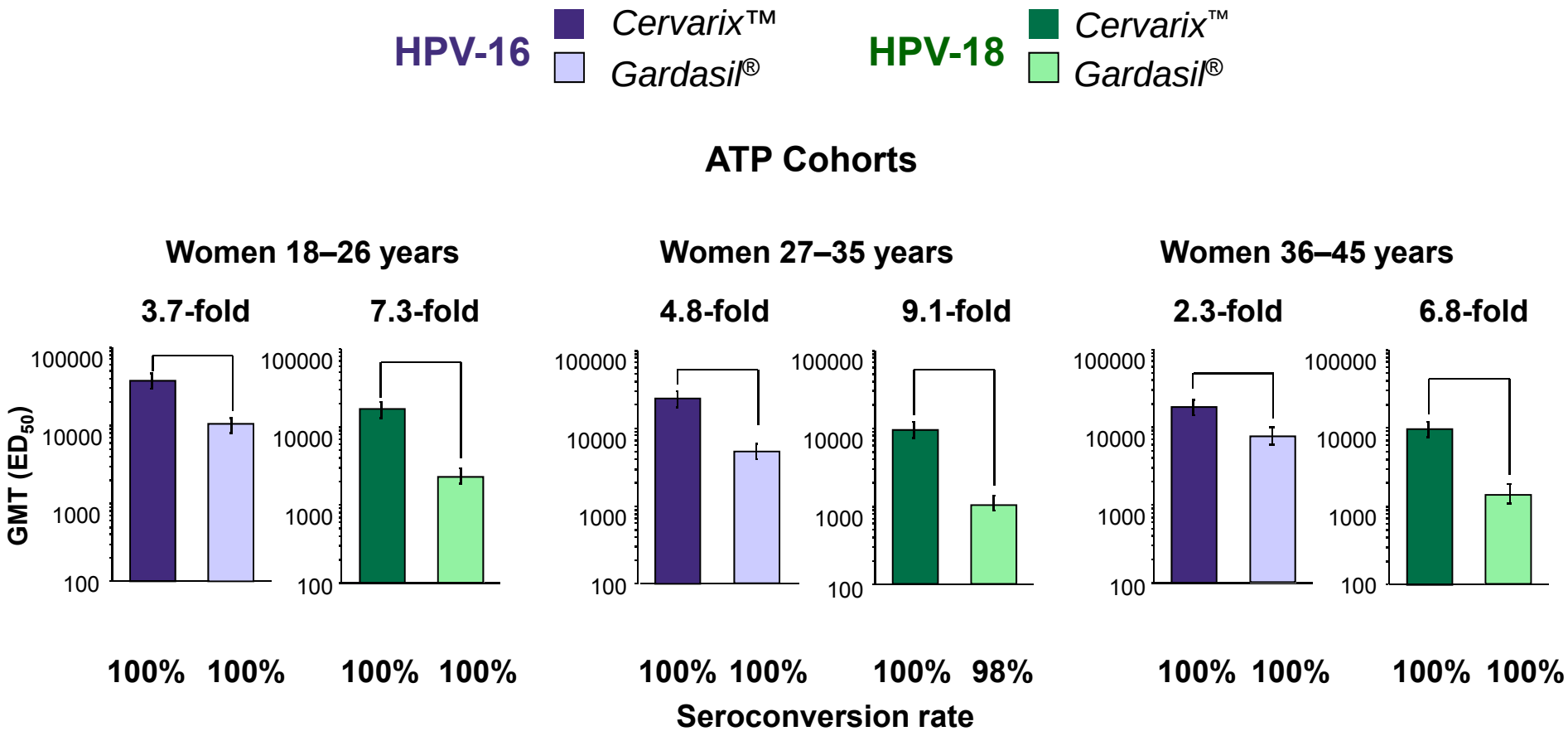
- Stratified by age (18–26, 27–35, 36–45 years) (N=1,106)
  - Randomized (1:1) to receive *Cervarix*™ or *Gardasil*® according to their recommended administration schedules

Month 0	Month 1	Month 2	Month 6
Cervarix™	*Cervarix*™	Placebo $Al(OH)_3$	*Cervarix*™
Gardasil®	Placebo $Al(OH)_3$	*Gardasil*®	*Gardasil*®

Cervarix™: 20 µg HPV16; 20 µg HPV18 & AS04
Gardasil®: 40 µg HPV16; 20 µg HPV18; 20 µg HPV6; 40 µg HPV11 & amorphous aluminum hydroxyphosphate sulfate

Einstein M et al. Abstract and presentation at 25th IPC, Malmö, Sweden, 2009

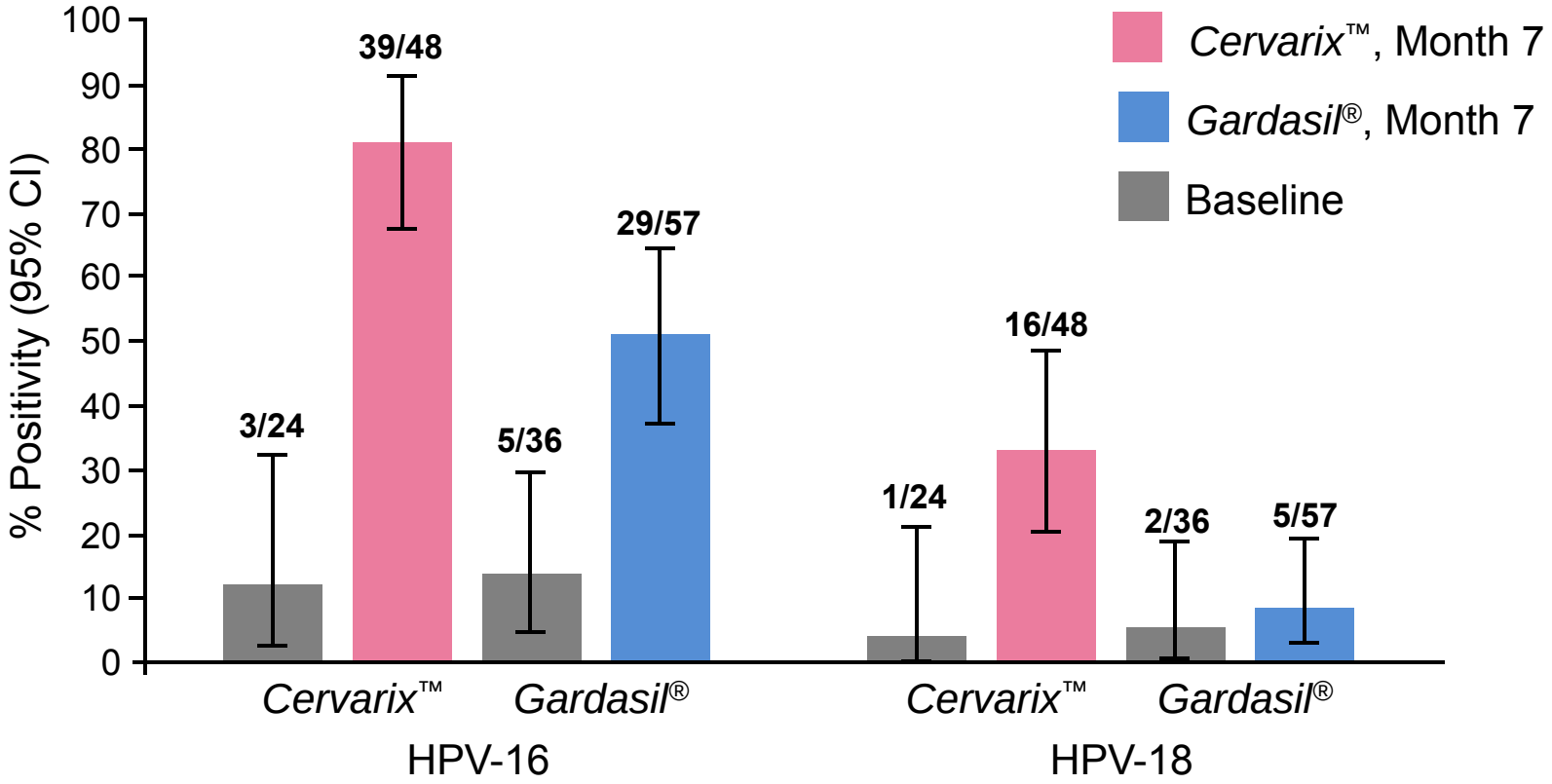
HPV 16 and 18 Neutralizing Antibody Responses: GMTs, GMT Ratio and Seroconversion Rate - Month 7



Einstein MH, on behalf of the HPV-010 study group. 25th International Papillomavirus Conference (Abstract O-01.02), 2009.
GSK. Data on file. 2009.

Comparative Study (HPV-010)
Neutralizing Antibodies in Cervico-vaginal Secretions (PBNA)

Positivity rates* at Month 7 for HPV-16 and -18 antibodies measured in cervico-vaginal secretions (CVS) by PBNA (ATP cohort)**

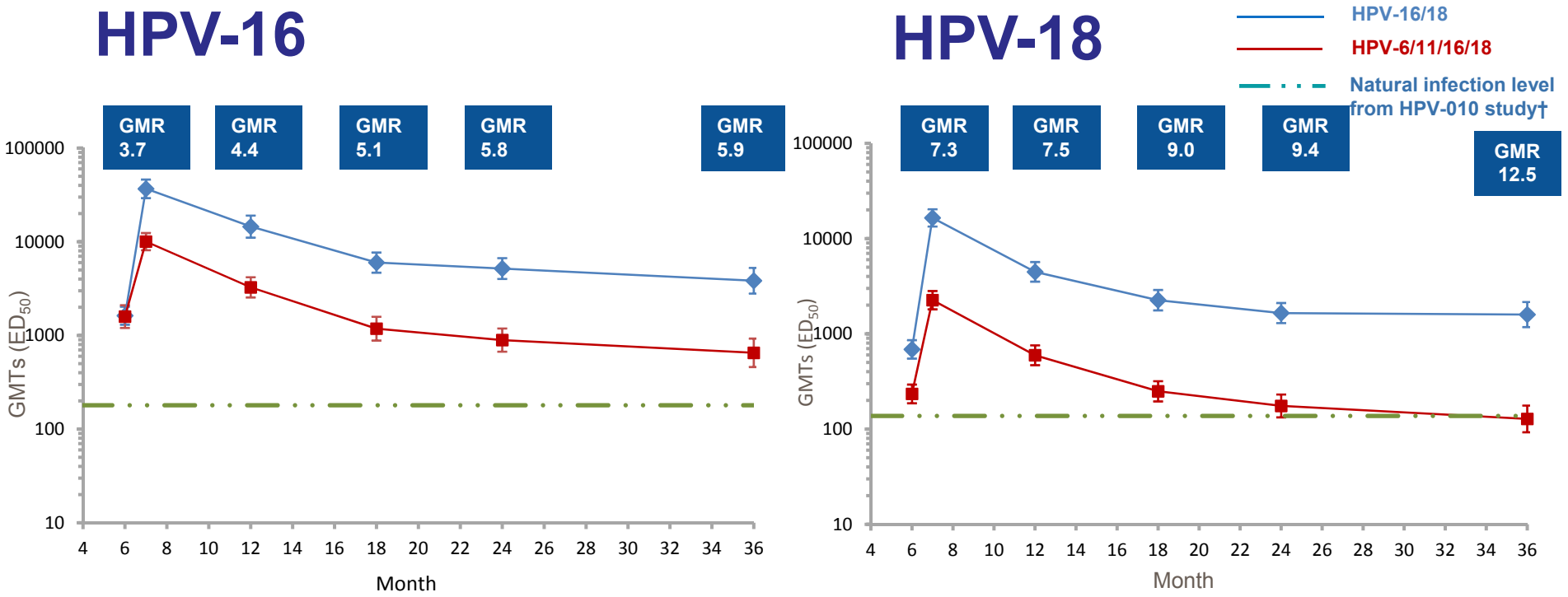


*Neutralizing antibody positivity defined as a CVS dilution greater than or equal to the assay threshold of 40 ED_{50} for each antigen with both vaccines

**ATP cohort: according-to-protocol cohort

Einstein M et al. Abstract and presentation at 25th IPC, Malmö, Sweden, 2009

Serum neutralizing antibody response (PBNA) through Month 36 (women 18–26 years*)



- **GMTs were also consistently higher with the HPV-16/18 vaccine in the older age groups (27–35 and 36–45 years)**
- **GMRs increased consistently over time for both HPV-16 and -18**
- **There was strong correlation between PBNA and ELISA antibody responses**

LR1

*ATP cohort for immunogenicity, subjects HPV DNA-negative and seronegative at baseline

†Natural infection defined as GMTs in women from the HPV-010 study (NCT00423046) who had cleared a natural infection before enrolment (i.e., those who were seropositive and DNA-negative at Month 0; Einstein MH *et al*. *Hum Vaccine* 2009; 5:1–15)

PBNA, pseudovirion-based neutralization assay; GMTs, geometric mean titers; GMRs, geometric mean ratios

Slide 54

LR1 TO MARIE: Please check definition of natural infection in footnote

Also please check ELISA serocurve slide in back-up (slide 15)
Lucy Reiman, 3/21/2011

Summary "Head to Head" Immune Parameters

- In general, *Cervarix™* induced a stronger immune response than *Gardasil®* against HPV 16 and 18 at Months 7, 12, 18, 24 & 36 for all analysed immune parameters:
  - Serum neutralizing antibodies
  - Cervico-vaginal secretions neutralizing antibody positivity rates

1. Einstein MH, *et al*. *Hum Vaccin* 2009; 5:705–719. 2. Einstein MH, *et al. ESGO* 2009; Abstract; 3. Einstein MH, *et al. IDSA* 2009; Abstract. 4. Einstein MH, *et al. EUROGIN* 2010; Abstract.

FR4

Conclusion I

- Traditional screening with Pap smears not a realistic option in many resource-poor settings
- Where screening is available, there are often limitations in terms of program efficacy, coverage and the quality of the test
- Adenocarcinomas account for up to 20% of all invasive cancers and are often missed on screening
  - Globally, most commonly associated with HPV 16, 18 & 45

Slide 56

FR4 Note to Faculty: The first bullet has been updated to reflect the GLOBOCAN 2008 data previously included
Faye Reddington (MTM), 6/30/2010

Conclusion II

- Females prior to sexual debut are most likely to benefit from vaccination, but women who are sexually active will also benefit, including those over age 26
- The Bivalent HPV vaccine (*Cervarix™)* has a clinically acceptable safety profile, with more than 25 million doses distributed since launch in 2007[1]
- Duration of protection likely to be long-lasting as predicted from immunogenicity studies

1. GSKBio_WWMA_DoF025_5_2010.

Thank you…

…for your attention