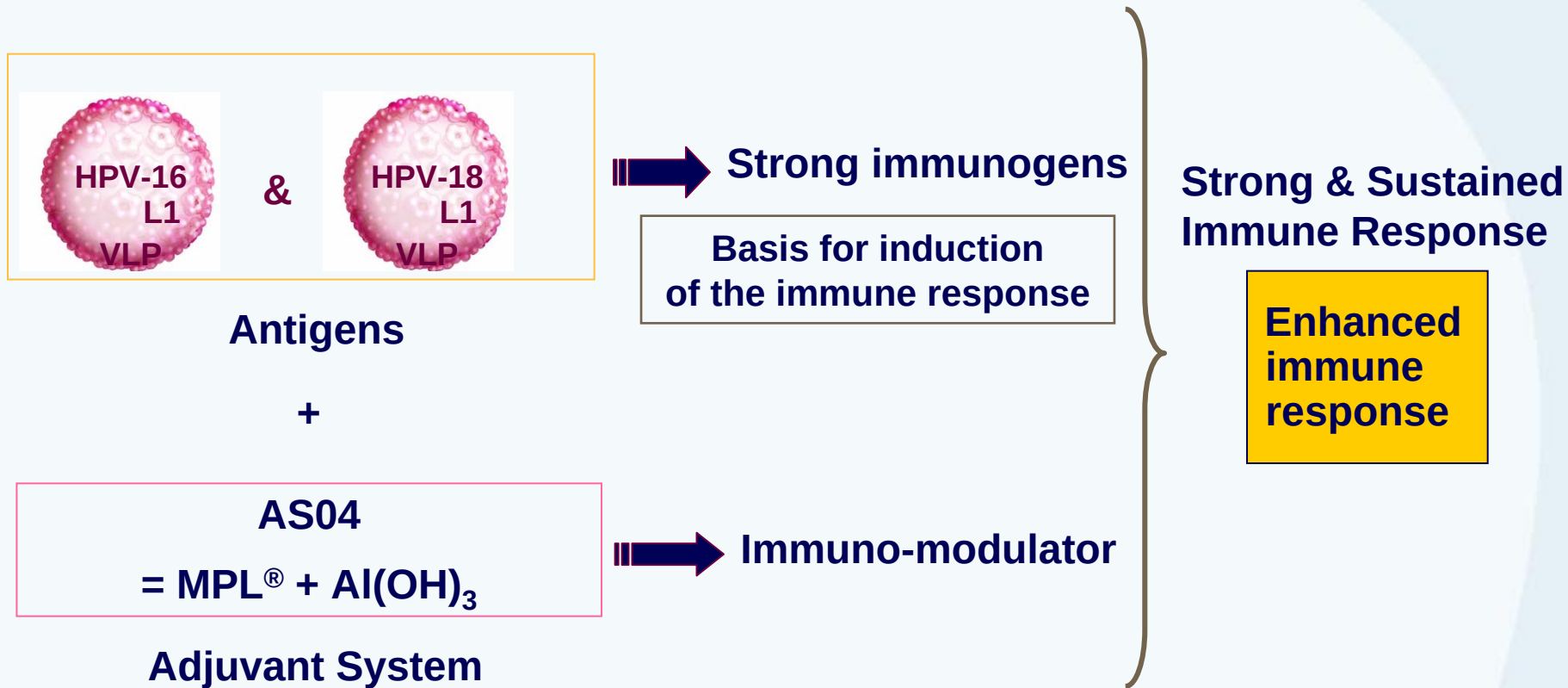


# 子宮頸癌預防新策略



**HPV 16/18 ASO4-adjuvanted  
Cervical Cancer Vaccine:  
Long-term Safety and Efficacy**

# GSK Candidate Cervical Cancer Vaccine





# AS04 vs. Alum

**HPV 16 / 18 VLPs formulated  
with AS04**

**versus**

**HPV 16 / 18 VLPs formulated with  
aluminium hydroxide**

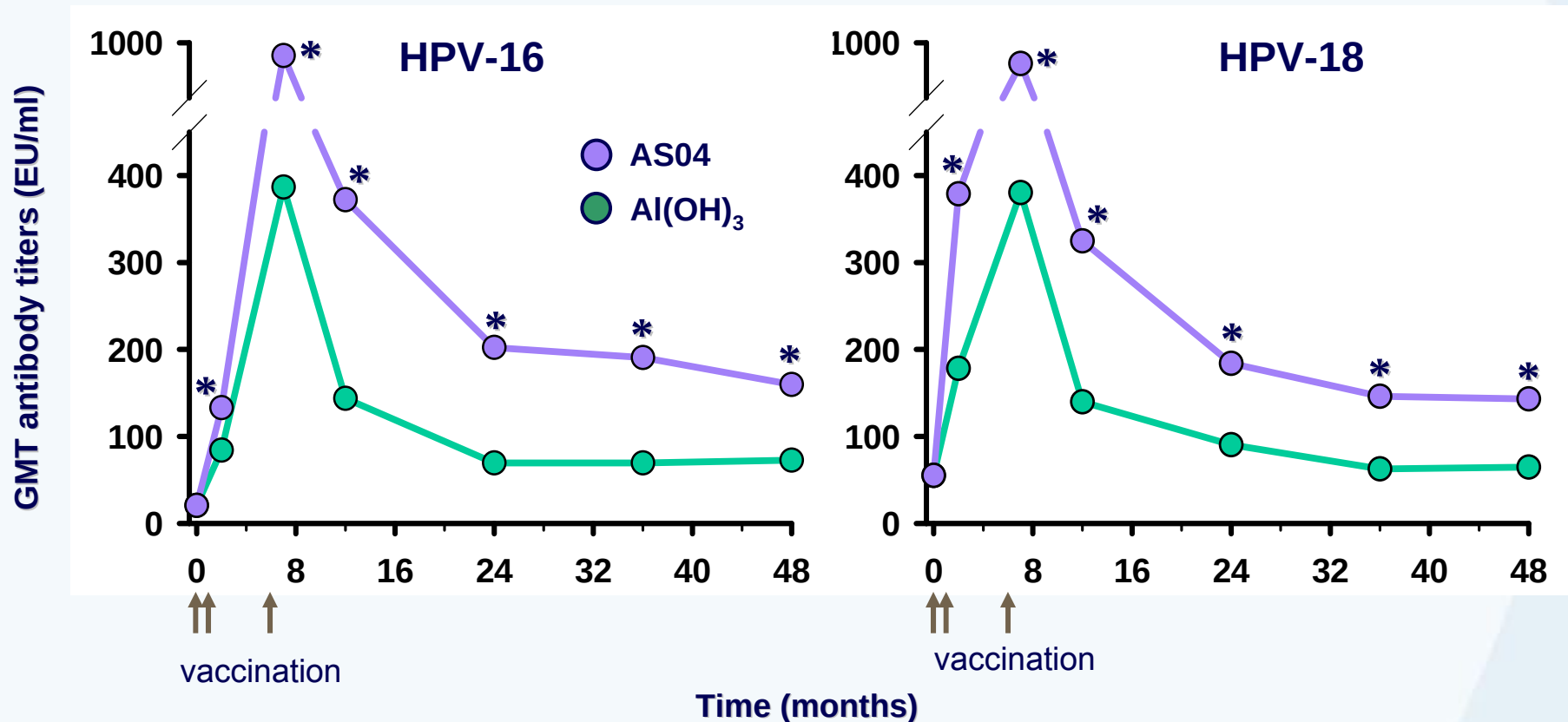
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# AS04 in GSK Cervical Cancer Candidate Vaccine

## Human Data: Antibodies

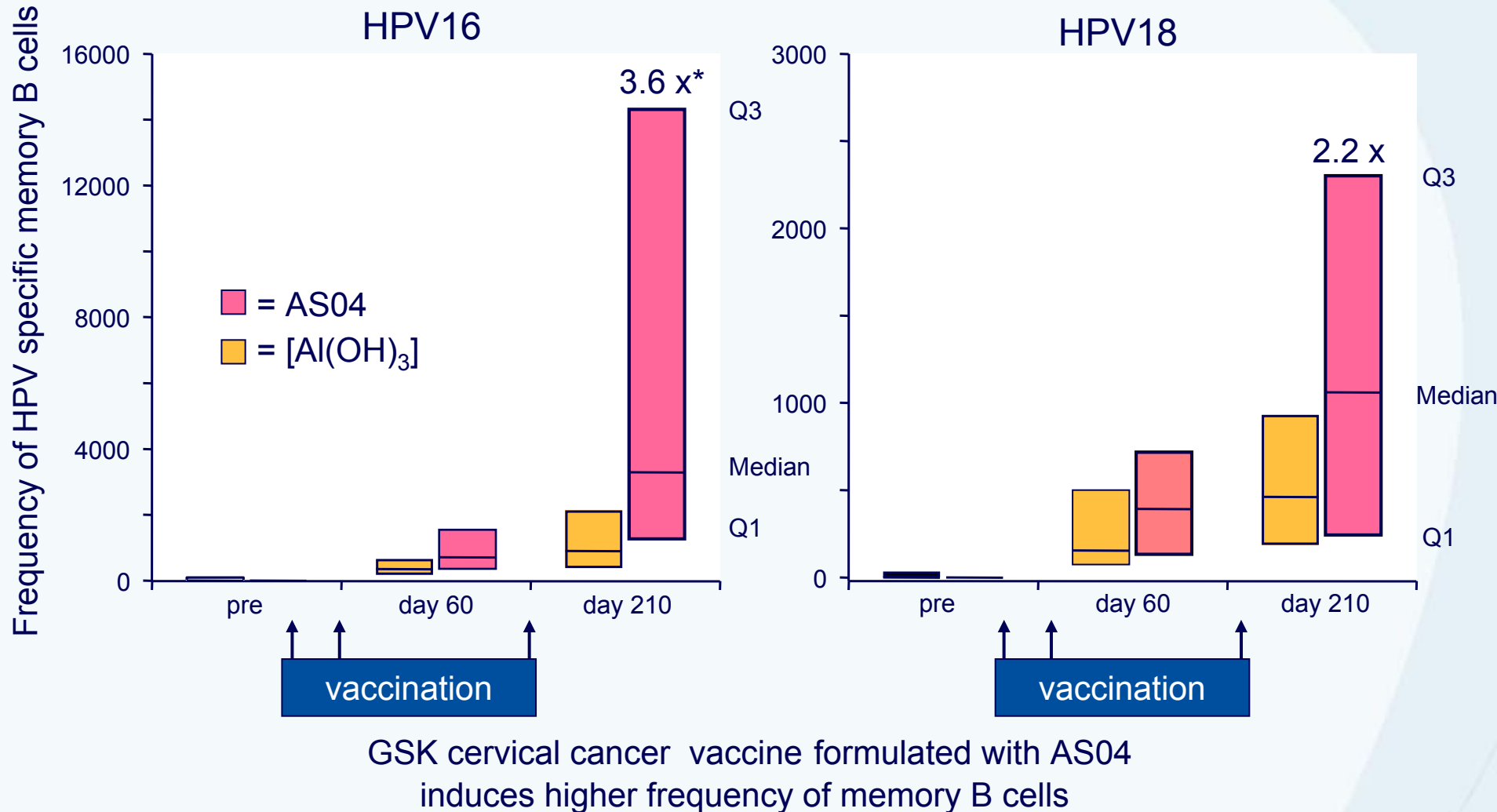
V5 epitope is targeted by HPV-16 neutralising antibodies

J4 epitope is targeted by HPV-18 neutralising antibodies



# AS04 in GSK Cervical Cancer Candidate Vaccine

## Human Data: 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  $\text{Al}(\text{OH})_3$

# 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

# HPV-001/007: 100% Protection Against HPV 16/18 Related CIN1+

| Endpoint                   | Vaccine<br>(Cases) | Control<br>(Cases) | Vaccine Efficacy |            |
|----------------------------|--------------------|--------------------|------------------|------------|
|                            |                    |                    | %                | 95% CI     |
| CIN1+ (HPV-001)            | 0                  | 6                  | 100              | NA         |
| CIN1+ (HPV-001/007) 4.5yrs | 0                  | 8                  | 100              | 42.4 – 100 |
| CIN1+ (HPV-001/007) 5.5yrs | 0                  | 11                 | 100              | 61.5 – 100 |

Harper et al., Lancet, 2004; 364: 1757. Harper et al., Lancet, 2006; 367: 1247-55.  
Gall S et al., AACR April 2007, USA

# HPV-001/007: 100% Protection Against HPV 16/18 Related CIN2+

| Endpoint                   | Vaccine (Cases) | Control (Cases) | Vaccine Efficacy |            |
|----------------------------|-----------------|-----------------|------------------|------------|
|                            |                 |                 | %                | 95% CI     |
| CIN2+ (HPV-001)            | 0               | 3               | 100              | NA         |
| CIN2+ (HPV-001/007) 4.5yrs | 0               | 5               | 100              | -7.7 – 100 |
| CIN2+ (HPV-001/007) 5.5yrs | 0               | 7               | 100              | 32.7 – 100 |

Harper et al., Lancet, 2004; 364: 1757. Harper et al., Lancet, 2006; 367: 1247-55.  
Gall S et al., AACR April 2007, USA

# HPV-001/007: First Preliminary Evidence of Cross Protection Against Infection by Types 45 & 31

Incident infection with most common oncogenic types beyond 16 & 18

| HPV Type | Vaccine |    |                                          | Placebo |    |                                          | Vaccine Efficacy (%)<br>(95% CI) |
|----------|---------|----|------------------------------------------|---------|----|------------------------------------------|----------------------------------|
|          |         |    | Event rate<br>(rate per 100)<br>(95% CI) |         |    | Event rate<br>(rate per 100)<br>(95% CI) |                                  |
|          | N       | n  | Rate                                     | N       | n  | Rate                                     |                                  |
| HPV-45   | 528     | 3  | 0.2 (0.0-0.6)                            | 518     | 24 | 1.7 (1.1-2.6)                            | 88 (61-98)                       |
| HPV-31   | 528     | 17 | 1.2 (0.7-1.9)                            | 516     | 35 | 2.6 (1.8-3.6)                            | 54 (15-76)                       |

Study not powered to evaluate cross protection against any individual types

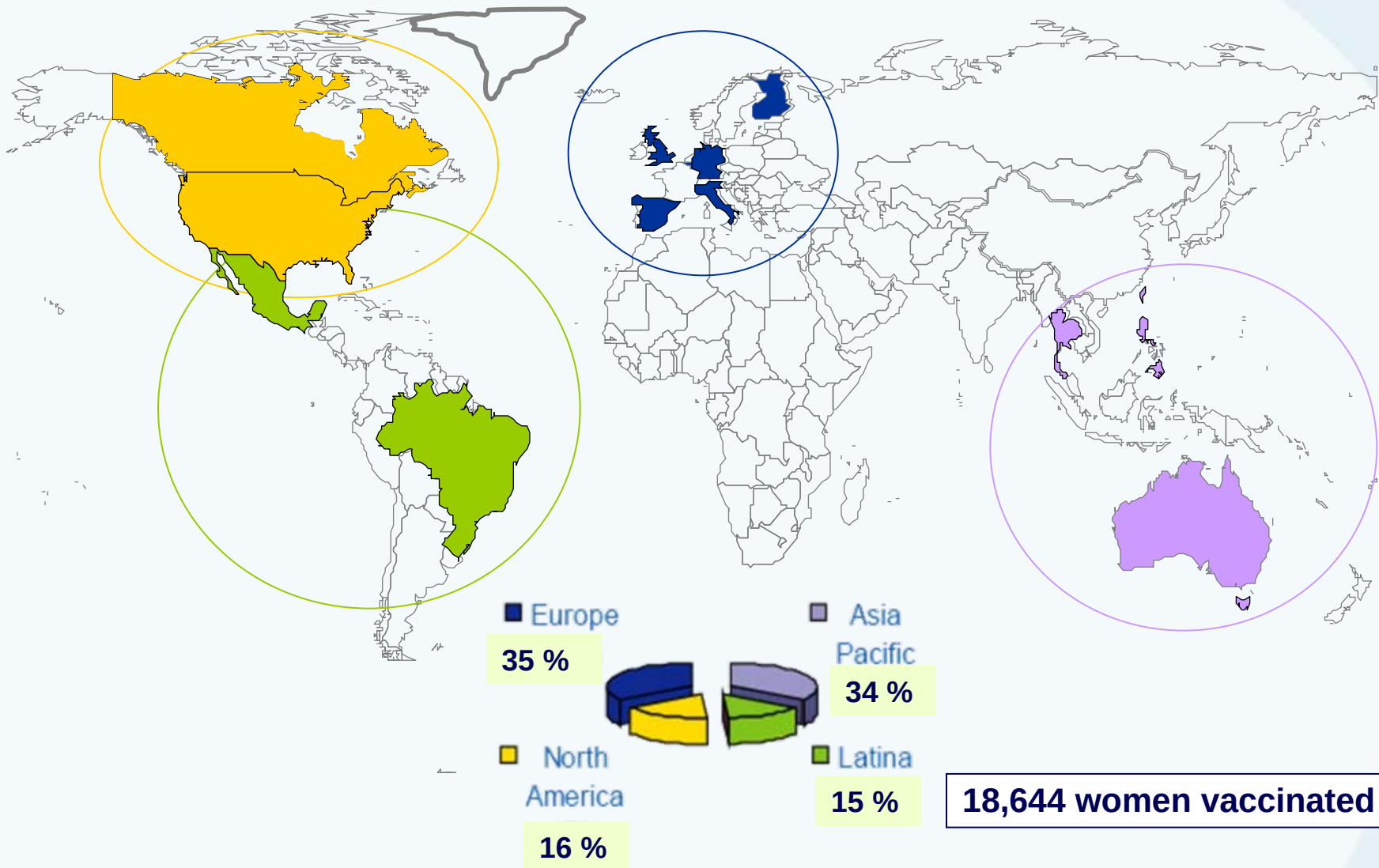


## GSK PhII Studies HPV-001/007 : Efficacy studies in Unexposed Women Aged 15-25 years Highlights of interim analysis at 5.5 years

### **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



# Efficacy Trial in a General Population: Endpoints

- Interim analysis triggered
  - When at least 23 cases of CIN2+ with HPV 16 or 18 in the lesion were available
- Primary endpoint:
  - CIN2+ lesions with HPV-16 or -18 detected in the lesion
- Pre-specified case definition:
  - Association based on DNA detection in the lesion only

# Efficacy Against HPV-16/18 CIN2+

**Pre-specified Case Definition based on PCR detection in the 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 |                             |      |      |         |

# Efficacy Against HPV-16/18 CIN2+

- More than 60% of CIN2+ lesions contained multiple HPV types

This high rate of multiple infections was not expected on the basis of published data

→ Additional analysis needed to attribute a causal association to an HPV type

- Causal association based on presence of HPV type in preceding cytology samples

Algorithm is based on the established association between persistent oncogenic infections and development of CIN2+ lesions<sup>1,2</sup>

# Efficacy Against HPV-16/18 CIN2+

One example:

Multiple HPV types in the CIN2+ lesion  
**and**

**No** detection of vaccine HPV type 16 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- <b>16</b> /58<br>36 days after<br>month 12 | CIN3: HPV-58<br>113 days after<br>month 12<br>Same lesion |

# Efficacy Against HPV-16/18 CIN2+

One example:

Multiple HPV types in the CIN2+ lesion  
**and**

**No** detection of vaccine HPV type 16 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<br>36 days after<br>month 12 | CIN3: HPV-58<br>113 days after<br>month 12<br>Same lesion |

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

# Efficacy Against HPV-16/18 CIN2+

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 |                             |      |      |         |

Additional- post hoc- analysis considering patterns of HPV types in preceding cytology 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 |                             |      |     |         |

# Efficacy Against 12 Month Persistent Infections with Oncogenic HPV-types Beyond 16 & 18

|                              | ITT              |                 |                  | ATP              |                 |                  |          |
|------------------------------|------------------|-----------------|------------------|------------------|-----------------|------------------|----------|
| HPV-type endpoint            | Cervarix (cases) | Control (cases) | Vaccine Efficacy | Cervarix (cases) | Control (cases) | Vaccine Efficacy | 97.9% CI |
| Oncogenic HPV beyond 16 & 18 | 100              | 137             | 27.1%            |                  |                 |                  |          |

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

# Efficacy Against 12 Month Persistent Infections with Oncogenic HPV-types Beyond 16 & 18

|                              | ITT              |                 |                  | ATP              |                 |                  |           |
|------------------------------|------------------|-----------------|------------------|------------------|-----------------|------------------|-----------|
| HPV-type endpoint            | Cervarix (cases) | Control (cases) | Vaccine Efficacy | Cervarix (cases) | Control (cases) | Vaccine Efficacy | 97.9% CI  |
| Oncogenic HPV beyond 16 & 18 | 100              | 137             | 27.1%            | 5                | 14              | 65.1%            | <0 – 92.3 |

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

# Cross-Protection Against 6 Months Persistent Infections

|        | TVC-E (at least 1 dose) |                 |                      |            |
|--------|-------------------------|-----------------|----------------------|------------|
| Type   | 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 |

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

# Efficacy Trial in a General Population: Safety Profile

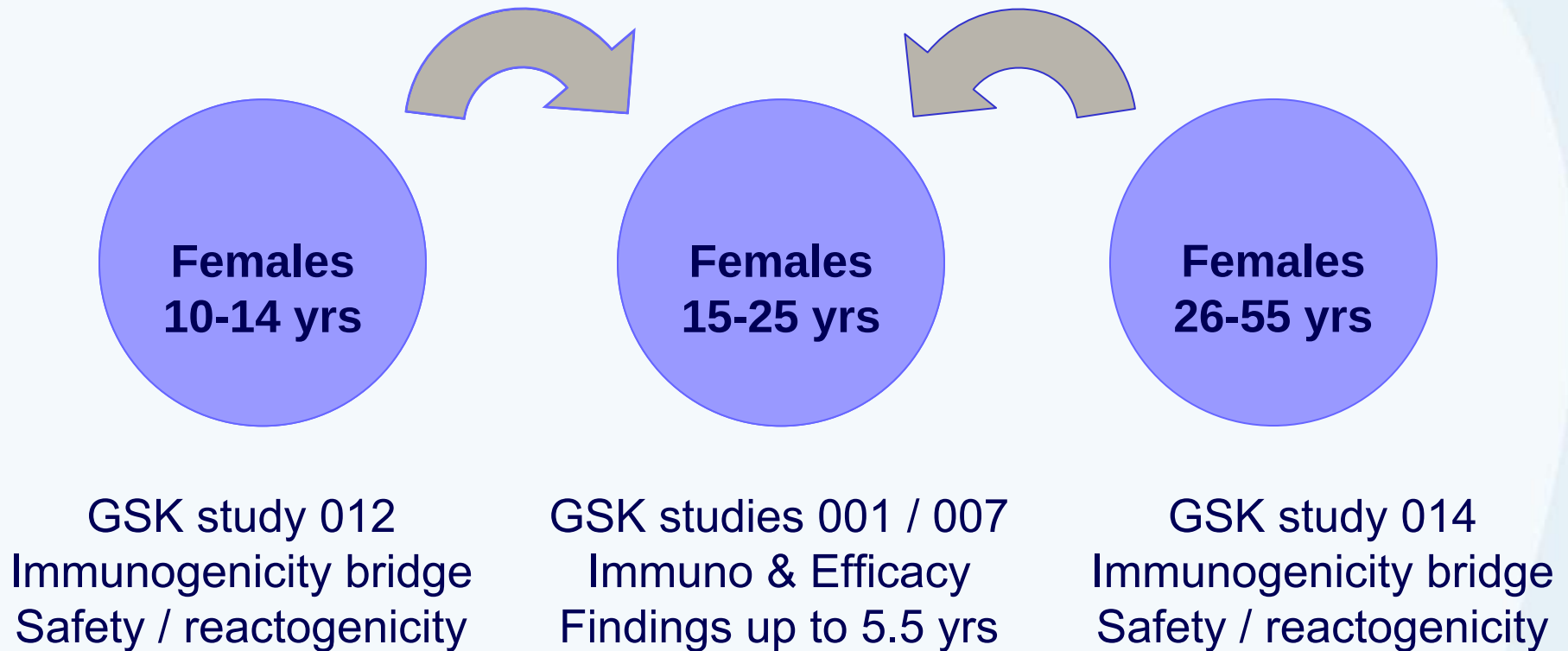
| Safety Outcomes                                                              | HPV<br>(N = 9319) | HAV<br>(N = 9325) |
|------------------------------------------------------------------------------|-------------------|-------------------|
| <b>Unsolicited Adverse Events:</b> % of women with at least 1 event (95% CI) |                   |                   |
| All unsolicited symptoms* (Day 0-29)                                         | 42.5% (60.8-44.3) | 43.6% (41.9-45.3) |
| Medically significant conditions                                             | 21.3% (20.5-22.2) | 21.8% (20.9-22.6) |
| New onset chronic diseases                                                   | 1.5% (1.3-1.8)    | 1.7% (1.4-1.9)    |
| New onset autoimmune diseases                                                | 0.3% (0.2-0.5)    | 0.3% (0.2-0.4)    |
| <b>Serious Adverse Events:</b> number (%)                                    |                   |                   |
| Number of women reporting                                                    | 330 (3.5%)        | 323 (3.5%)        |
| Number of SAEs reported                                                      | 389 (4.2%)        | 372 (4.0%)        |

\*Diary card subset (3184 HPV recipients and 3187 HAV recipients)

# GSK Phase III Efficacy trial HPV 008: Interim Analysis Conclusions

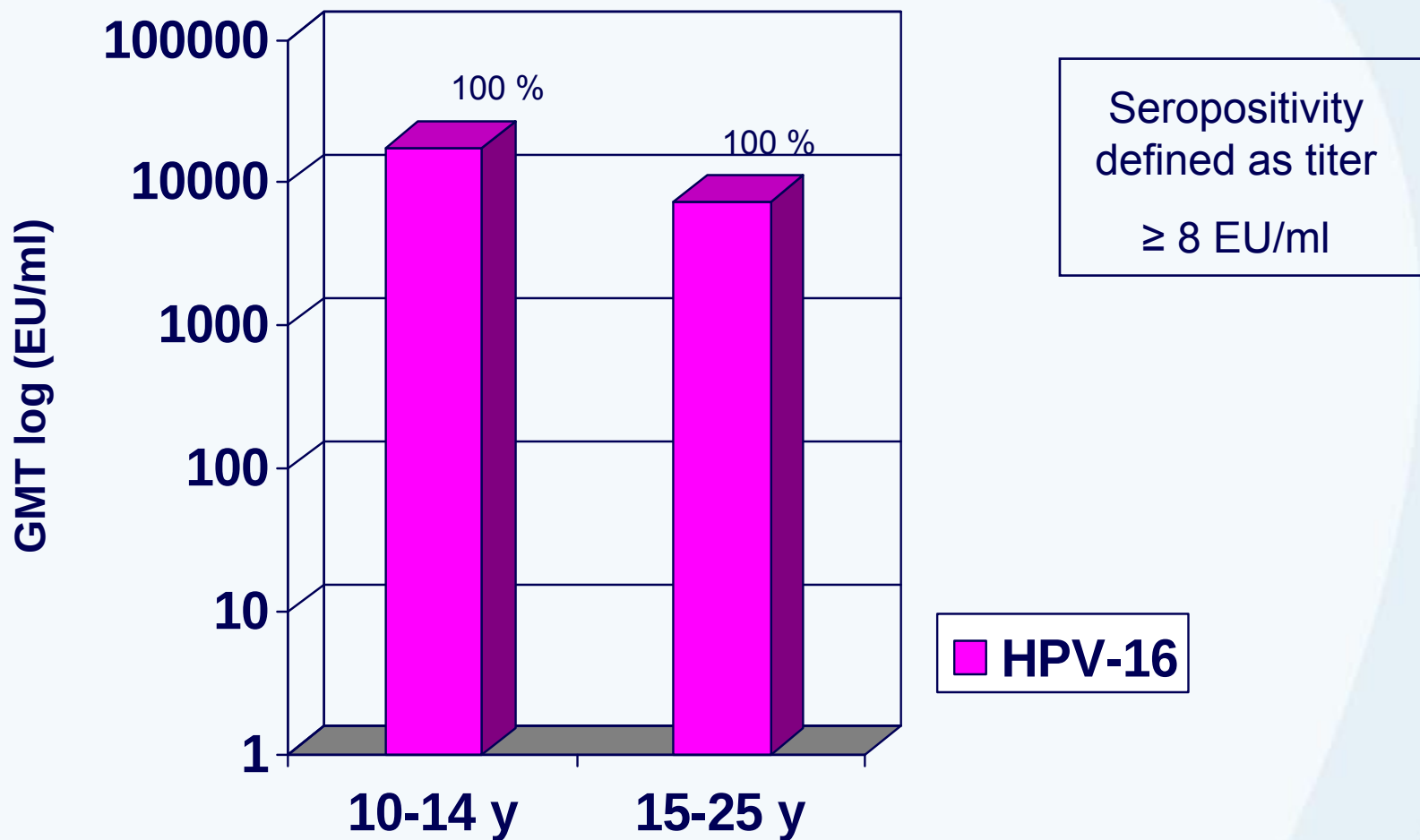
- Highly immunogenic
- Generally well tolerated
- High level protection against HPV-16/18 CIN2+ confirmed in a broad population of women (TVC-E)
  - **90% vaccine efficacy against any CIN2+ with HPV-16/18 detected in the lesion**
  - **100% vaccine efficacy against CIN2+ where HPV-16/18 was causally 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



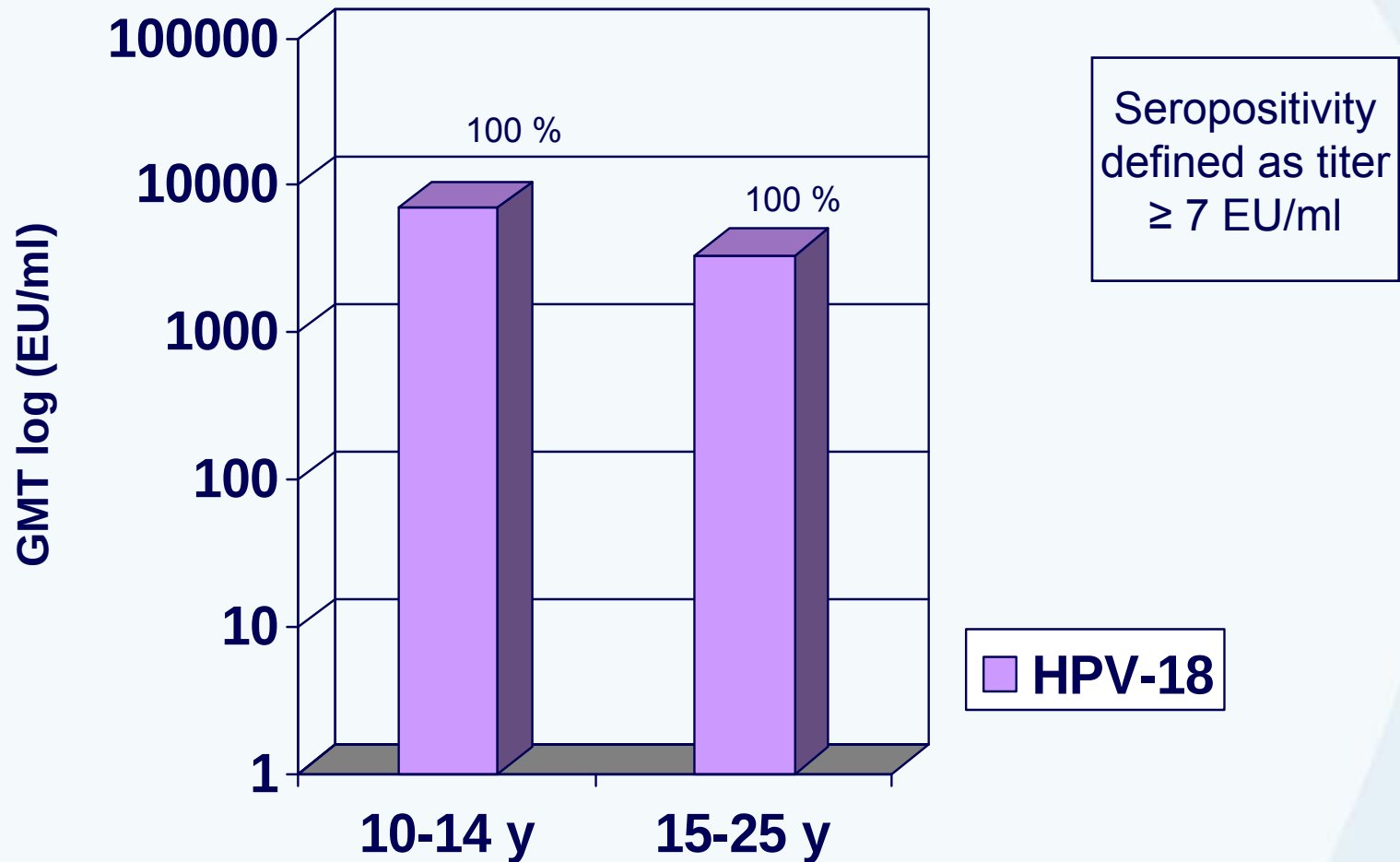
# HPV 012 Results

## Results at month 7: GMT and seroconversion rate



# HPV 012 Results

## Results at month 7: GMT and seroconversion rate

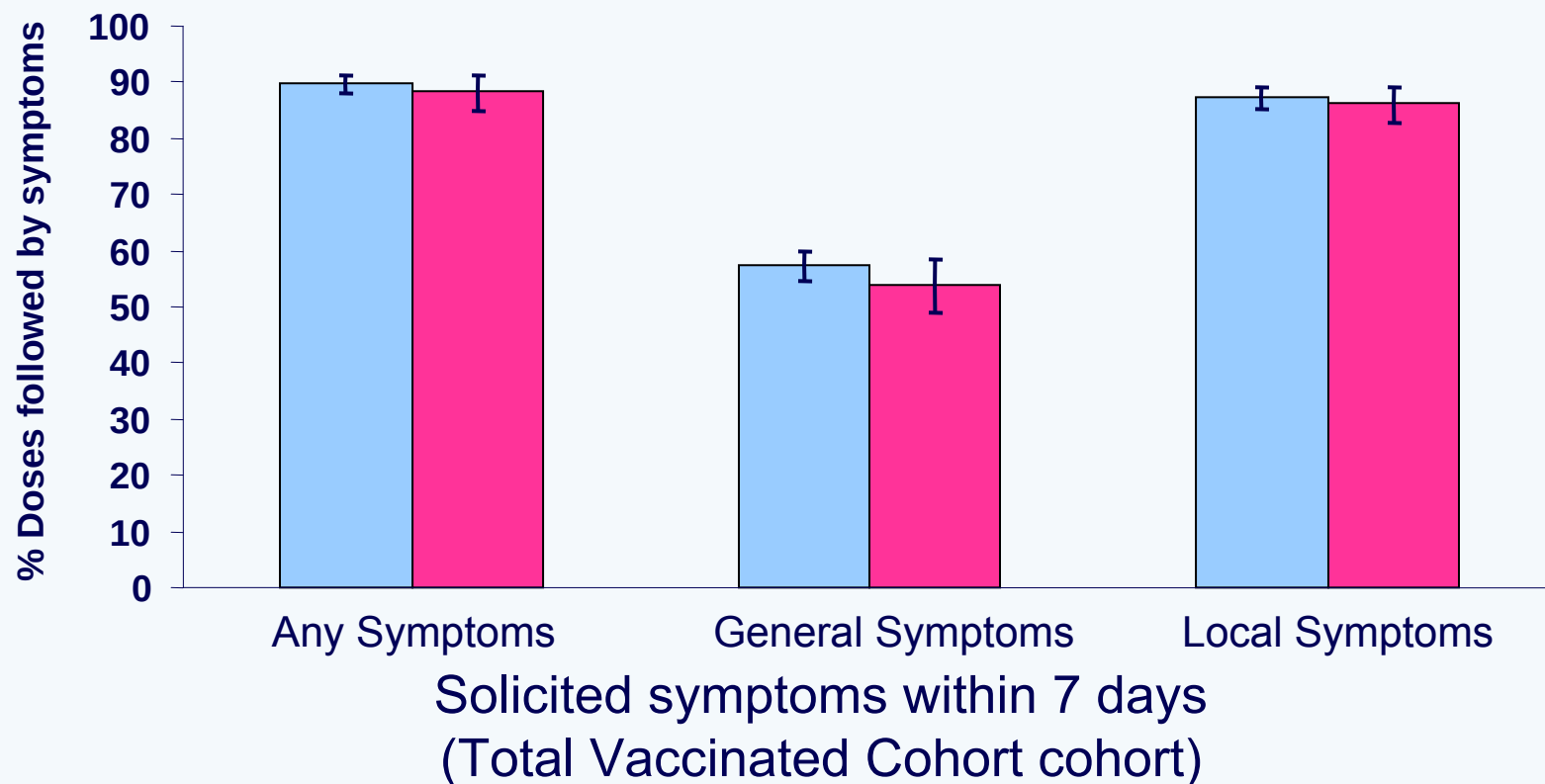


# GSK HPV 012 Study

## Safety data

No serious adverse events related to vaccination

15-25 yrs  
10-14 yrs



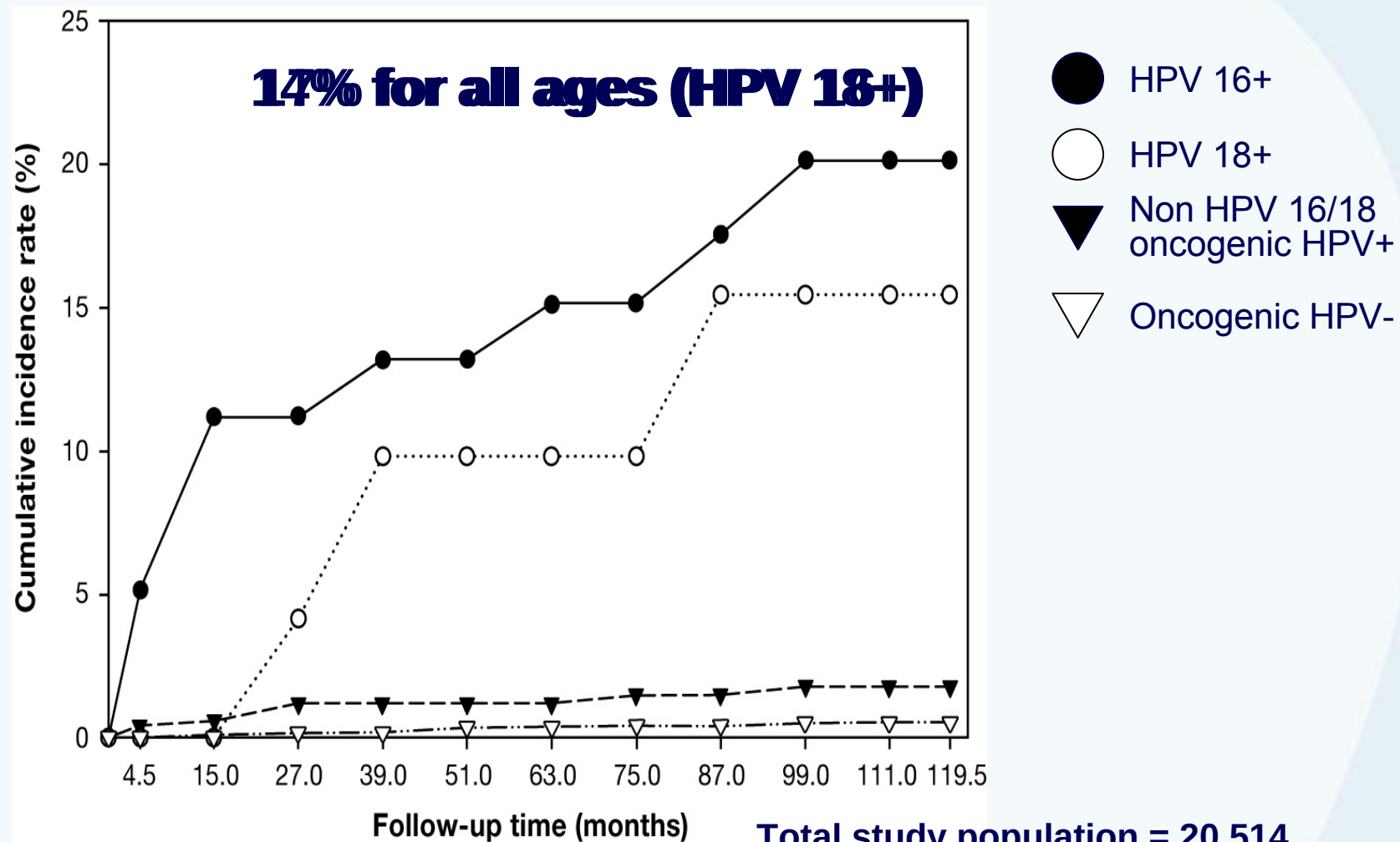
# GSK HPV 012 Study Summary

- **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**

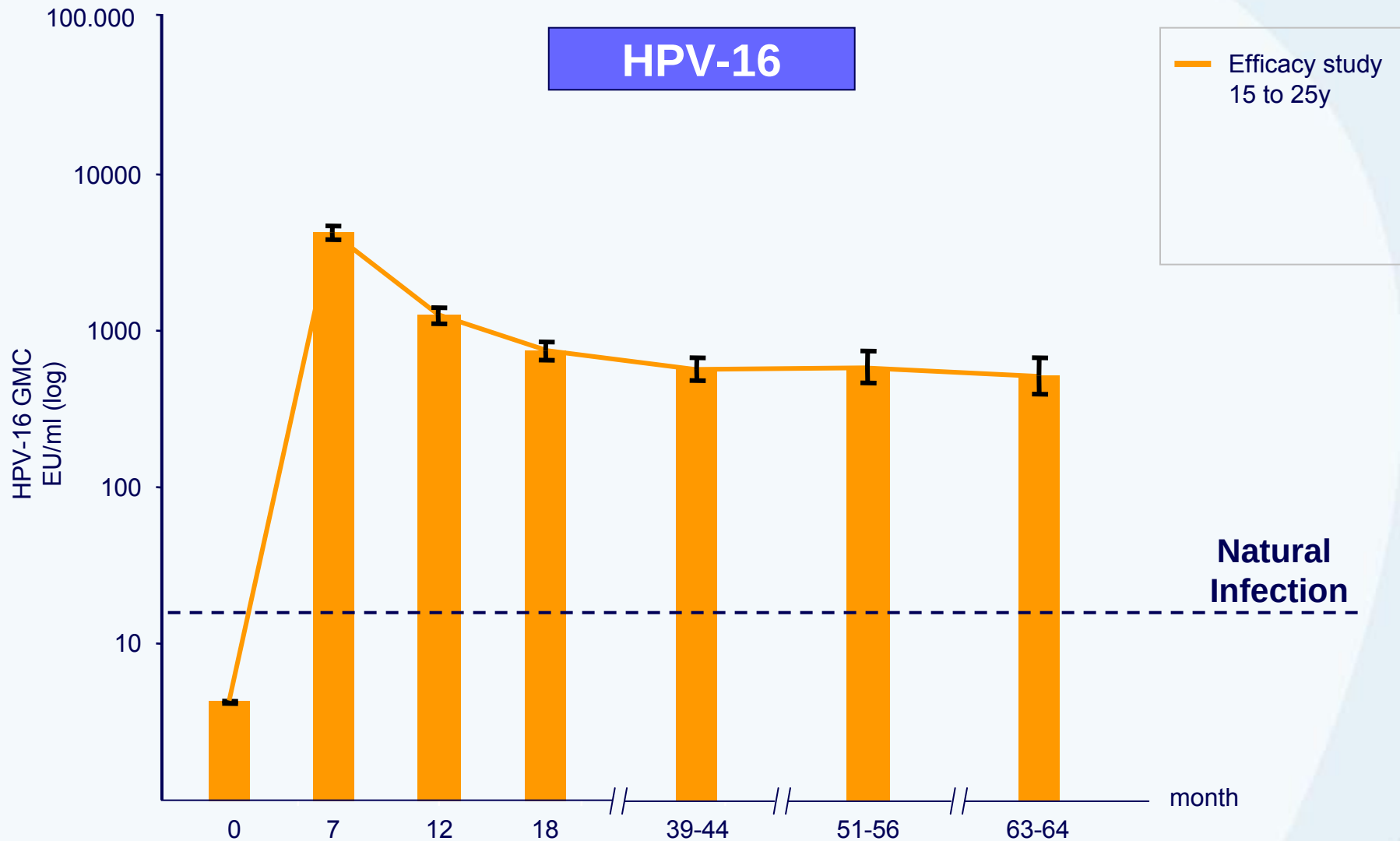
# HPV infections occur in women over 25 years of age

- Annual incident infection rate with oncogenic HPV types is estimated at 5.3% in women 25-55 years of age (range 5-10%) <sup>1-3</sup>
- Although new infections decrease with age, risk of persistence increases with age <sup>4</sup>

# One in five HPV-16+ women aged $\geq 30$ will develop a CINIII+ lesion over a 10-year period

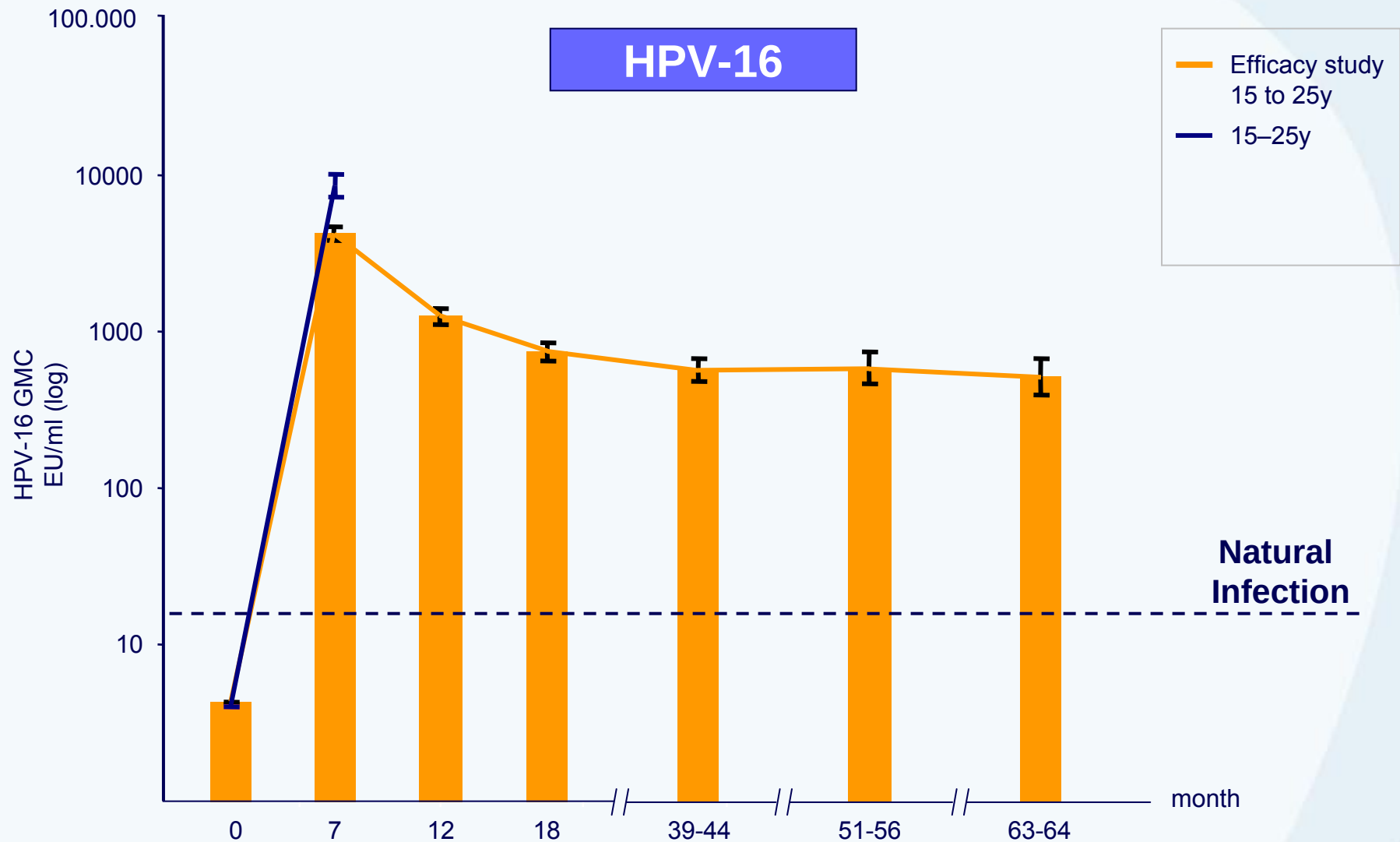


# HPV-16 Antibody Levels Observed in Efficacy Study HPV-001/007 up to 5.5 y

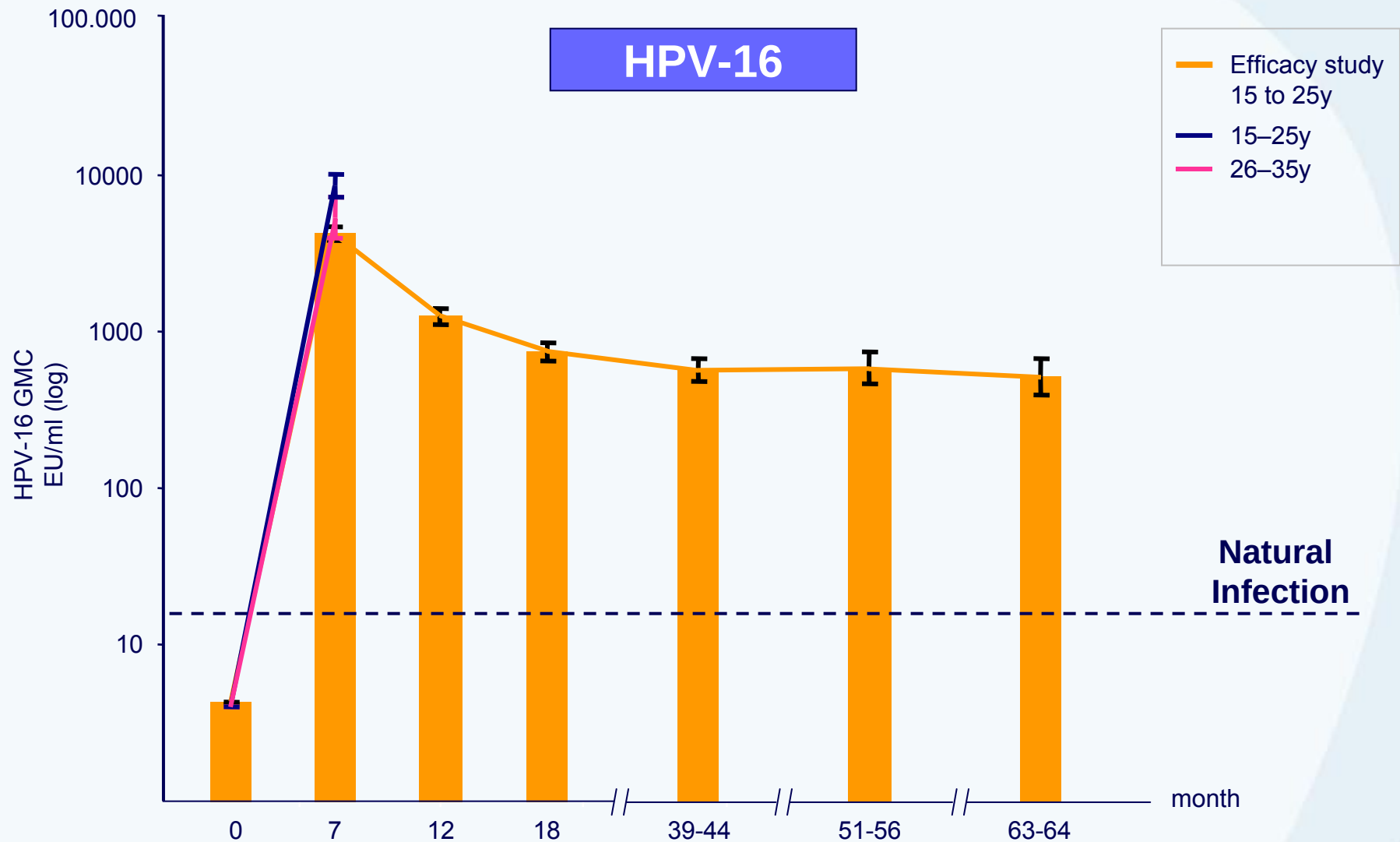




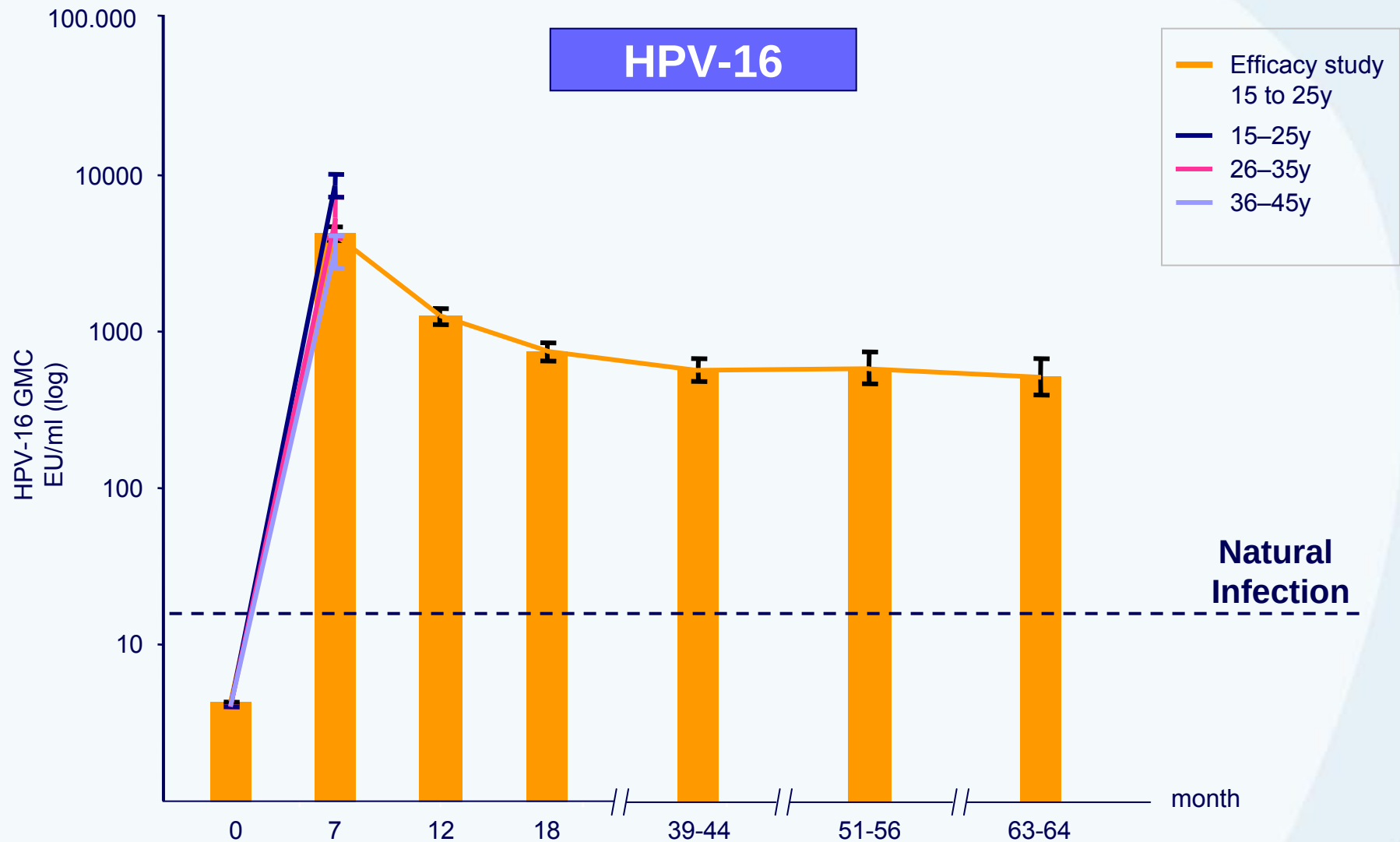
# Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



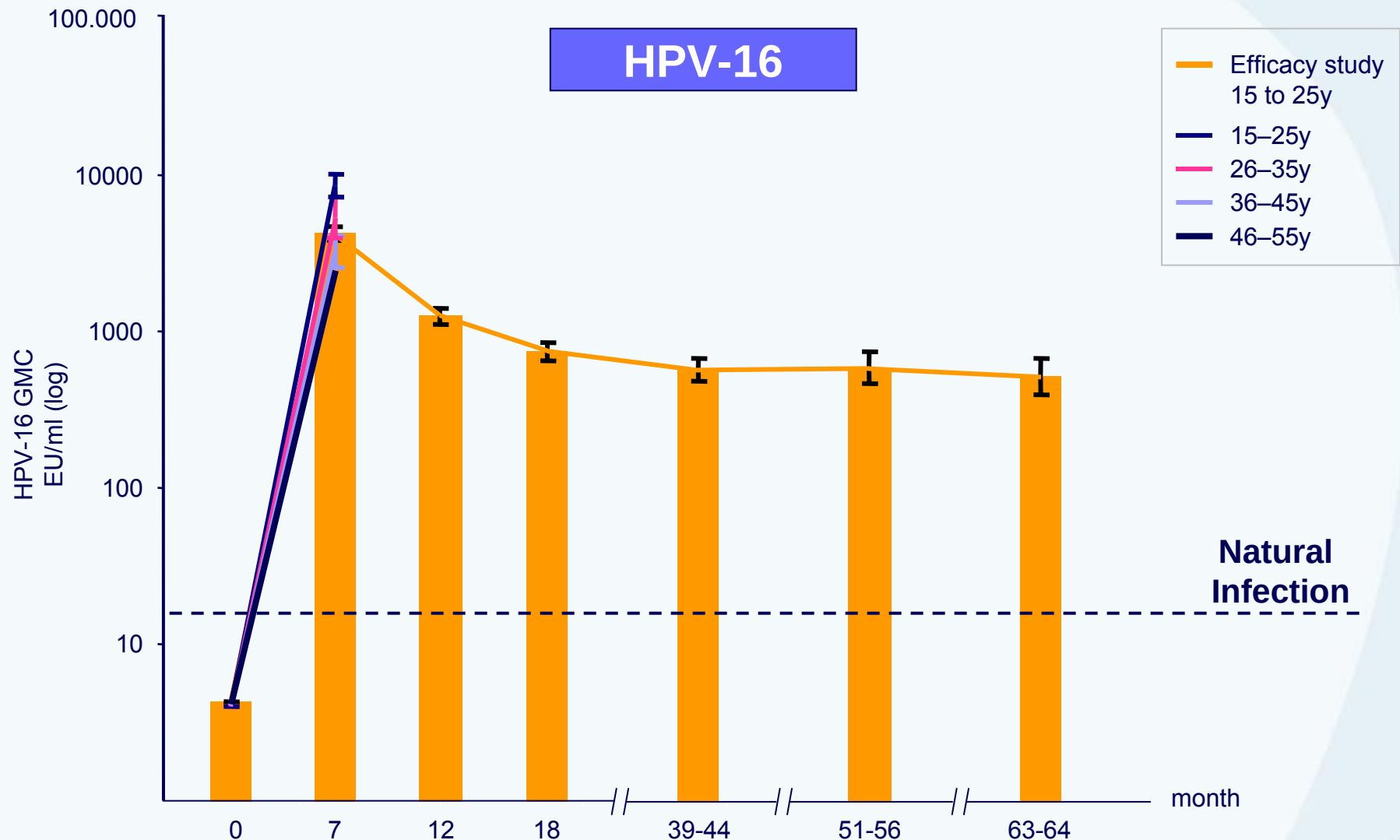
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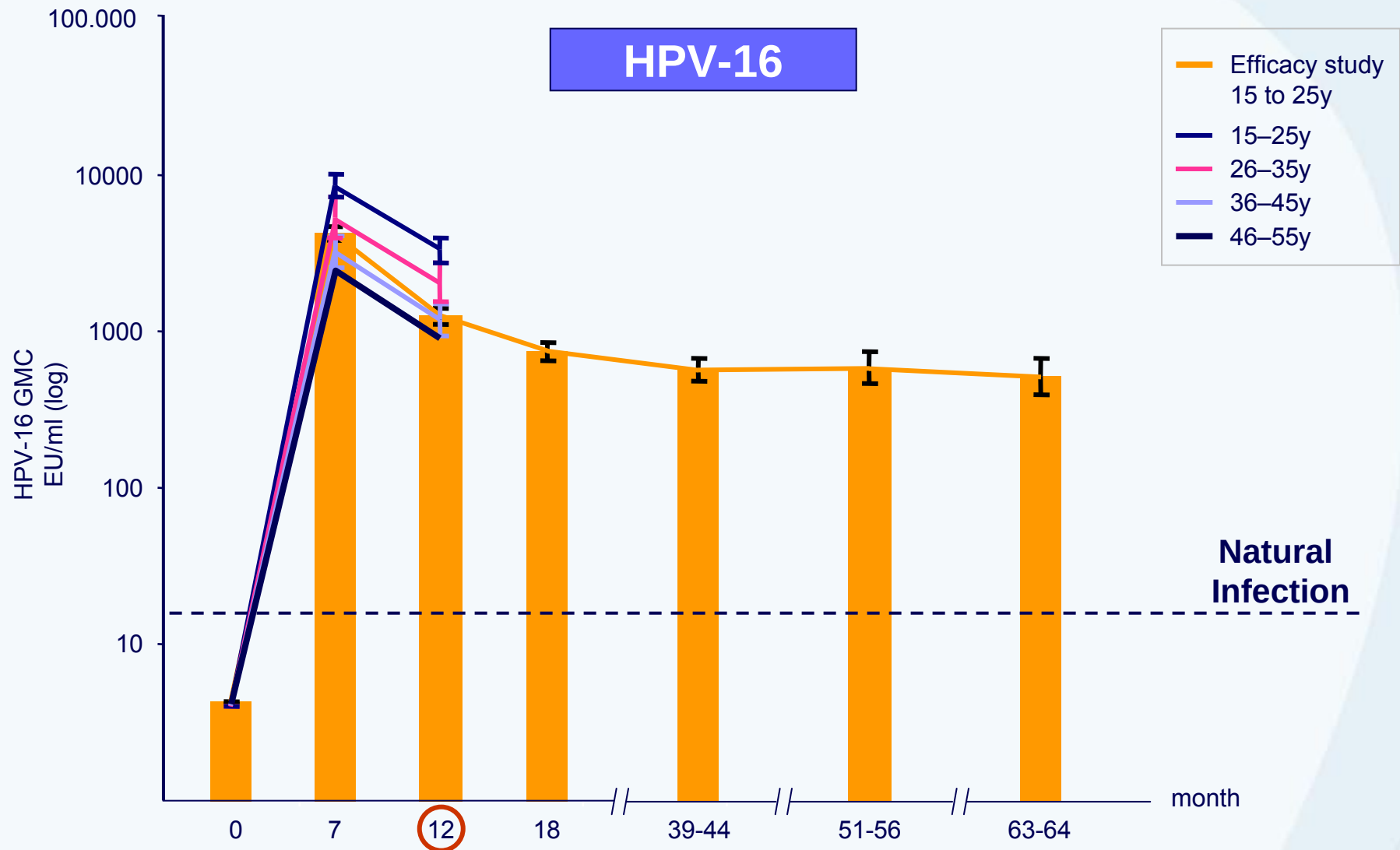
# Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



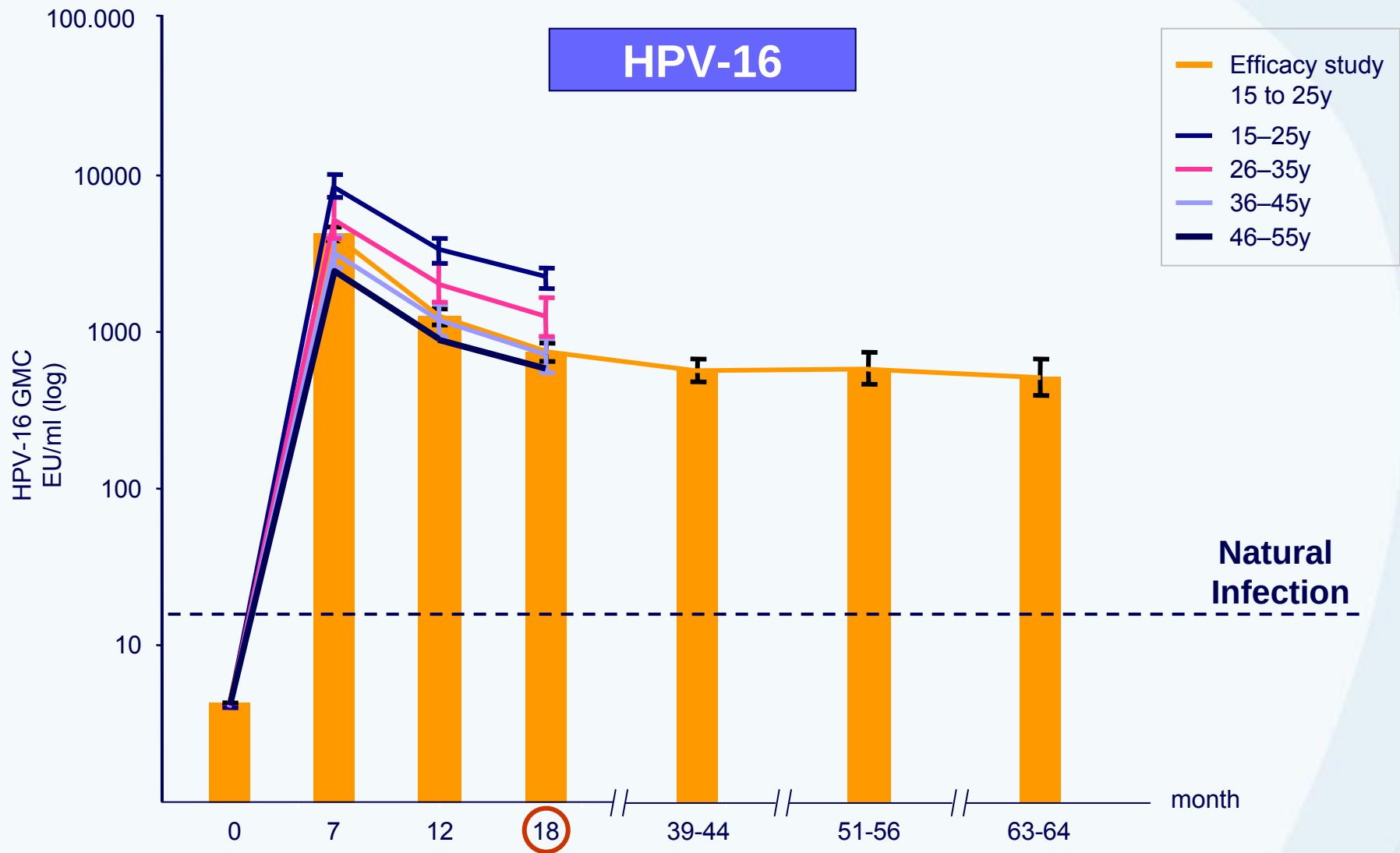
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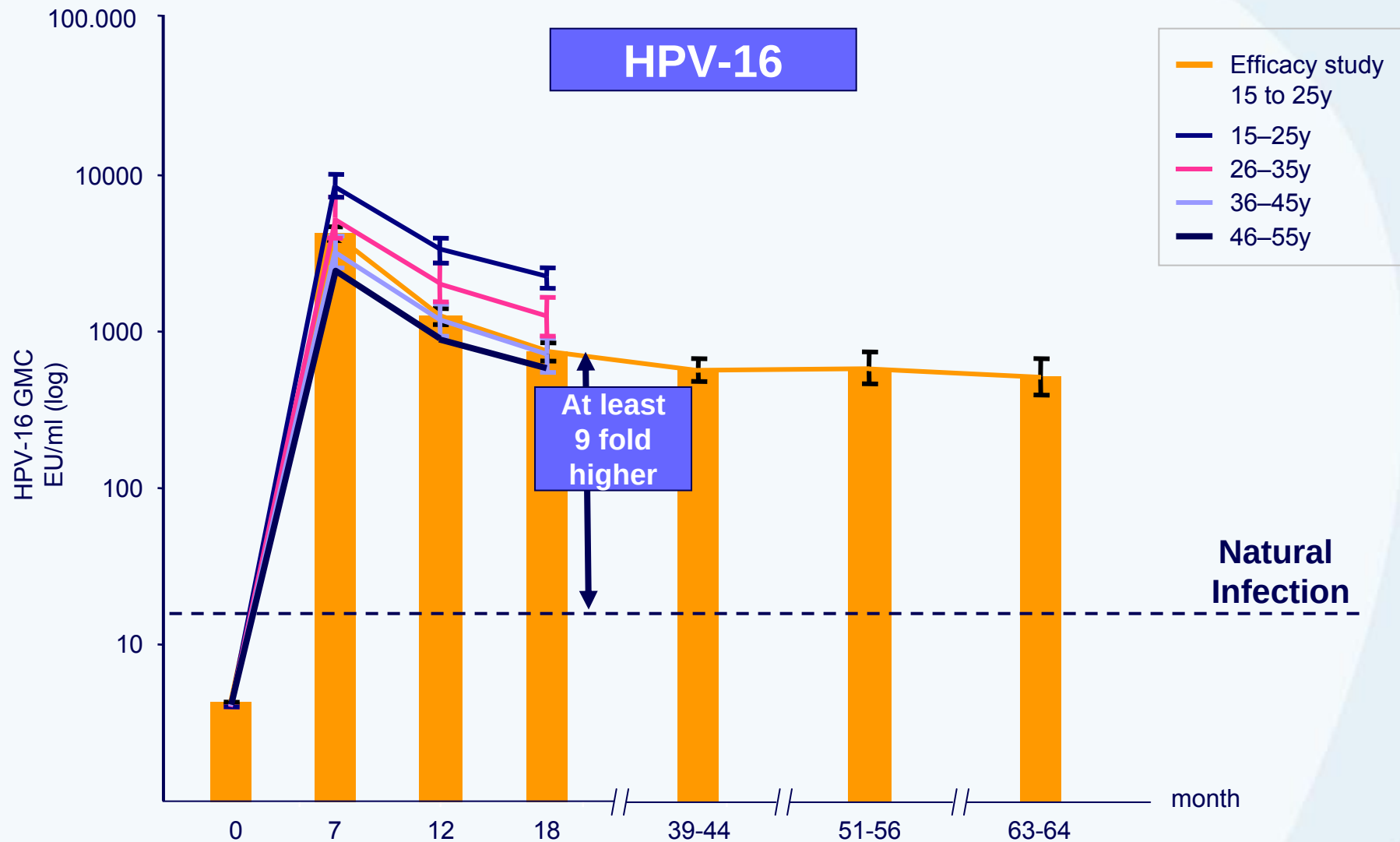


# Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007

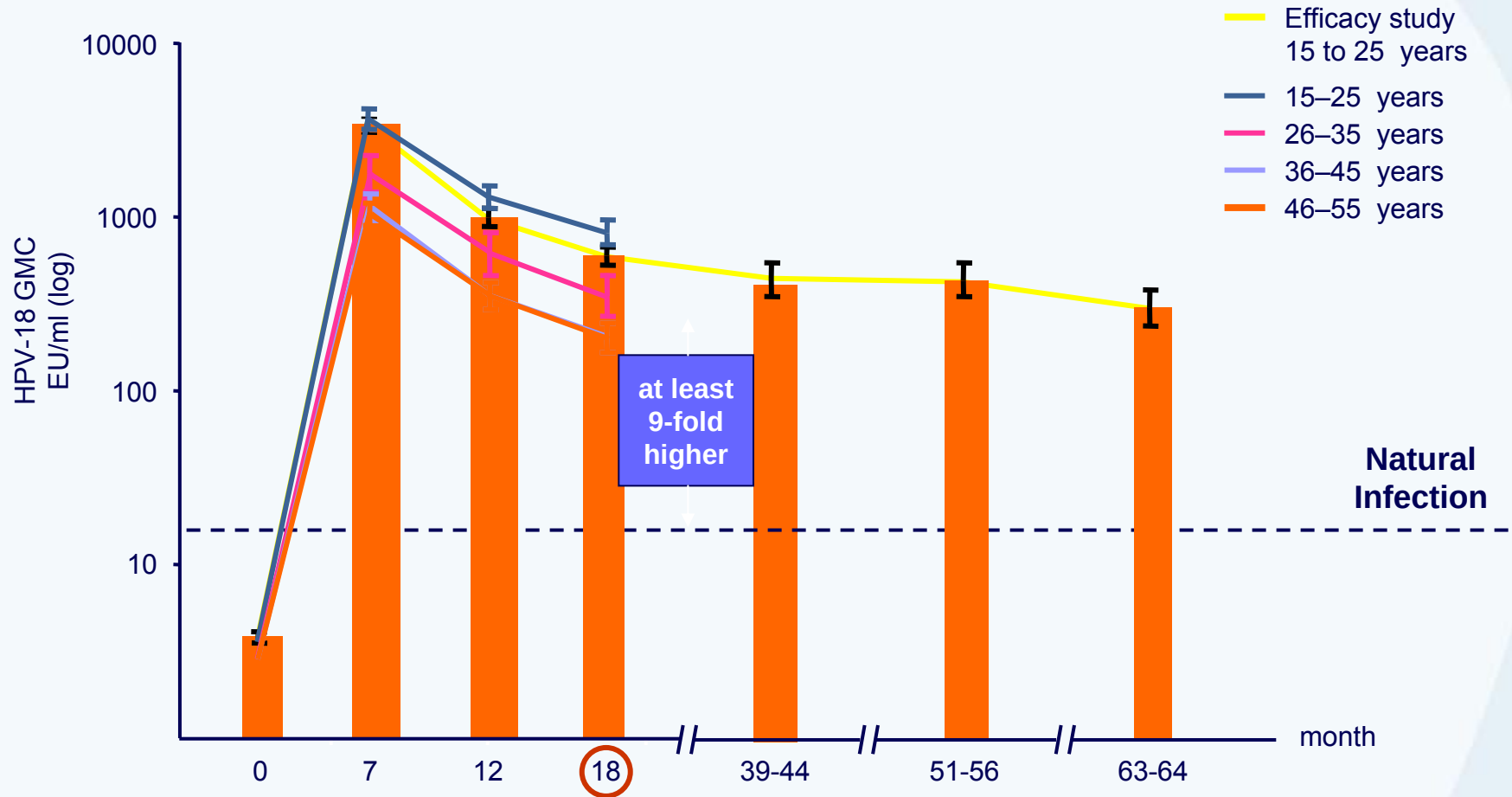




# Antibody Levels in 15-55 Year Old Women Comparable to those Observed in Efficacy Study HPV-001/007



# HPV-18 Antibody Levels in all age groups Comparable to those Observed in Efficacy Study





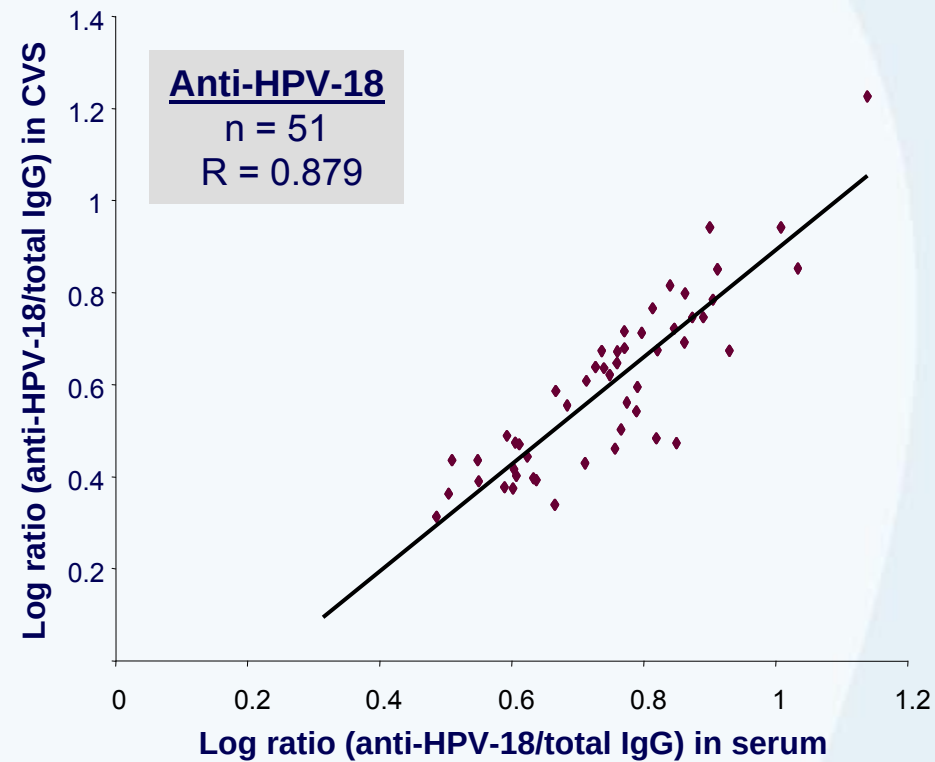
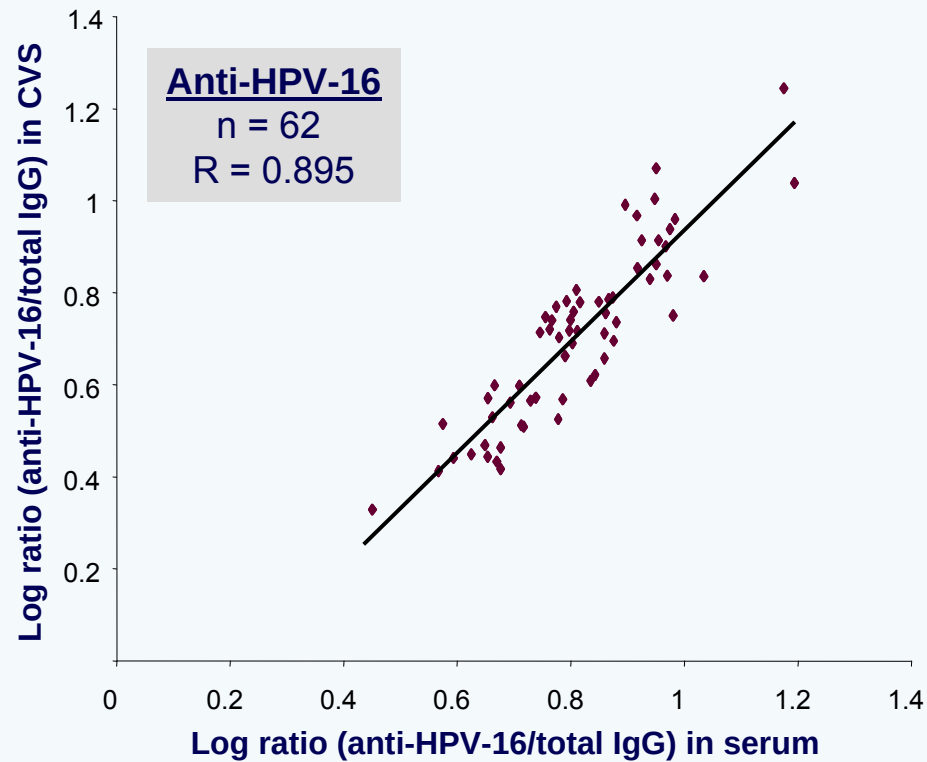
## HPV-014 – 18 Months Confirmation of Strong & Sustained Immune Response in Women >25 Years

- 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)

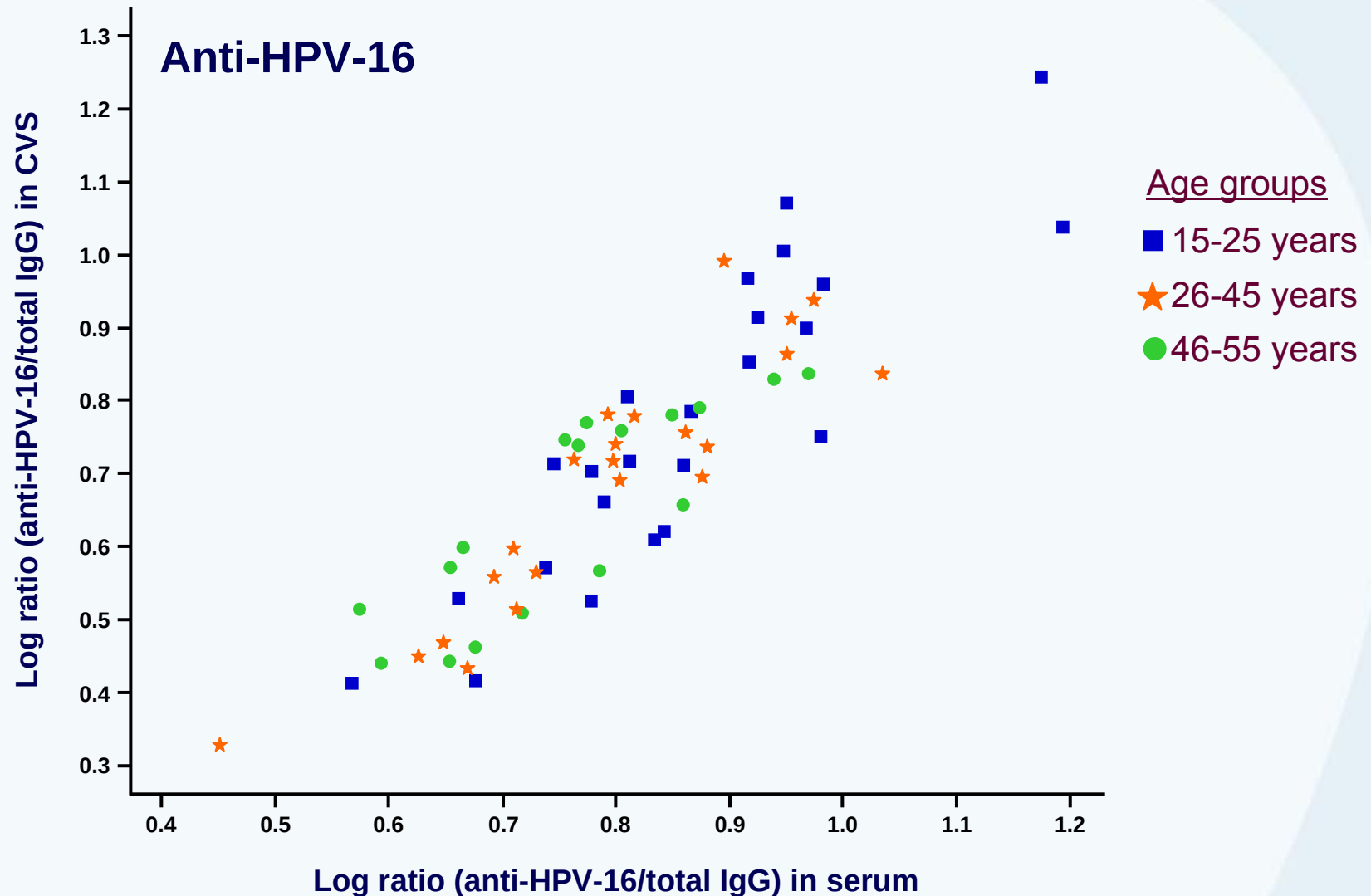
# Immune response at mucosal level

- Serum antibody responses against anti-HPV-16 and anti-HPV-18 elicited by the HPV-16/18 candidate vaccine are likely to represent an important, if not essential, aspect of providing protection against HPV-16 and/or HPV-18 cervical infections.
- One additional aspect of protection may be the detection of an effective immune response at disease-relevant sites, namely the genital mucosa.
- One possible mechanism of protection of the cervix is transudation of serum IgG into cervical secretions.

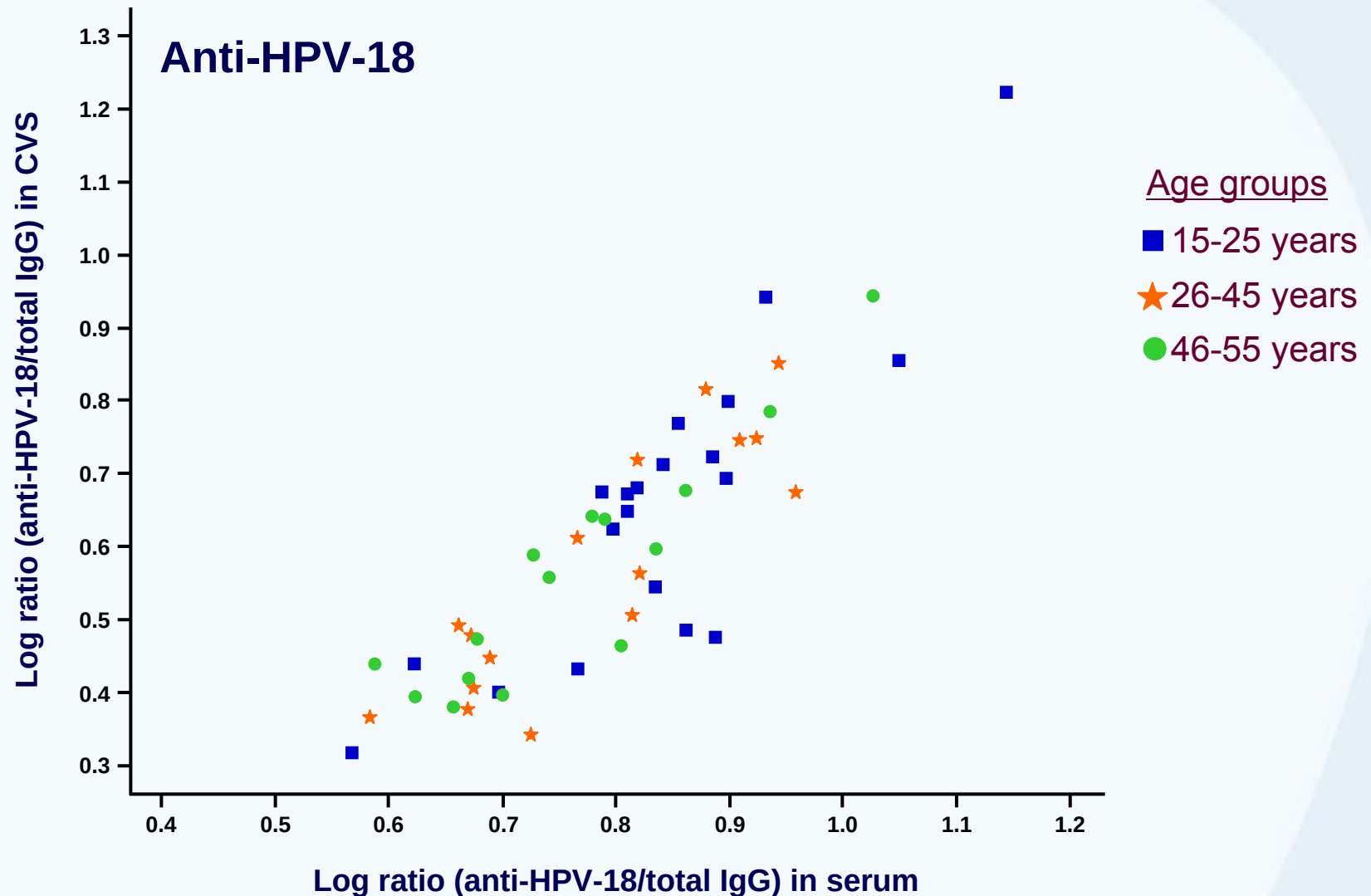
# Correlation between CVS and serum antibodies in combined age groups 15-55 years



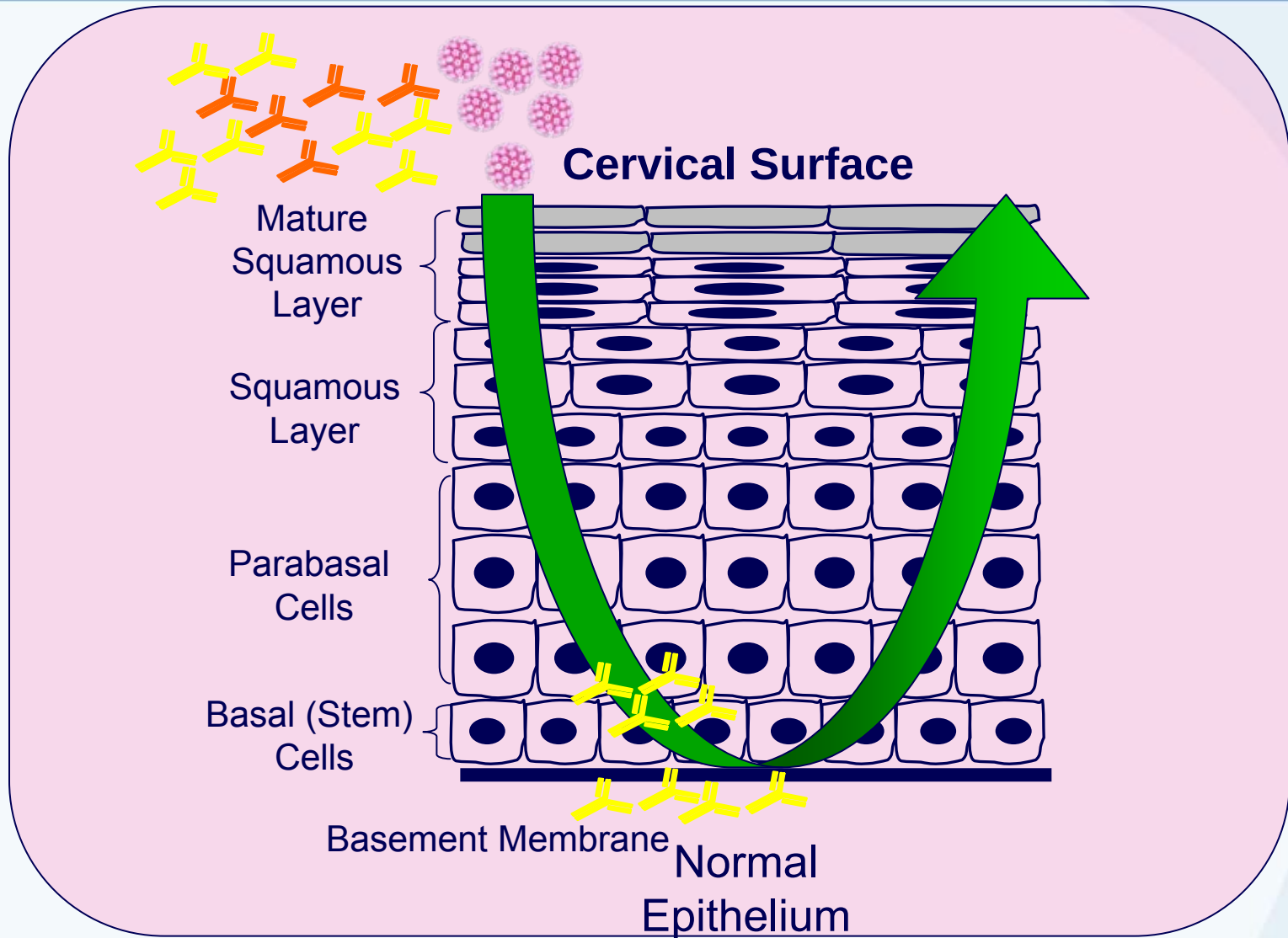
# High Correlation between Cervico-Vaginal Secretions (CVS) and serum antibodies according to age group



# High Correlation between Cervico-Vaginal Secretions (CVS) and serum antibodies according to age group



# 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**

# Summary

- **GSK's Cervical Cancer Candidate Vaccine with AS04 against HPV 16 and 18 persistent infection and disease**
  - **A stronger and more sustained humoral response to HPV 16 and 18**
  - **A higher frequency of antigen-specific memory B cell** as compared to the same vaccine formulated with  $\text{Al}(\text{OH})_3$
  - **Broad protection beyond HPV 16 and 18**
  - **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)