



GlaxoSmithKline
Biologicals

GSK Cervical Cancer Vaccine: Overview of Clinical Data

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Regional Medical Affairs – HPV Vaccines

GSK Biologicals

Asia Pacific, Australasia, China/Hong Kong, Japan

“An ounce of prevention is worth a pound of cure”

PREVENTION Concept originated from China since 2600 BC

- *“A Sage cures a disease BEFORE it occurs, and deals with a disorder BEFORE it happens”*
- *Superior doctors PREVENT the disease; Mediocre doctors treat the disease BEFORE clinical evidence; Inferior doctors treat the disease AFTER clinical evidence*

上医医未病之病
中医医将病之病
下医医已病之病
~ 黄帝内经 ~



*“The Yellow Emperor’s Canon of Internal Medicines”,
Huang Di Nei Jing
《黄帝内经》*



**'What is the value of that
which protects something
as precious as
life itself?'**

Predicted Number of Cervical Cancer Cases In 2020 By World Area and Age

GLOBOCAN 2002	2002	2020 (% change)	2020 % burden
World	493,000	702,500 (42%)	100%
Women aged <65	396,500	549,000 (38%)	78%
Women aged ≥65	96,500	153,500 (59%)	22%
Less devel. areas	409,000	639,500 (56%)	83%
Women aged <65	336,000	507,500 (51%)	79%
Women aged ≥65	73,000	132,000 (80%)	21%
More devel. areas	83,000	92,500 (11%)	17%
Women aged <65	60,000	62,500 (30%)	67%
Women aged ≥65	23,000	30,000 (31%)	33%



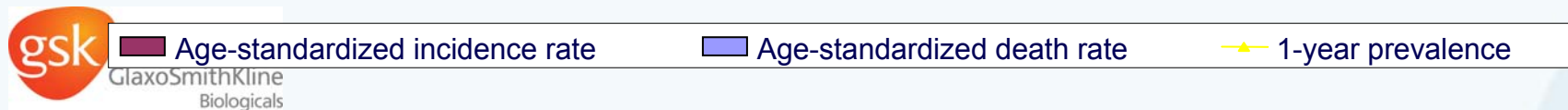
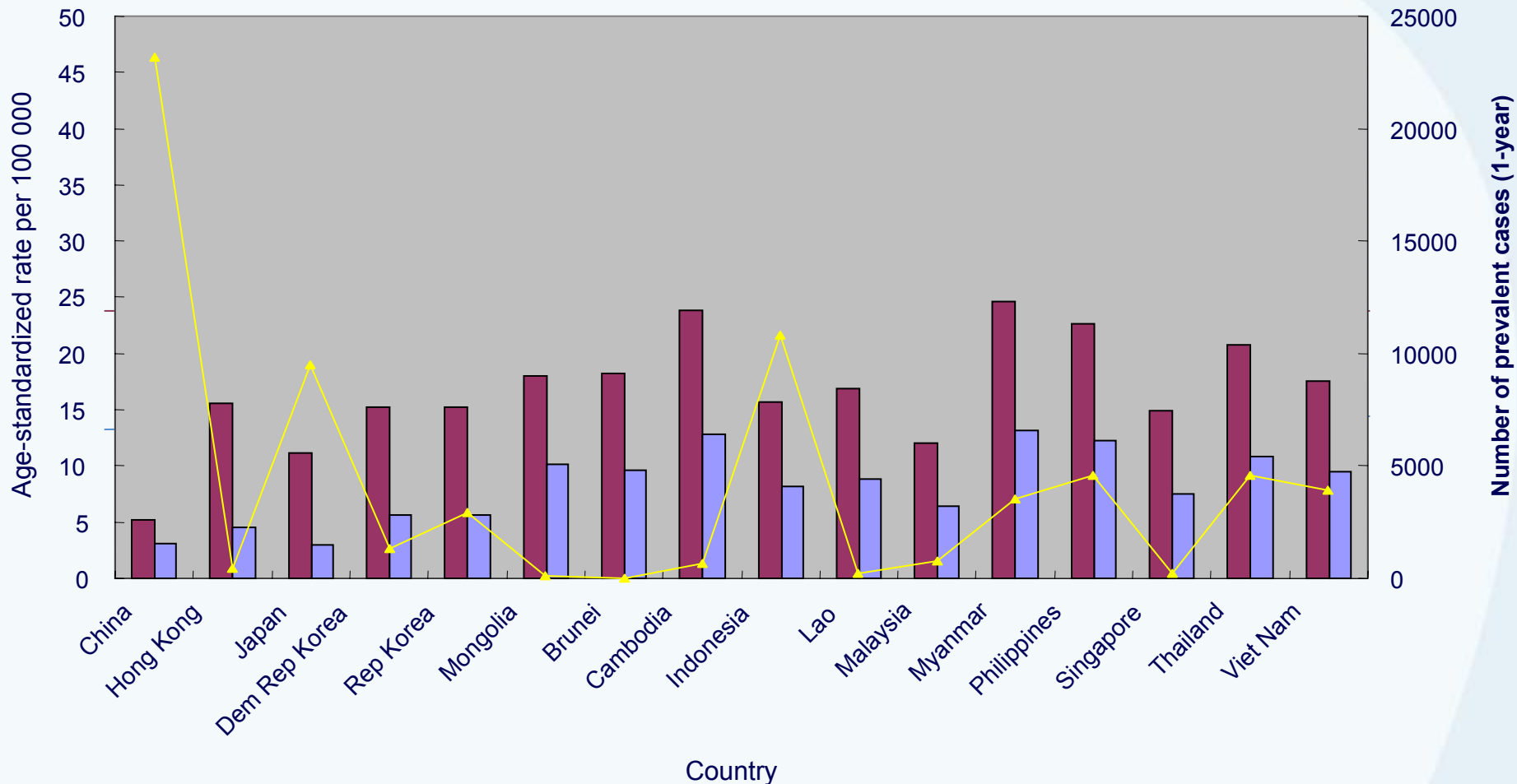
Projections assume rates estimated for 2002 hold into the future.

HPV infection-attributable cancer in 2002 (Developed and developing countries)

SITE	Attrib to HPV (%)	DEVELOPED COUNTRIES			DEVELOPING COUNTRIES		
		TOTAL cancers	Attrib to HPV	% all cancer	TOTAL cancers	Attrib to HPV	% all cancer
CERVIX	100	83,400	83,400	1.7%	409,400	409,400	7.0%
PENIS	40	5,200	2,100	0.0%	21,100	8,400	0.1%
VULVA, VAGINA	40	18,300	7,300	0.1%	21,700	8,700	0.1%
ANUS	90	14,500	13,100	0.3%	15,900	14,300	0.2%
MOUTH	3	91,200	2,700	0.1%	183,100	5,500	0.1%
ORO PHARYNX	12	24,400	2,900	0.1%	27,700	3,300	0.1%
ALL SITES		5,016,100	111,500	2.2%	5,827,500	449,600	7.7%

Cervical Cancer in Asia: By Country

Incidence, Prevalence and Mortality



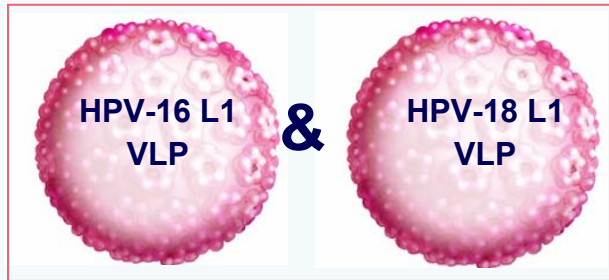
GSK's Cervical Cancer Vaccine: Development Vision

- **Every sexually active woman is at risk of oncogenic HPV**
 - ➔ **Our objective is to develop a vaccine which targets prevention of cervical cancer in females from 10 years onwards**

- **HPV-16/18 are responsible for ~70% of invasive cervical cancers worldwide**
 - ➔ **Cervical cancer vaccine based on 16 and 18 L1 virus-like particles**

- **Implementation of vaccination in a broad age range**
 - ➔ **AS04 adjuvant system ($\text{Al}(\text{OH})_3$ + MPL) to enhance immune responses in a broad age range**

GSK's Cervical Cancer Vaccine: Composition



Antigens: 20 μ g each

+

AS04

Adjuvant System

50 μ g MPL + 500 μ g Al(OH)₃

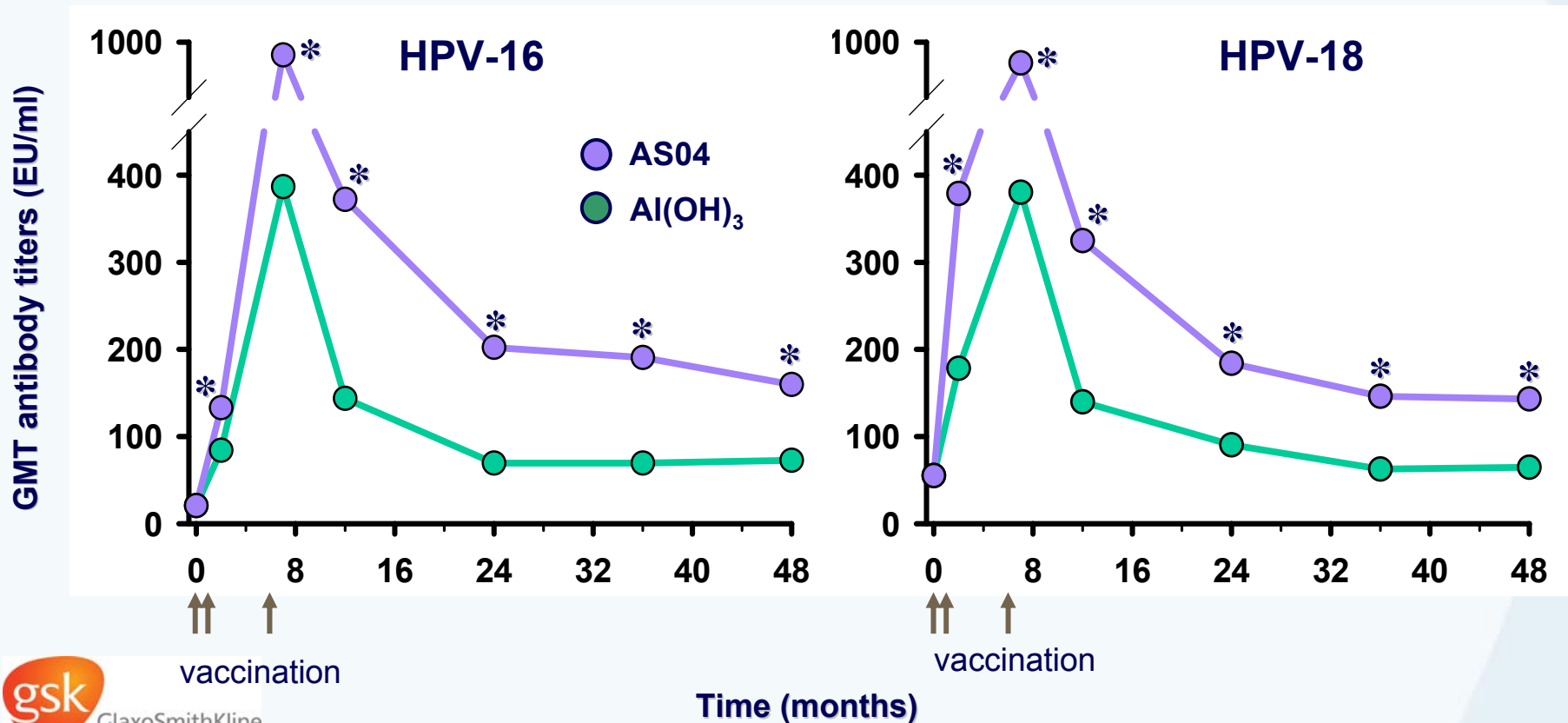


**Strong & Sustained
Immune Response**

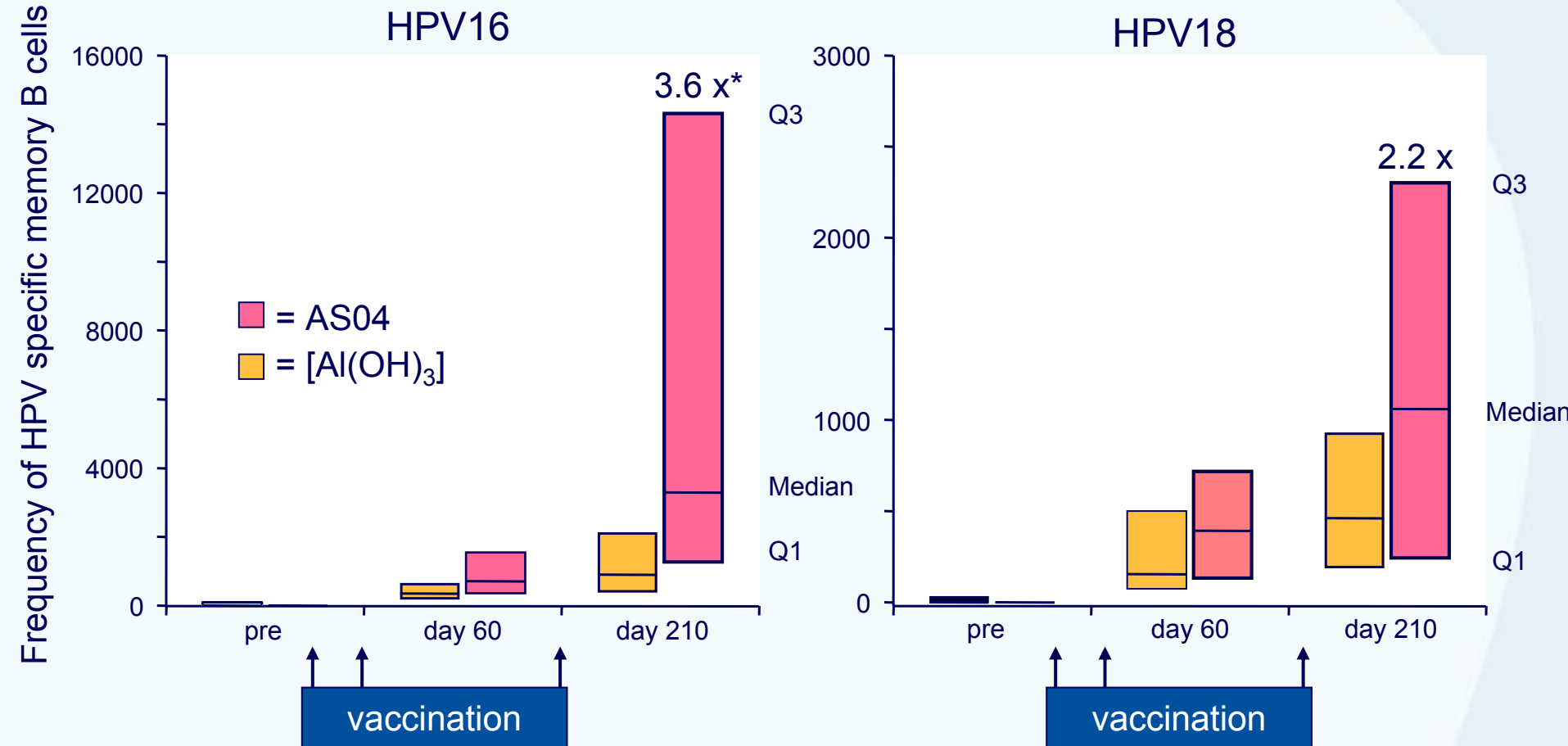
AS04 in GSK Cervical Cancer Vaccine Human Data: Antibodies

V5 epitope is targeted by HPV-16 neutralising antibodies

J4 epitope is targeted by HPV-18 neutralising antibodies



AS04 in GSK Cervical Cancer Vaccine Human Data: Memory B Cells



GSK cervical cancer vaccine formulated with AS04 induces higher frequency of memory B cells



Summary: AS04 Adjuvant

- Modern vaccine technology provides new means to control quality and/or quantity of vaccine antigen-specific immune responses
- AS04 represents a new generation of vaccine adjuvants, activating innate immunity to potentiate protective, adaptive immune responses
- GSK's Cervical Cancer Candidate Vaccine *with* AS04 induces:
 - **A stronger and more sustained humoral response to Human Papilloma Virus types 16 and 18**
 - **A higher frequency of antigen-specific memory B cells**as compared to the same vaccine formulated with $\text{Al}(\text{OH})_3$

GSK's Cervical Cancer Candidate Vaccine: Summary of Ongoing Phase IIb/III Trials

2005

2006

2007

2008

2009

HPV-012 (immuno 10-25y) → LT follow-up

HPV-013 (safety/immuno 10-14 yrs) → LT follow-up

HPV-014 (immuno 15-55y) → LT follow-up

HPV-010 (GSK HPV vaccine vs Gardasil 18-45 yrs)

HPV-001/007 (efficacy in 15-25 yr old women) N = 1113

4.5 yrs

5.5 yrs

6.5 yrs

Interim analyses virological/histopath endpoints

HPV-009 (efficacy in 18-25 yr old women in Costa Rica) N = 7,462

HPV-008 (efficacy in 15-25 yr old women) N = 18,644 vaccinated

Interim analysis CIN2+

HPV-015 (efficacy in women >25yrs) N=5,700



Immunogenicity



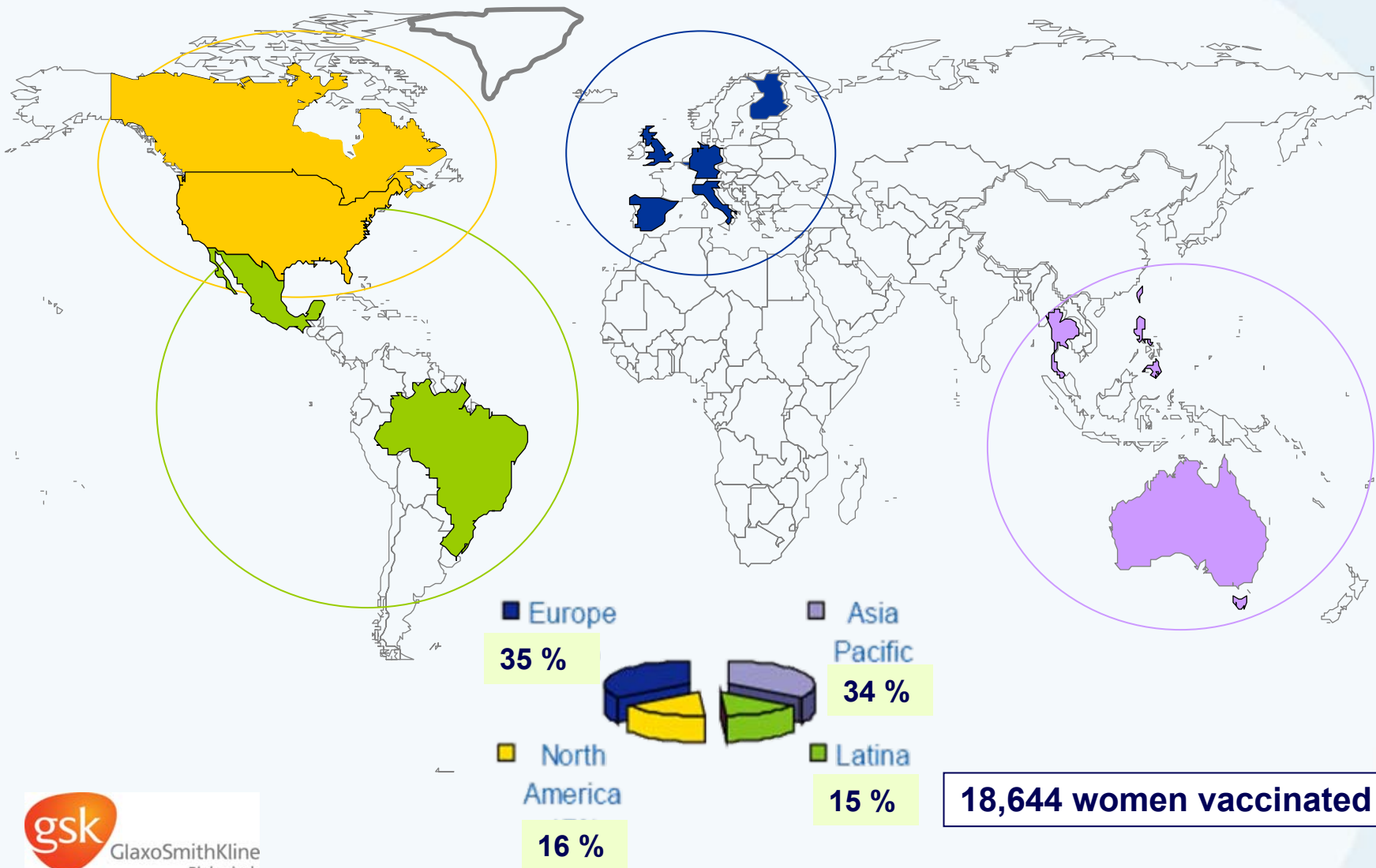
Efficacy & immuno

GSK PhII Studies HPV-001/007 : Efficacy studies in Unexposed Women Aged 15-25 years Highlights of interim analysis at 5.5 years

Up to *5.5 years* :

- **100% protection against HPV-16/18 CIN1+ & CIN2+**
- **Preliminary evidence of oncogenic type specific cross protection against incident infection with HPV-45 and 31**
- **Safety profile was comparable between vaccine and control groups**

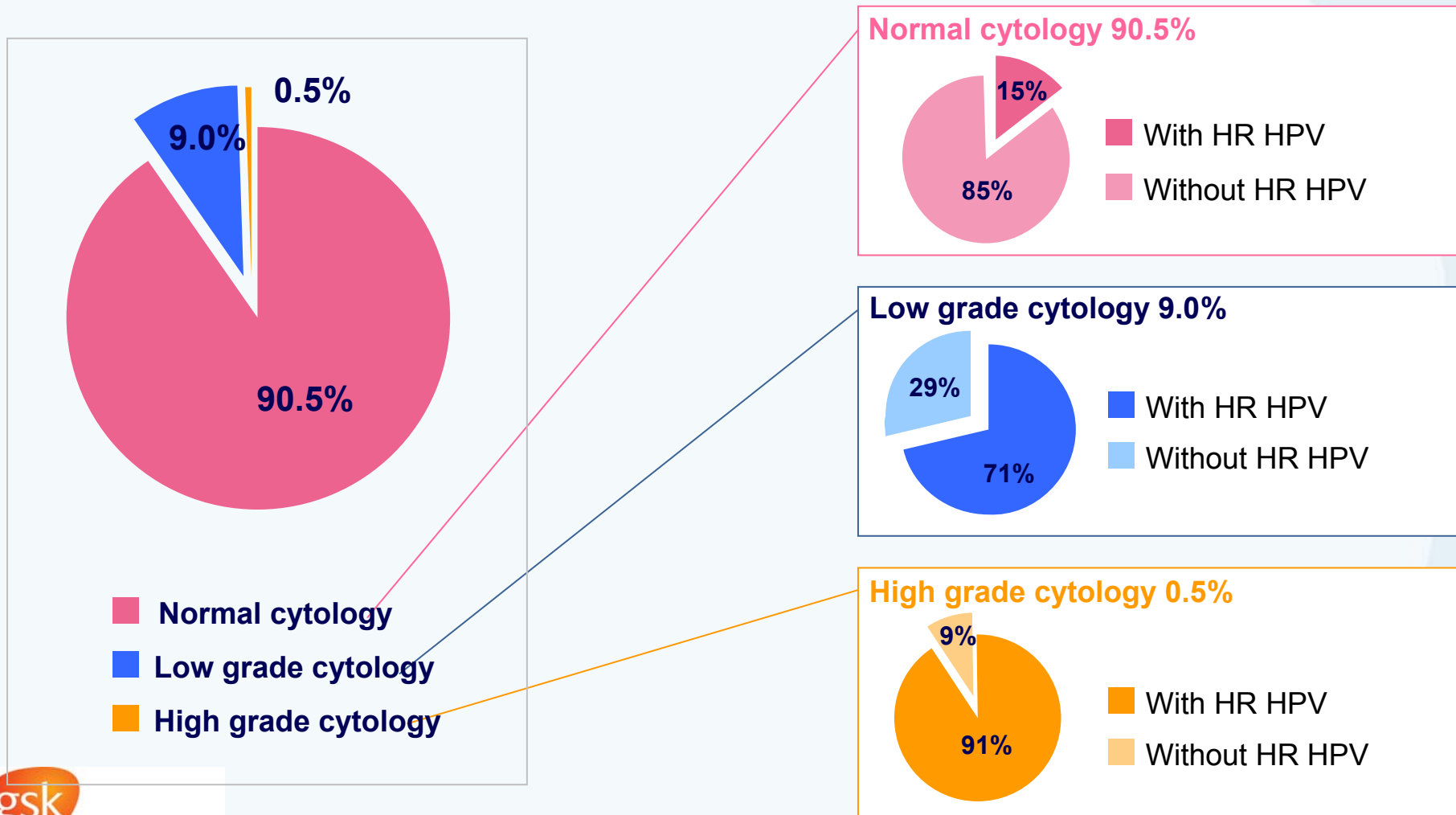
GSK Phase III Efficacy trial HPV 008: Study Population



18,644 women vaccinated



GSK Phase III Efficacy trial HPV 008: Study Population, Baseline Characteristics



GSK Phase III Efficacy trial HPV 008: Efficacy against HPV-16/18 CIN2+ (TVC-E)

Pre-specified case definition:

Association based on DNA detection in the lesion (**only**)

23 CIN2+ CASES

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graph TD; A[23 CIN2+ CASES] --> B[9 Cases with one HPV type detected in the lesion.]; A --> C[14 (61%) Cases with more than one HPV type detected in the lesion.]; C --> D[Which one of the HPV types caused the lesion?]; D --> E[Pattern A 11 cases]; D --> F[Pattern B 3 cases];
```

9 Cases with one HPV type detected in the lesion.

14 (61%) Cases with more than one HPV type detected in the lesion.

This high rate of multiple infections in CIN lesions was not expected, based on published data

Which one of the HPV types caused the lesion?

Pattern A
11 cases

Pattern B
3 cases

GSK Phase III Efficacy trial HPV 008: 14 CIN2+ with Multiple HPV Types Detected: **2 Patterns**

Pattern A: multiple HPV types in the CIN2+ lesion
and

HPV types 16 or 18 detected in preceding samples

CERVICAL SAMPLES				Month 12 Triggered Management	
	Month 0	Month 6	Month 12	Punch	LEEP
HPV DNA	N	HPV-16/51/59	HPV-16/51/52	CIN2: HPV-16/51 29 days after month 12	CIN2: HPV-16/51/56/68 76 days after month 12

These cases are considered to be causally associated with vaccine types

GSK Phase III Efficacy trial HPV 008: 14 CIN2+ with Multiple HPV Types Detected: 2 Patterns

Pattern B: Multiple HPV types in the CIN2+ lesion
and

No detection of vaccine HPV types (16 or 18) in any
preceding samples

Three such cases :

Which one of the HPV types caused the lesion?

GSK Phase III Efficacy trial HPV 008: 14 CIN2+ with Multiple HPV Types Detected: 2 Patterns

One example of a pattern B case with multiple HPV types in the CIN2+ lesion

CERVICAL SAMPLES				Month 12 Triggered Management	
	Month 0	Month 6	Month 12	Punch Biopsy	LEEP
HPV DNA				CIN3: HPV-16/58 36days after month 12	CIN3: HPV-58 113days after month 12 Same lesion

GSK Phase III Efficacy trial HPV 008: 14 CIN2+ with Multiple HPV Types Detected: 2 Patterns

One example of a pattern B cases with multiple HPV types in the CIN2+ lesion
and

No detection of vaccine HPV types (16 or 18) in any preceding samples

CERVICAL SAMPLES				Month 12 Triggered Management	
	Month 0	Month 6	Month 12	Punch Biopsy	LEEP
HPV DNA	HPV-58	HPV-58	HPV-58	CIN3: HPV- 16 /58 36days after month 12	CIN3: HPV- 58 113days after month 12 Same lesion

GSK Phase III Efficacy trial HPV 008: 14 CIN2+ with Multiple HPV Types Detected: 2 Patterns

One example of a pattern B cases with multiple HPV types in the CIN2+ lesion
and

No detection of vaccine HPV types (16 or 18) in any preceding samples

CERVICAL SAMPLES			Month 12 Triggered Management		
	Month 0	Month 6	Month 12	Punch Biopsy	LEEP
HPV DNA	HPV-58	HPV-58	HPV-58	CIN3: HPV-16/58 36days after month 12	CIN3: HPV-58 113days after month 12 Same lesion

**The HPV type 16 detected in the lesion
is unlikely to be the cause the lesion**

Efficacy against HPV-16/18 CIN2+ (TVC-E)

Additional- post hoc- analysis considering patterns of HPV types in preceding cytological samples

Endpoint	Group	N	n	Vaccine Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	HPV	7788	0	100	74.2	100	<0.0001
	Control	7838	20				
CIN2+ HPV-16	HPV	6701	0	100	64.5	100	<0.0001
	Control	6717	15				
CIN2+ HPV-18	HPV	7221	0	100	-49.5	100	0.0625
	Control	7258	5				

Pre-specified Case Definition based on PCR detection in lesion only

Endpoint	Group	N	n	Vaccine Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	HPV	7788	2	90.4	53.4	99.3	<0.0001
	Control	7838	21				
CIN2+ HPV-16	HPV	6701	1	93.3	47.0	99.9	0.0005
	Control	6717	15				
CIN2+ HPV-18	HPV	7221	1	83.3	-78.8	99.9	0.1249
	Control	7258	6				

GSK Phase III Efficacy trial HPV 008: Cross-Protection against 6 Months persistent infections

Type	TVC-E (at least 1 dose)			
	Vaccine (cases)	Control (cases)	Vaccine Efficacy (%)	97.9% CI
HPV-45	10	25	59.9	2.6 – 85.2
HPV-31	47	74	36.1	0.5 – 59.5
HPV-52	16	30	31.6	3.5 – 51.9

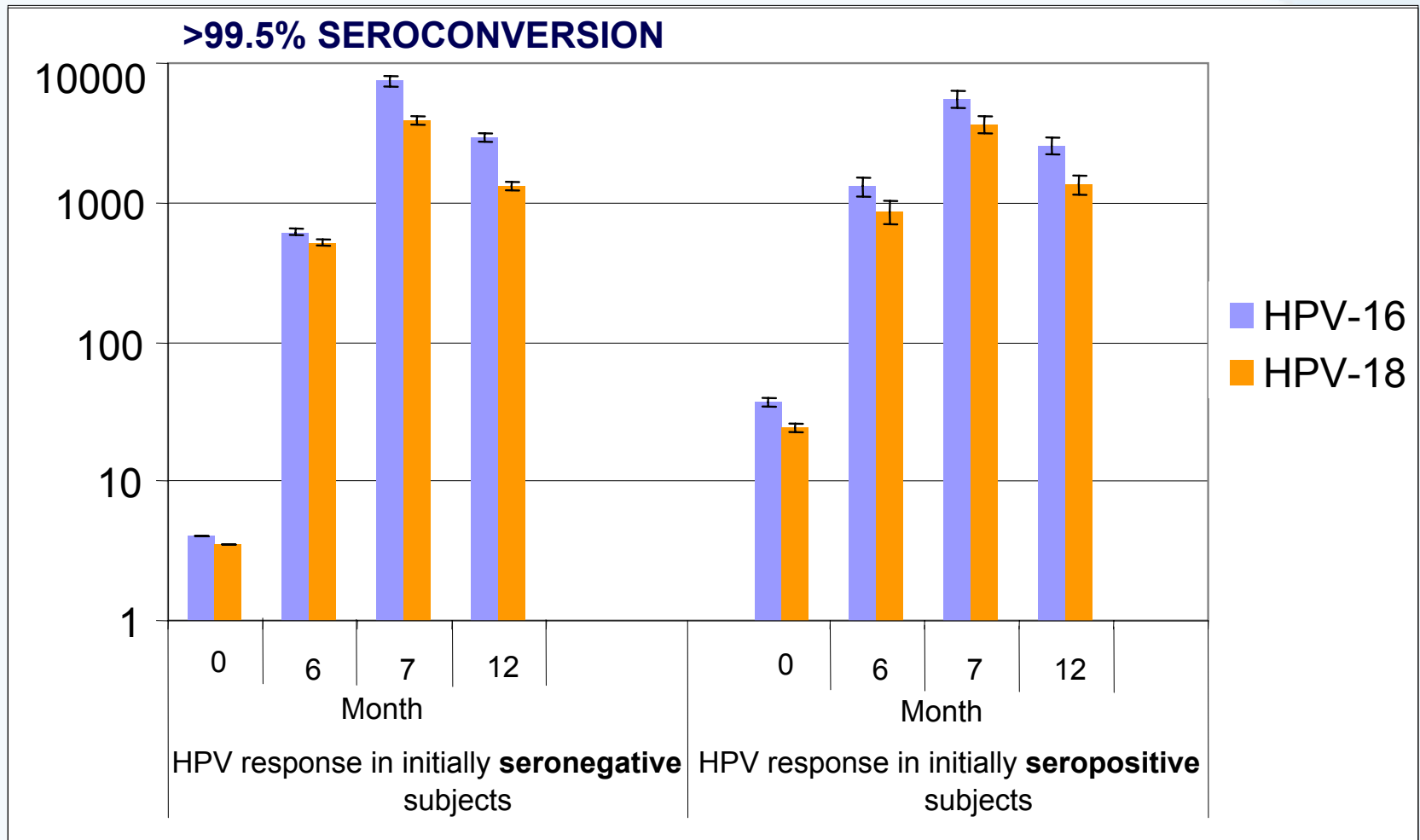
In ~ 70% of these cases the onset of infection was before completion of the vaccination course.

GSK Phase III Efficacy trial HPV 008: Broad Protection against 12 Months Persistent Infection

HPV-type endpoint	TVC-E (at least 1 dose)			
	Vaccine (cases)	Control (cases)	Vaccine Efficacy (%)	97.9% CI
Oncogenic HPV BEYOND 16 & 18	100	137	27.1	0.5 – 46.8

In ~90% of these cases the onset of infection was before completion of the vaccination course

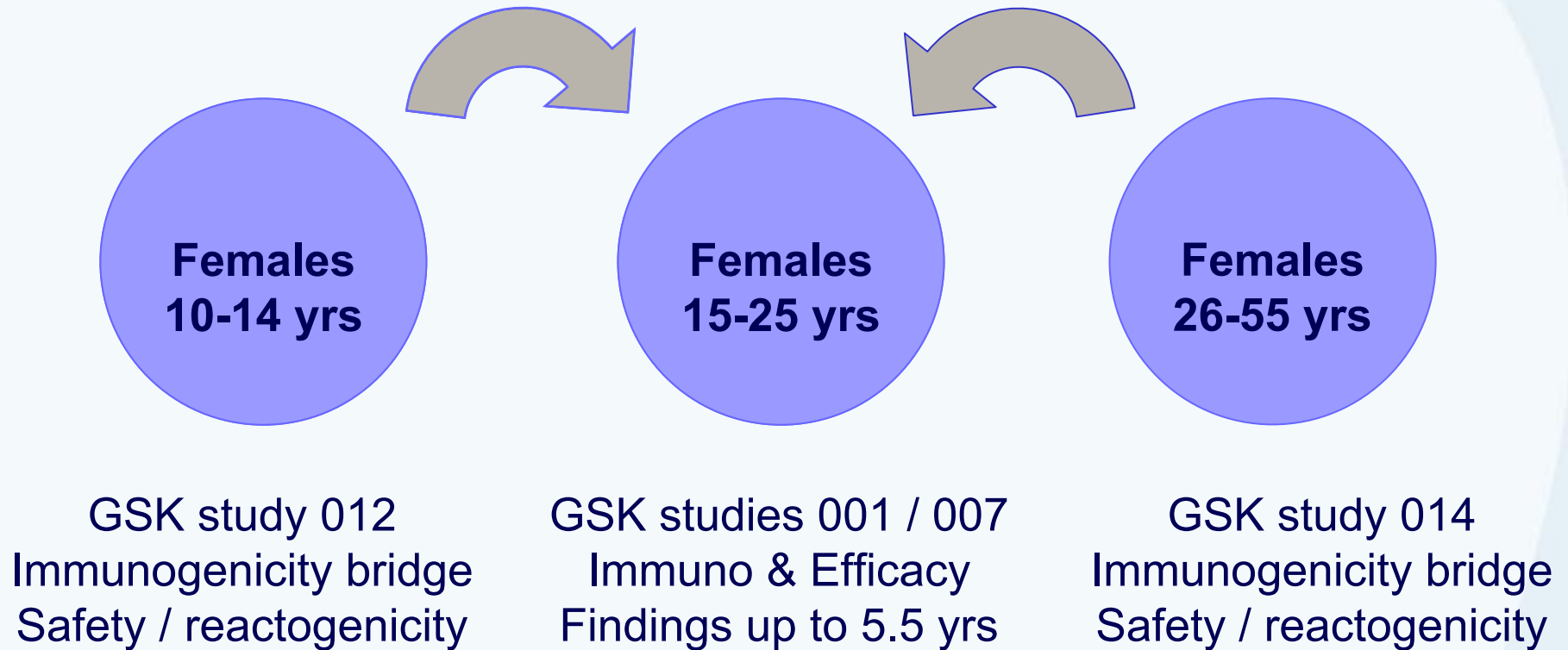
GSK Phase III Efficacy trial HPV 008: Immunogenicity (ATP cohort, ELISA)



GSK Phase III Efficacy trial HPV 008: Interim Analysis Conclusions

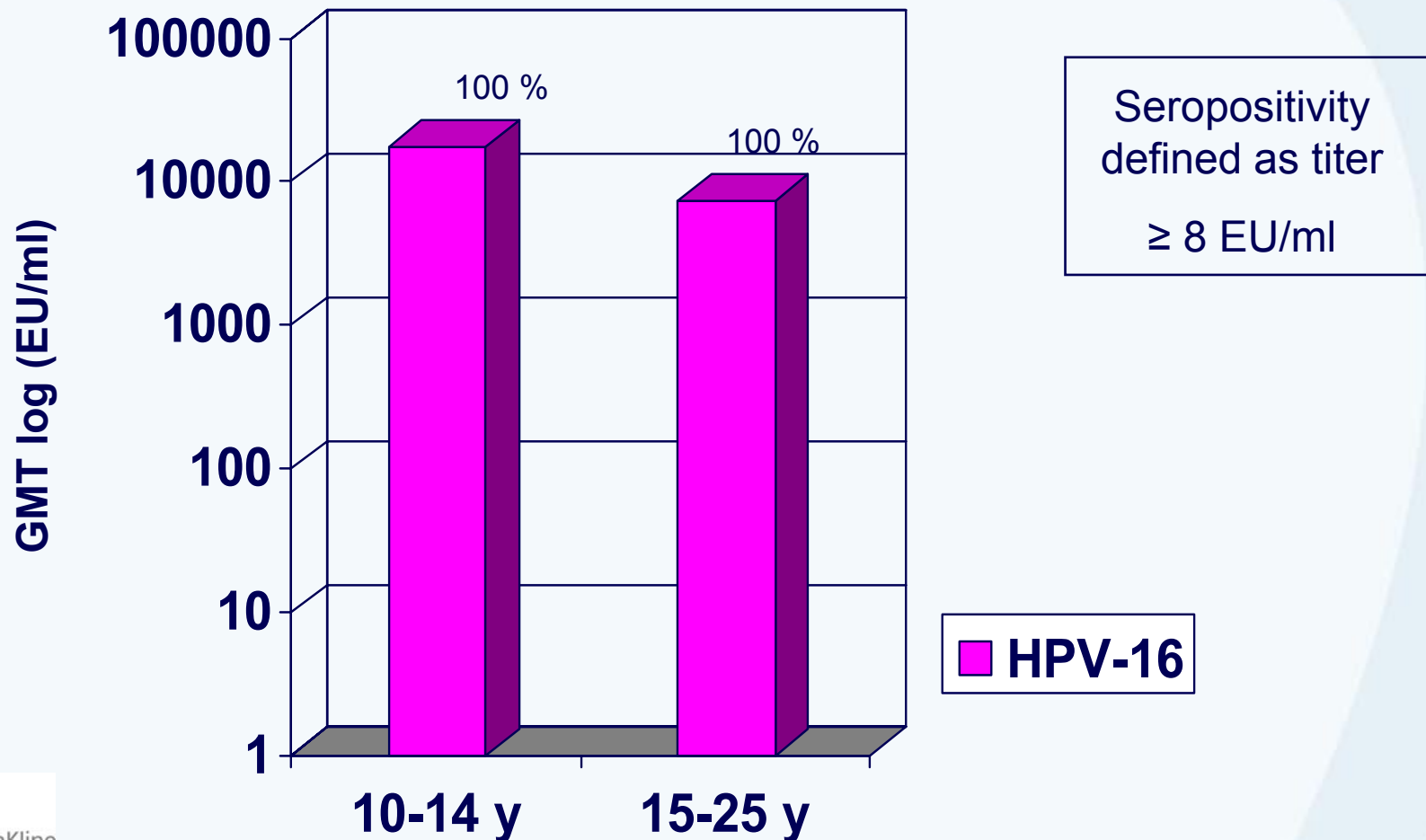
- Highly immunogenic
- Generally well tolerated
- High level protection against HPV-16/18 CIN2+ confirmed in a broad population of women (TVC-E)
 - 90% vaccine efficacy against any CIN2+ with HPV-16/18 detected in the lesion**
 - 100% vaccine efficacy against CIN2+ where HPV-16/18 was causally associated with lesion**
- Extention of evidence of cross-protection now based on persistent infection
 - against HPV-45, 31, 52 (6 month persistent infection)**
 - beyond HPV 16 and 18 (12 month persistent infection)**
- Majority of endpoints (CIN2+ and persistent infection) resulted from infections starting prior to completion of 3-dose series
 - suggests early onset of vaccine effect**

Principles of Immunobridging



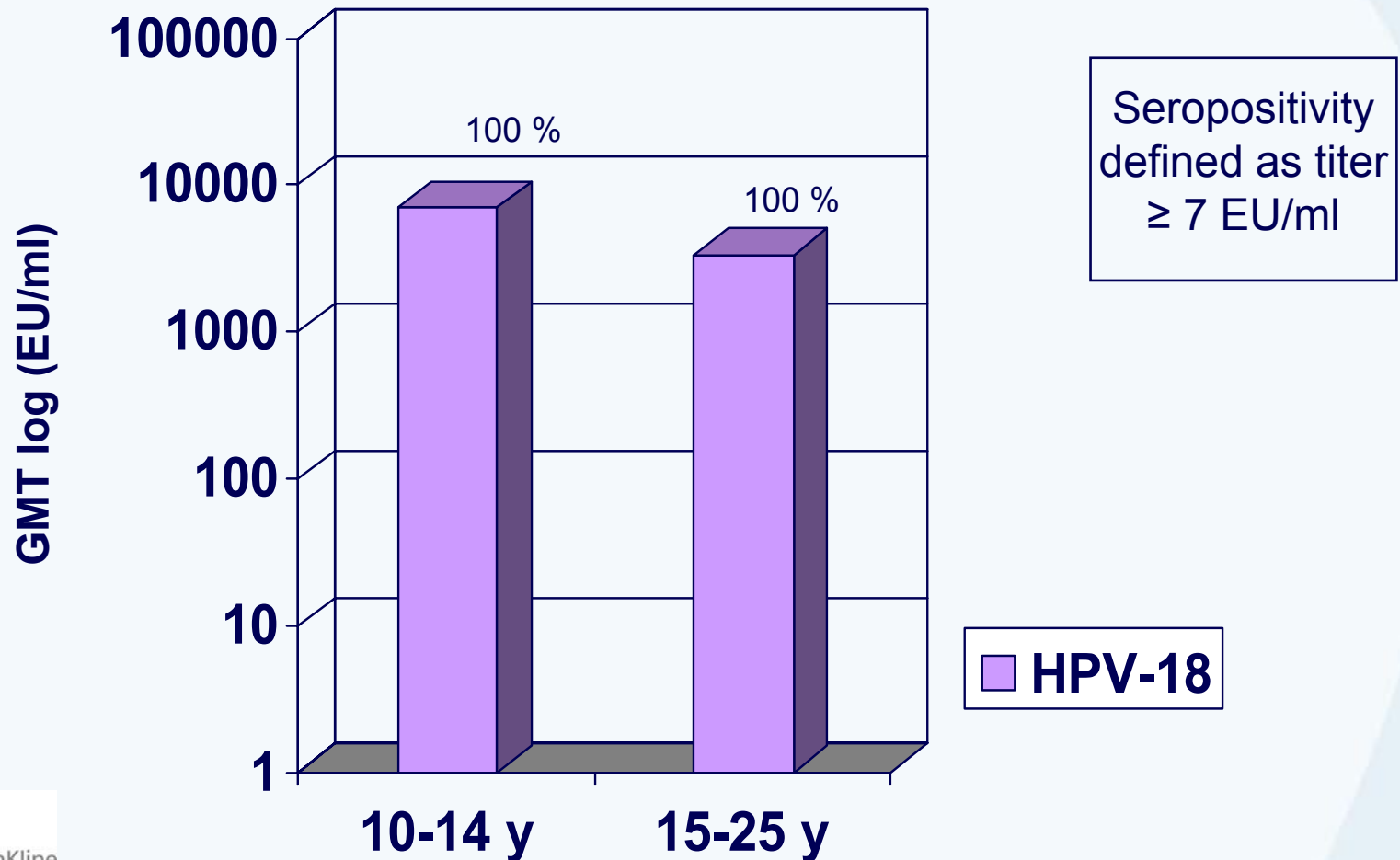
HPV 012 Results

Results at month 7: GMT and seroconversion rate



HPV 012 Results

Results at month 7: GMT and seroconversion rate

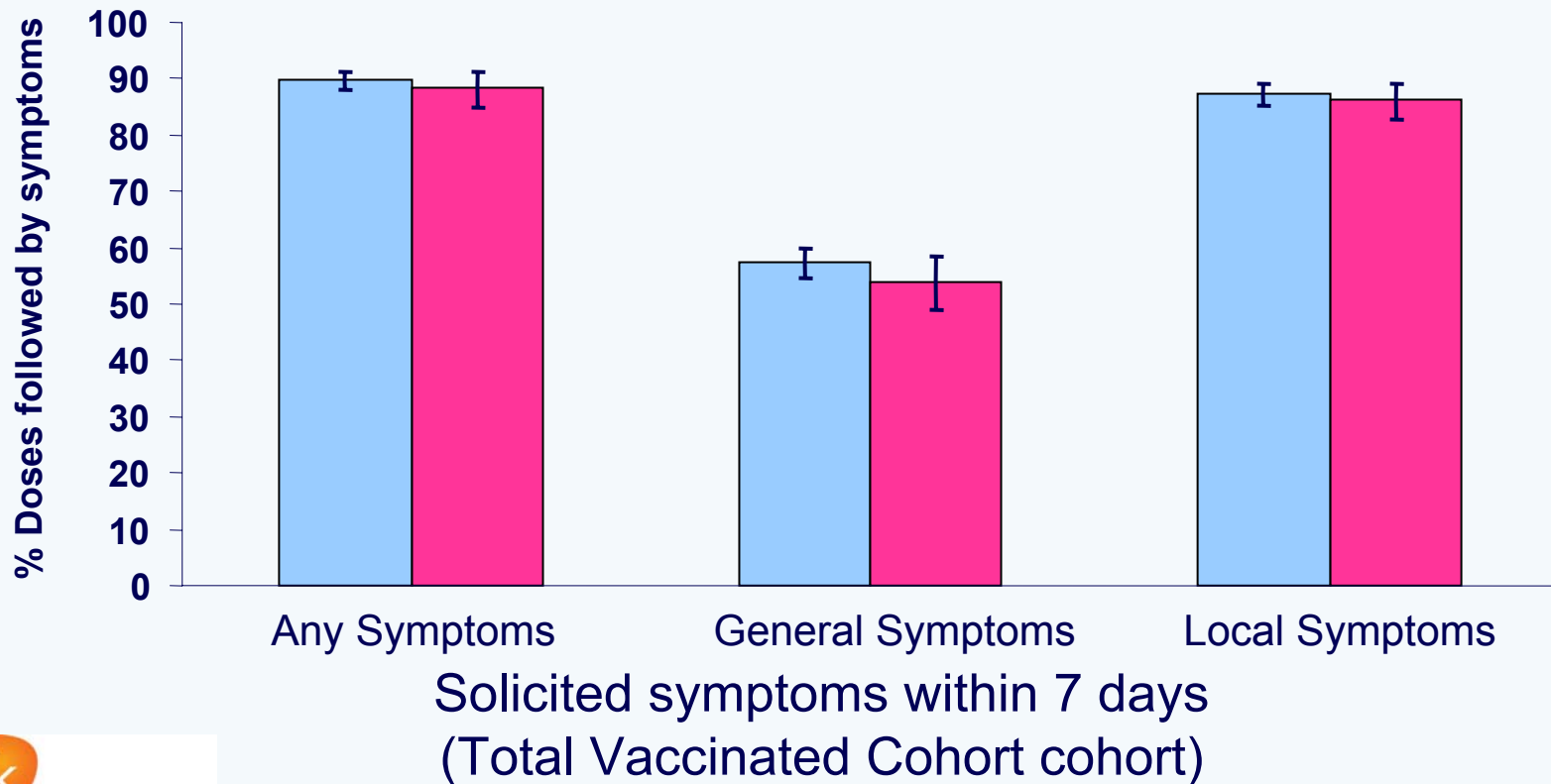


GSK HPV 012 Study

Safety data

No serious adverse events related to vaccination

15-25 yrs
10-14 yrs



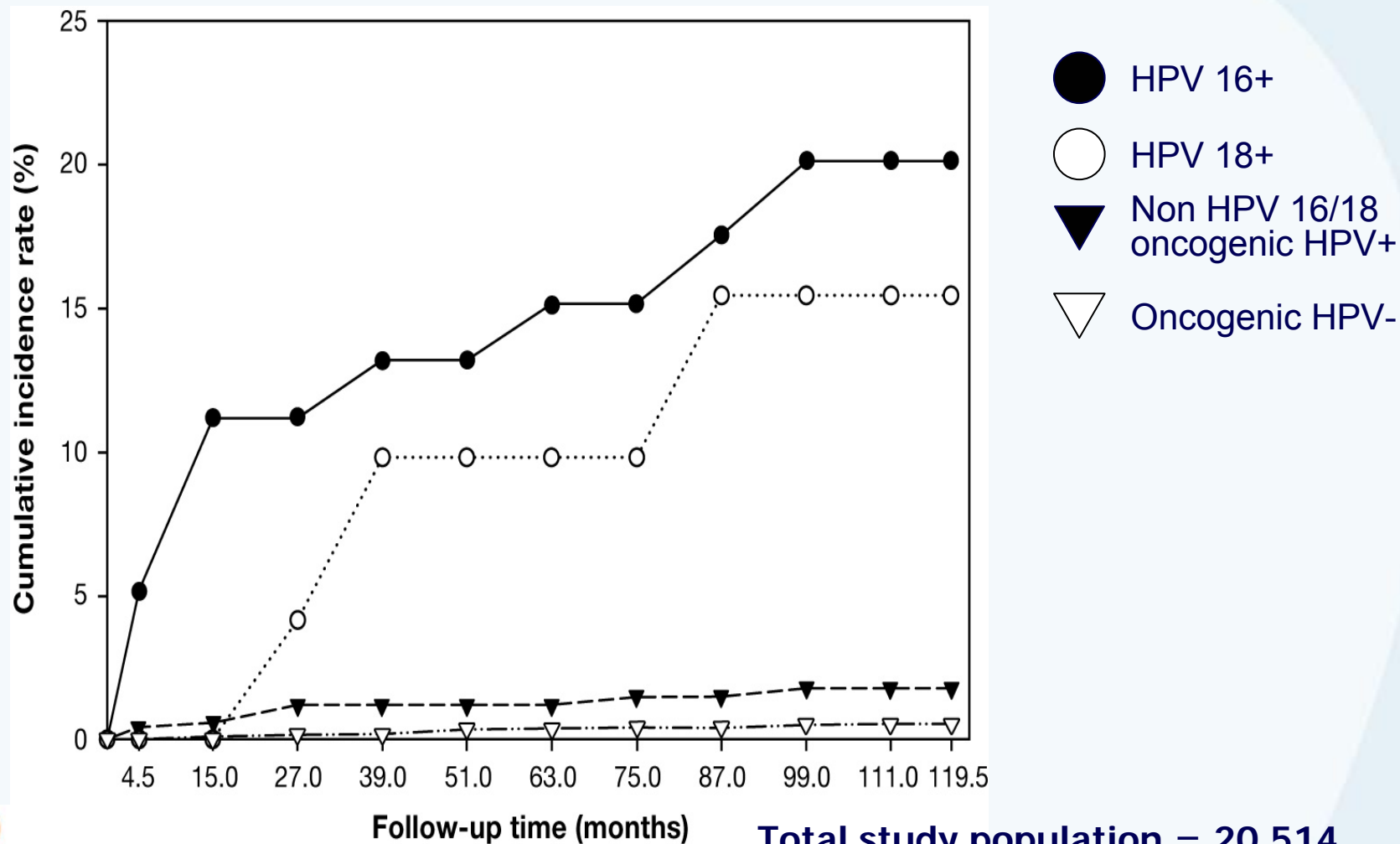
GSK HPV 012 Study Summary

- **100% of initially seronegative subjects seroconverted to both HPV-16 and HPV-18**
- **Overall, 10-14 year olds achieved significantly higher GMTs (>2 fold) against both antigens**
- **Similar safety profile in 10-14 and 15-25 year olds**

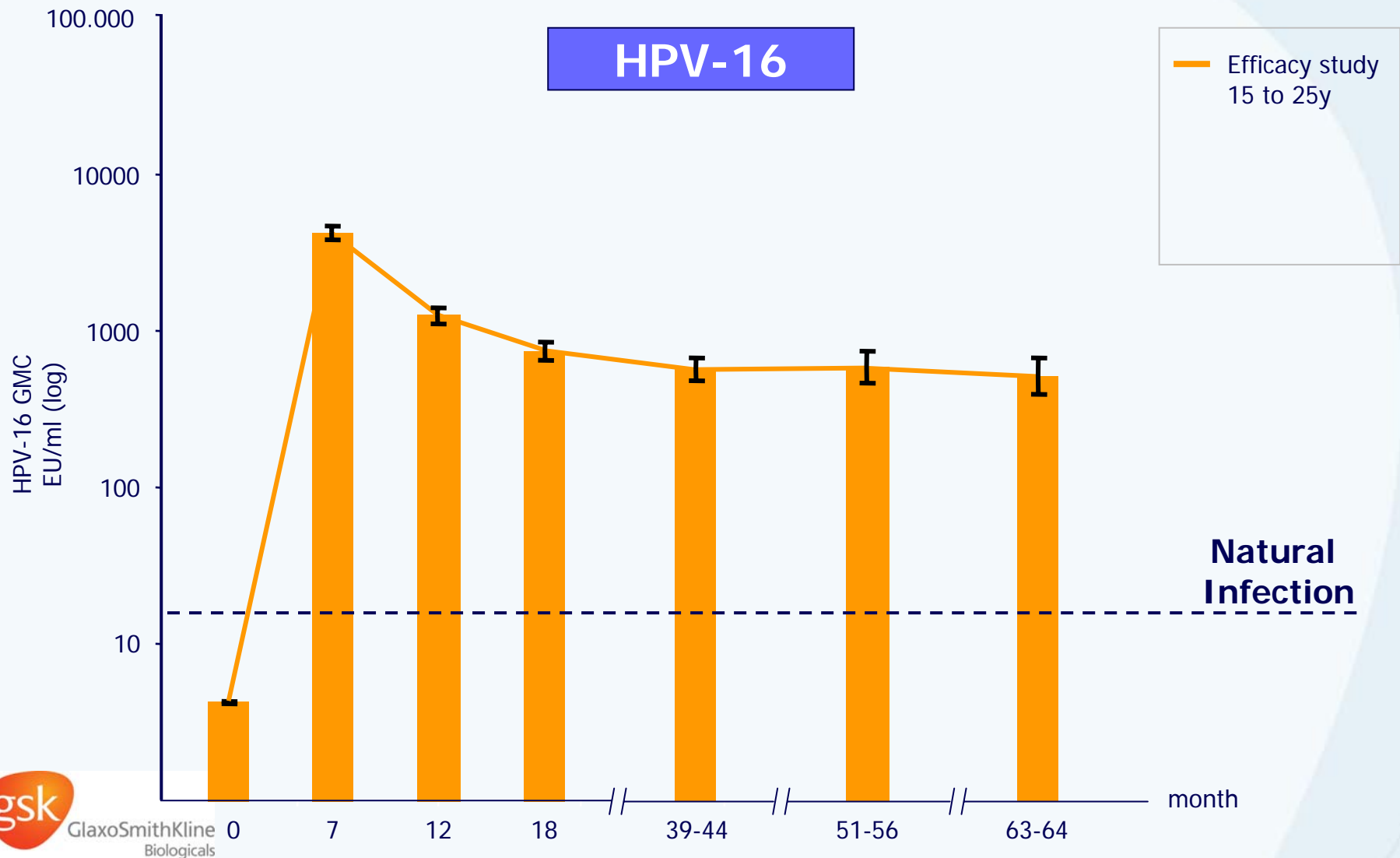
HPV infections occur in women over 25 years of age

- Annual incident infection rate with oncogenic HPV types is estimated at 5.3% in women 25-55 years of age (range 5-10%)¹⁻³
- Although new infections decrease with age, risk of persistence increases with age⁴

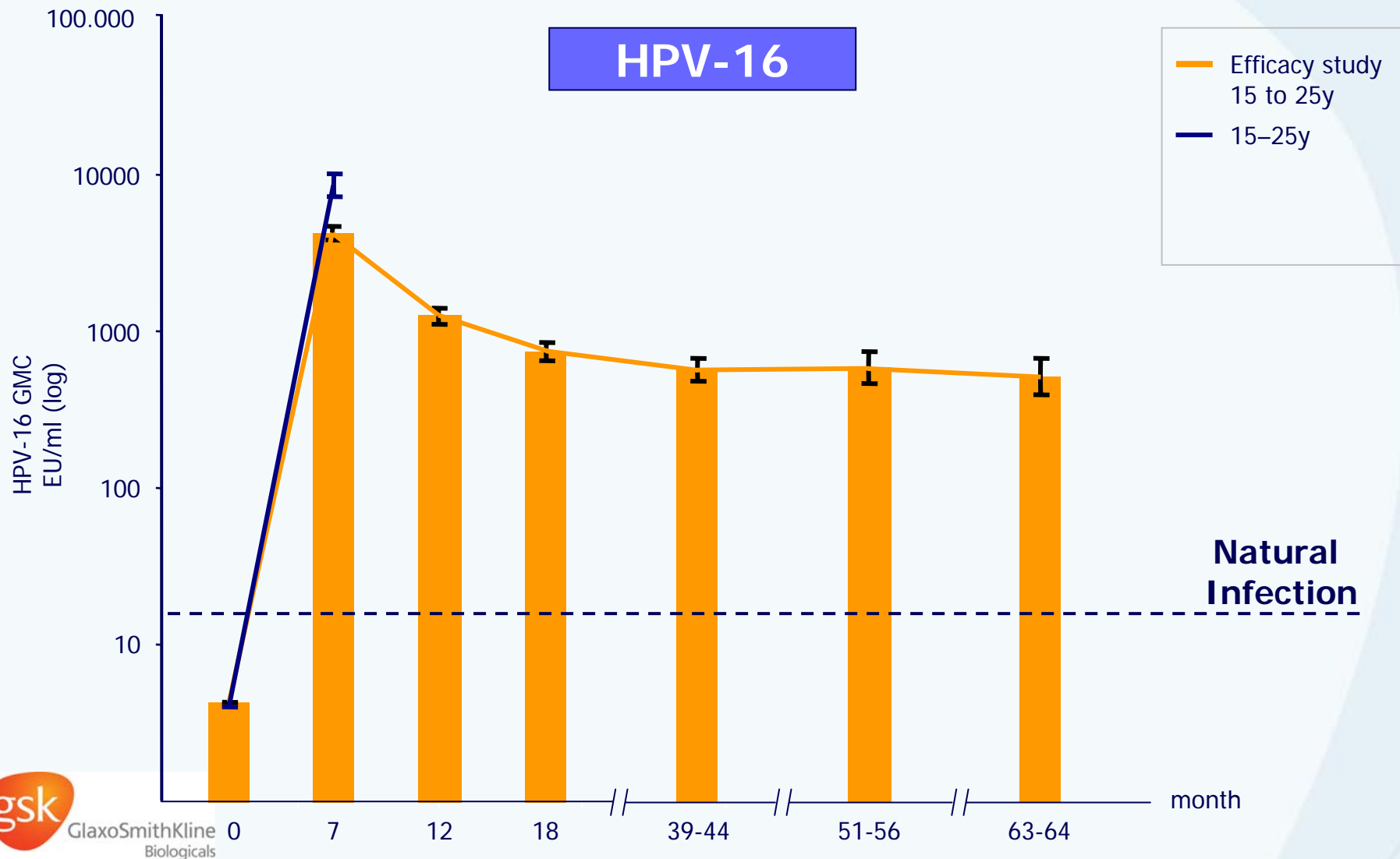
One in five HPV-16+ women aged ≥ 30 will develop a CINIII+ lesion over a 10-year period



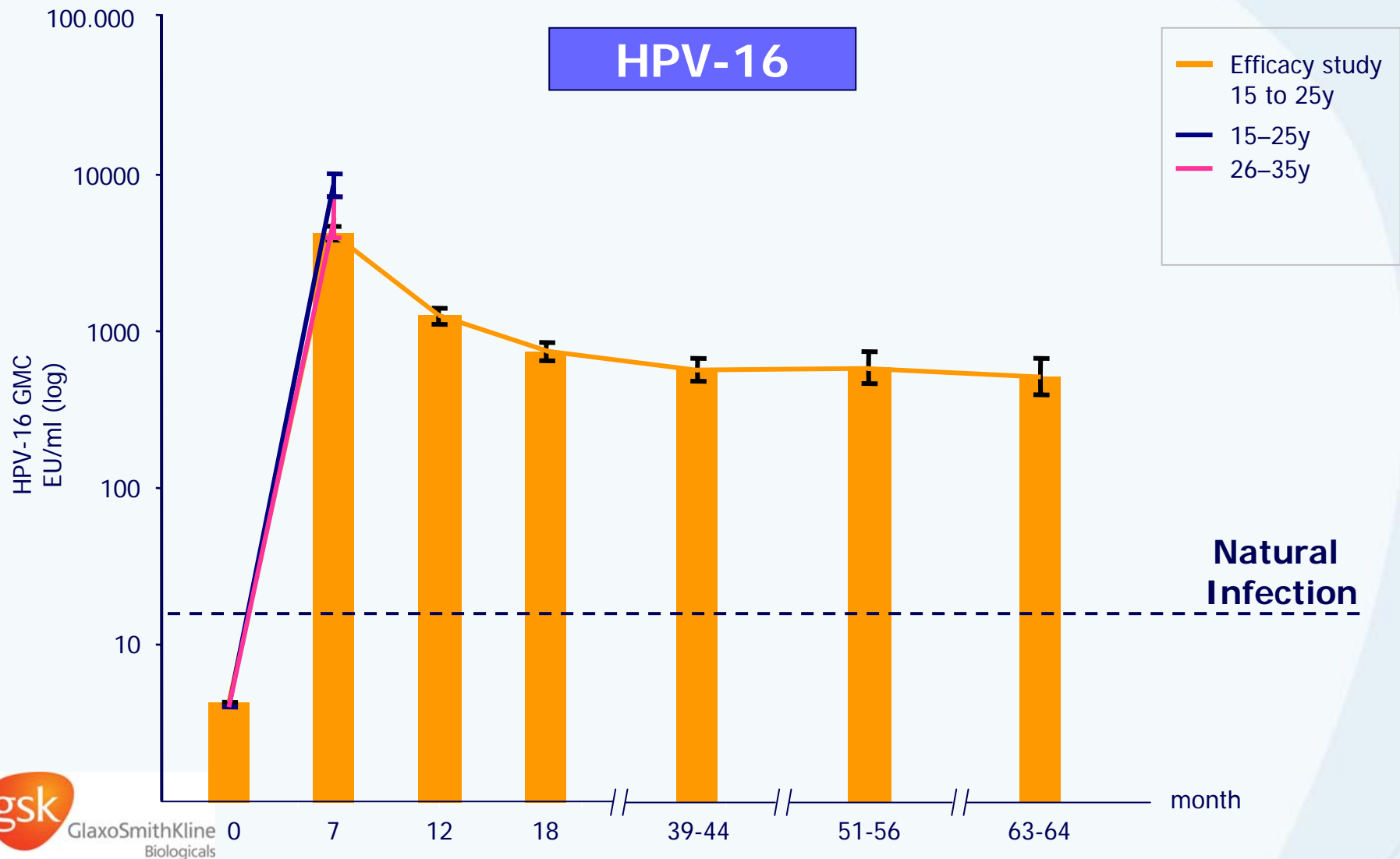
HPV-16 Antibody Levels Observed in Efficacy Study HPV-001/007 up to 5.5 y



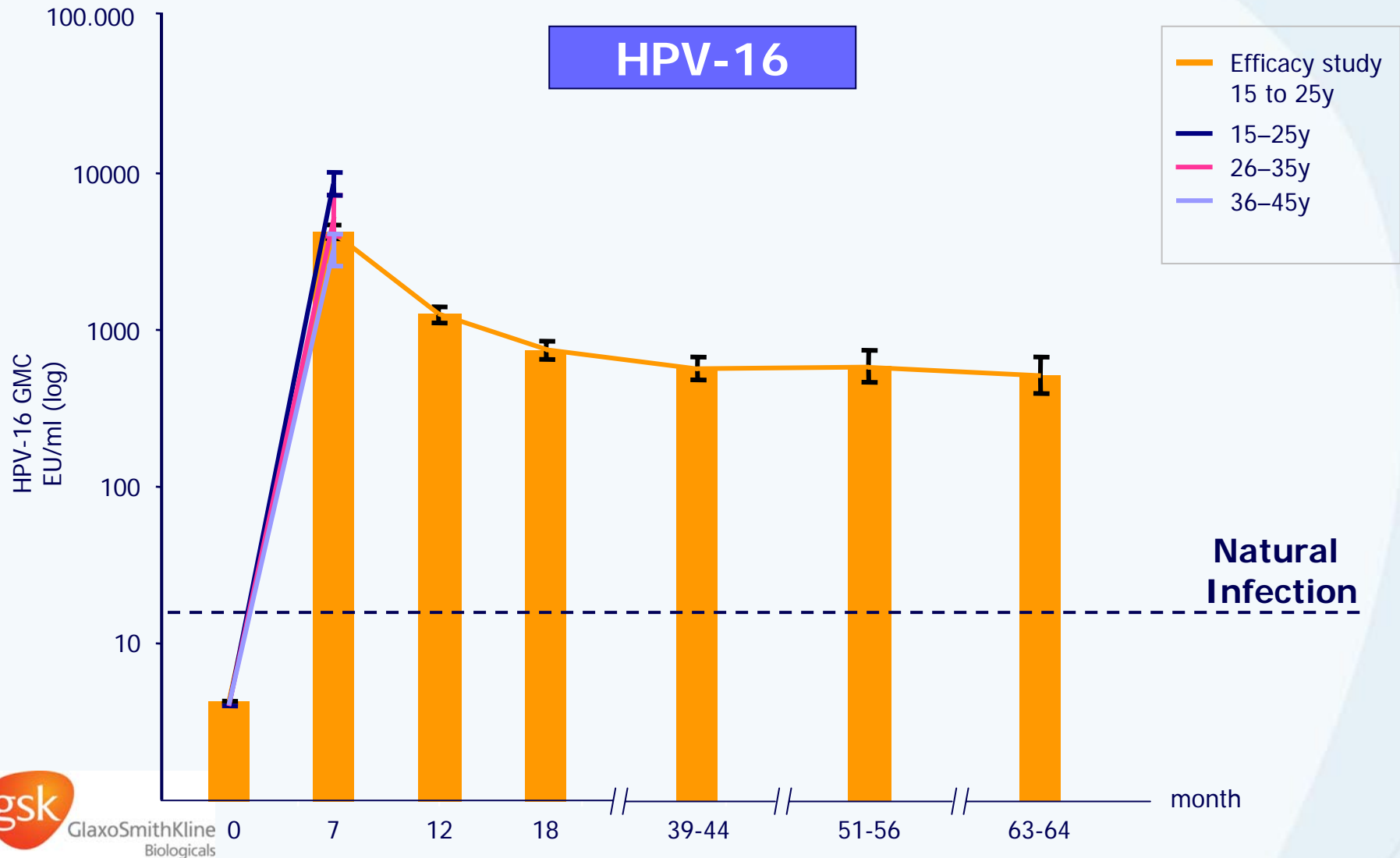
Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



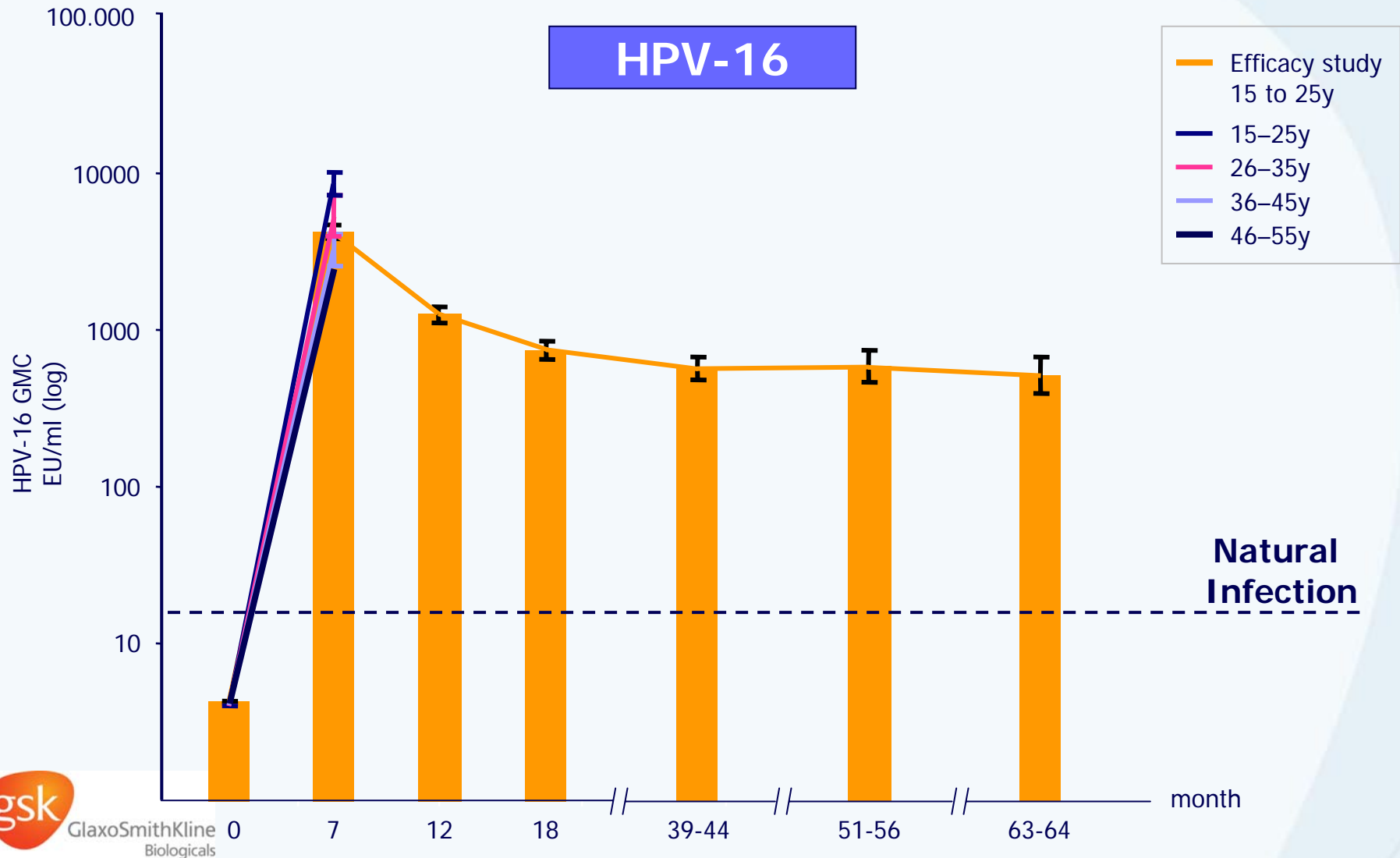
Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



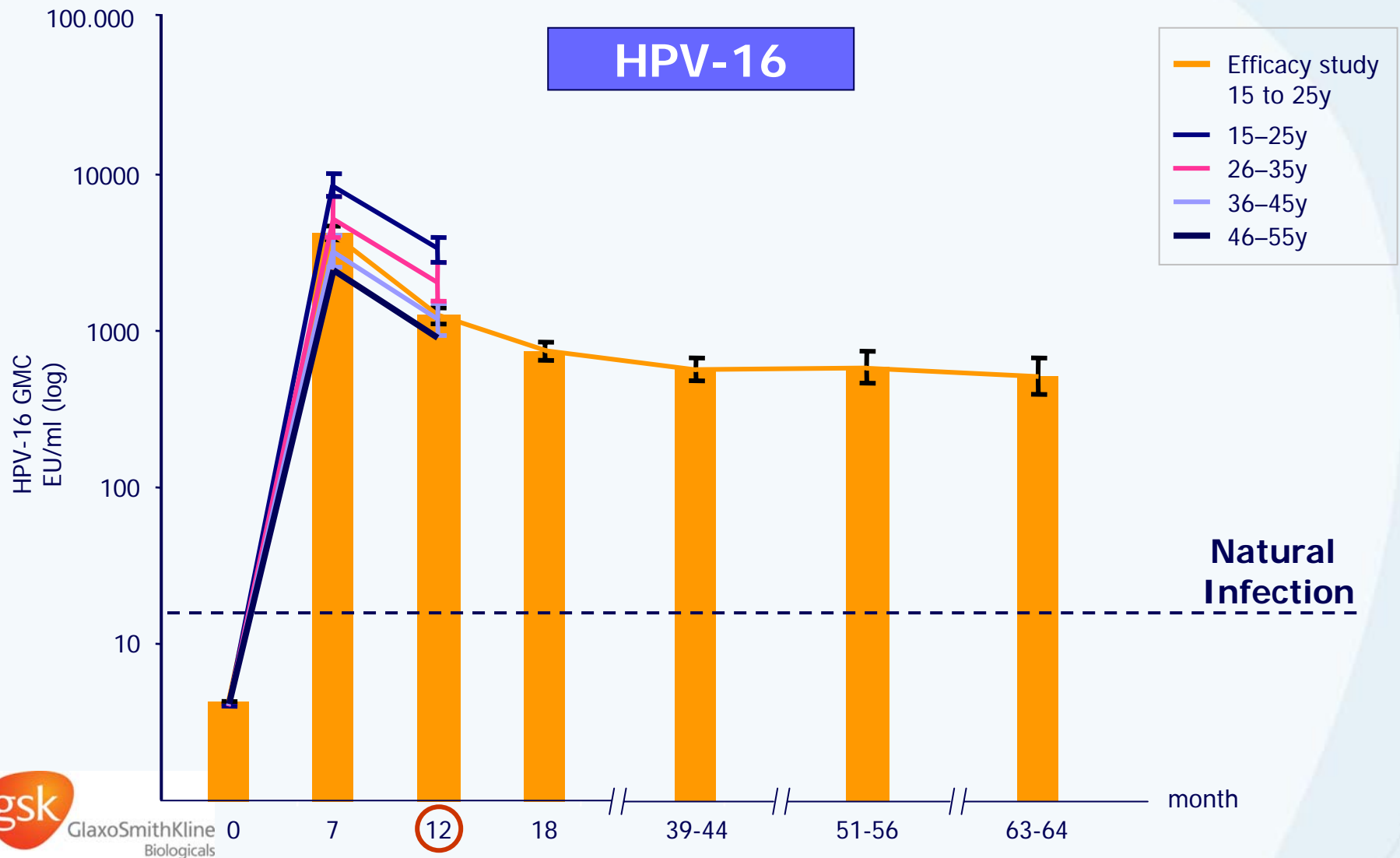
Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



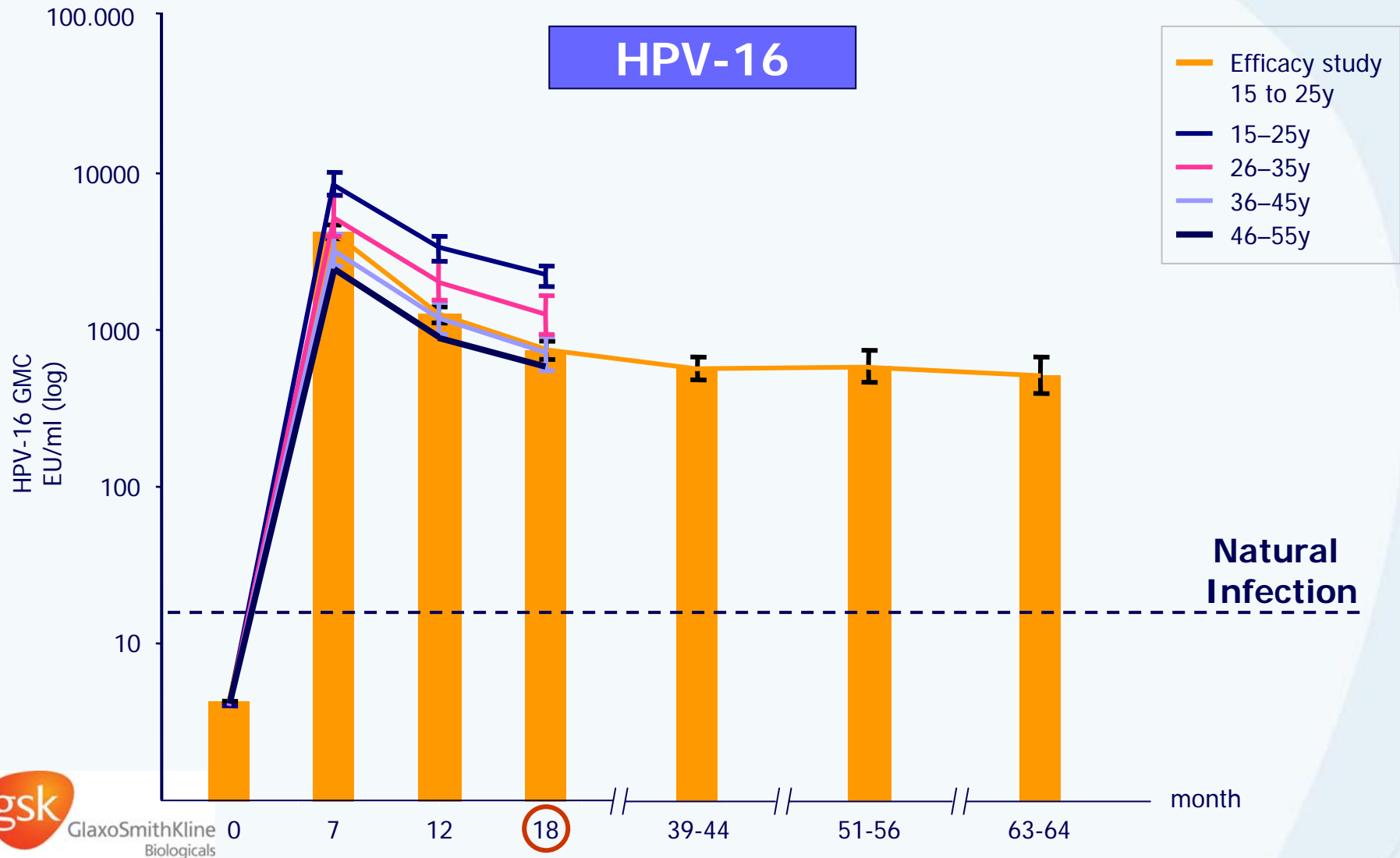
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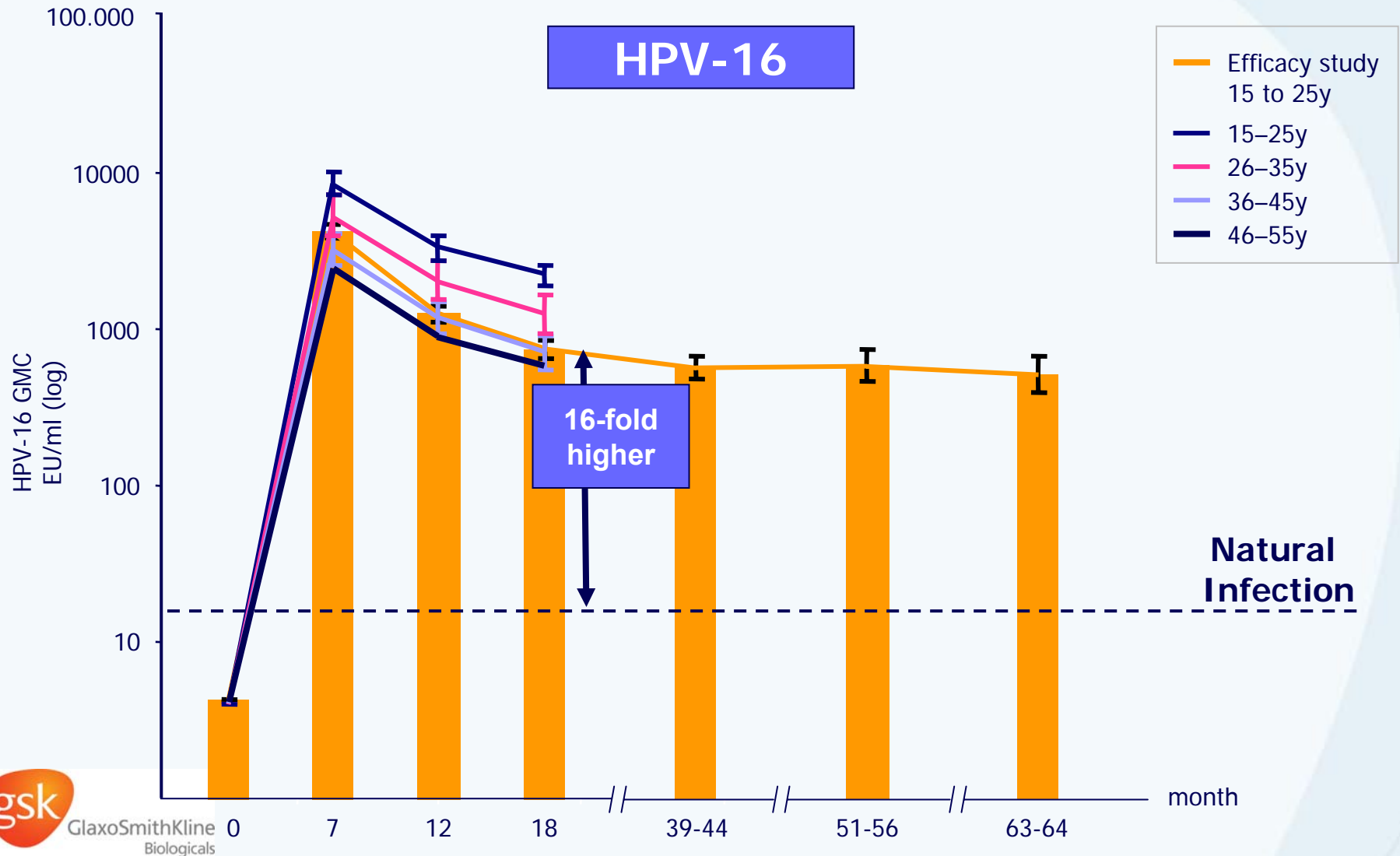
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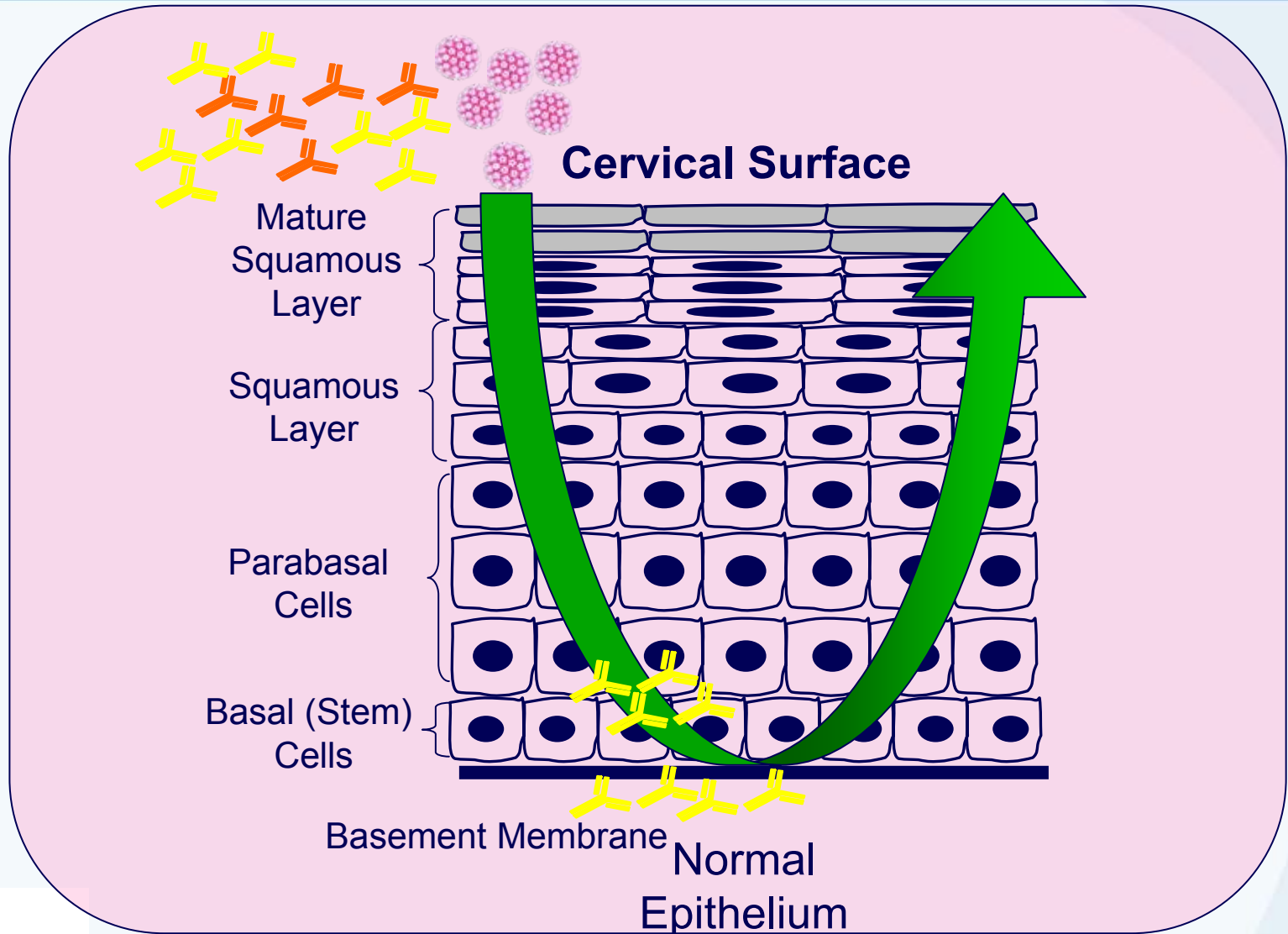
Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



HPV-014 – 18 Months Confirmation of Strong & Sustained Immune Response in Women >25 Years

- Generally well tolerated
- Highly immunogenic:
 - **seroconversion:** 100% for both antigens in all age groups
 - **antibody levels:** HPV 16/18 antibody titers in women >25 yrs were in the same order of magnitude as those observed over 5.5 years in women 15-25 year old where efficacy has been demonstrated (Study 001/007)

Vaccine Induced Transudating Neutralising Antibodies



Protection at the Site of Infection

Importance of Mucosal Immunity

- **Systemic immunization with the HPV-16/18 L1 VLP AS04 cervical cancer candidate vaccine induces high titres neutralizing antibodies in both the serum and CVS**
- **Strong correlation between CVS and serum IgG antibodies indicate transudation to the cervical epithelium**
- **Correlation equally strong in all age groups**

GSK's HPV16/18 Cervical Cancer Candidate Vaccine

■ **HPV 16/18 cervical cancer candidate vaccine confers**

- **Broad protection**
- **Sustained protection**
- **Strong protection**

against HPV 16 and 18 persistent infection and disease

**'What is the value of
that
which protects
something
as precious as
life itself?'**

. . . priceless!

