



GSK Cervical Cancer Candidate Vaccine: The Use of the AS04 Adjuvant System to Enhance Immune Responses

Martine Wettendorff, PhD

Vice President, Viral and Allergy Programs, R&D

GlaxoSmithKline Biologicals, Rixensart

ACIP 25 Oct 2007

Topics to be Covered

- GSK HPV Vaccine Development Strategy
- Immune Responses and Mode of Action of MPL
- Immunological Benefits of AS04

GSK's HPV16/18 Cervical Cancer Vaccine

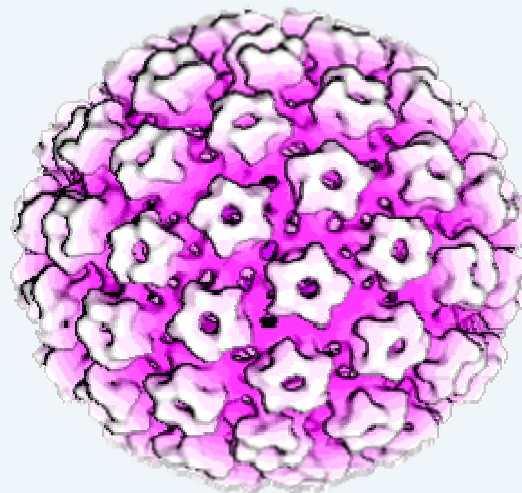
Development Strategy

- HPV-16/18 are responsible for ~ 70% of invasive cervical cancers worldwide
 - No compromise on HPV16 and 18 – theoretical risk of interference
- New infections with oncogenic HPV types occur in a broad age range of sexually active women
 - Vaccine targets prevention of cervical cancer in females from 10 years onwards
- Natural HPV infections do not induce consistent antibody responses
 - Vaccine designed to induce strong and sustained immune responses

Product Composition

Recombinant
L1 protein

Self-assemble
into Virus Like
Particles (VLP)



Resemble intact
viruses

Non infectious

Composition

20 µg L1 VLP HPV-16

20 µg L1 VLP HPV-18

500 µg Al(OH)₃

50 µg MPL

} **AS04 Adjuvant System**

AS04 is GSK's Novel Proprietary Adjuvant System

- AS04 is a combination of MPL and $\text{Al}(\text{OH})_3$
- MPL is:
 - 3- O-desacyl-4'-monophosphoryl lipid A
 - Derived from lipopolysaccharide (*Salmonella minnesota*), a potent adjuvant
 - Ubiquitous in environment and human exposure is common
 - Chemically modified and retains adjuvant activity

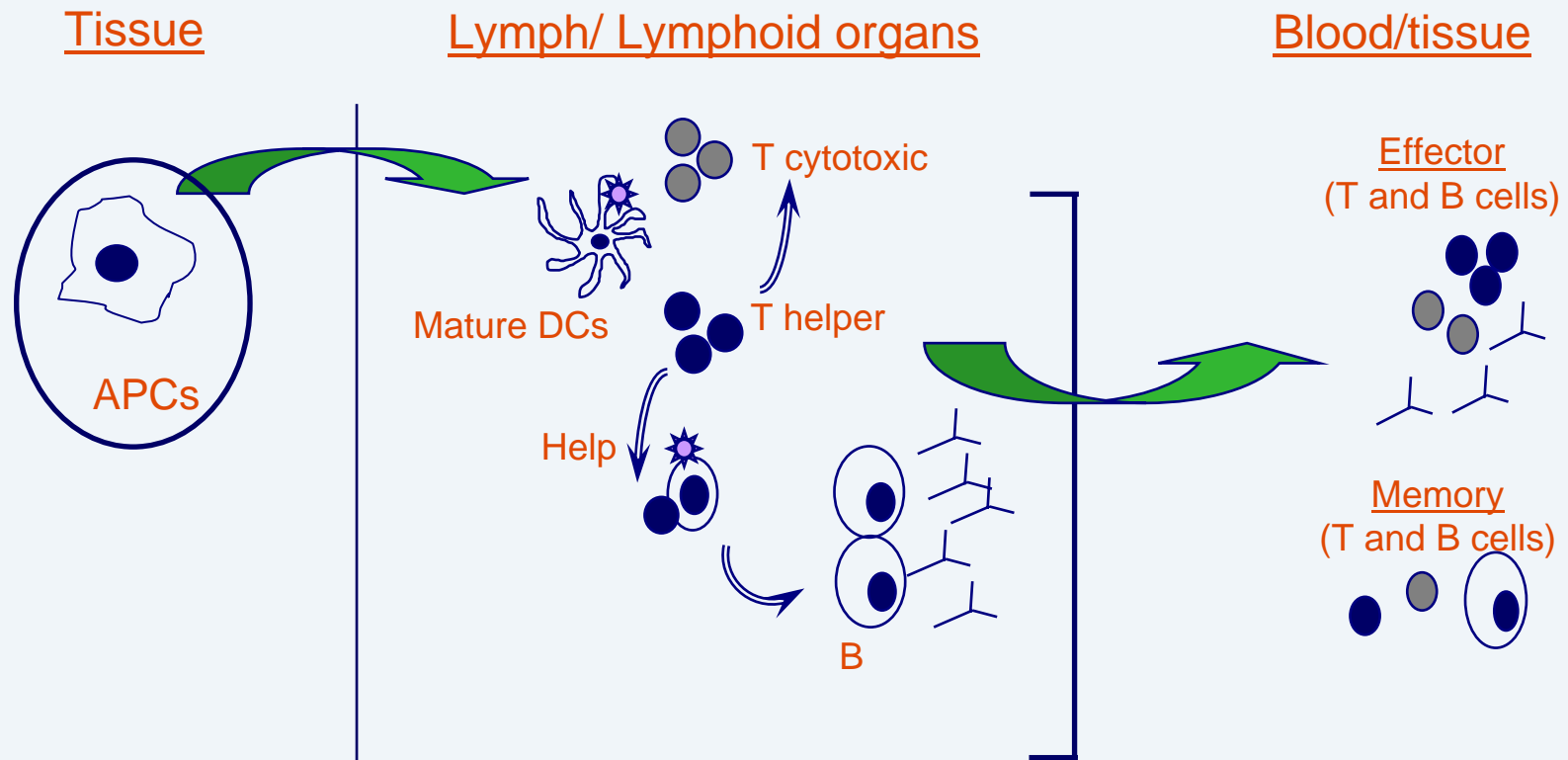
Rationale for AS04 Selection

- Designed to enhance immunogenicity and increase duration of protection
 - Adolescents / young adults: duration of protection
 - Older women: age related decline in immune response to vaccines
 - Higher serum antibody levels drive higher levels at site of infection (genital mucosa)

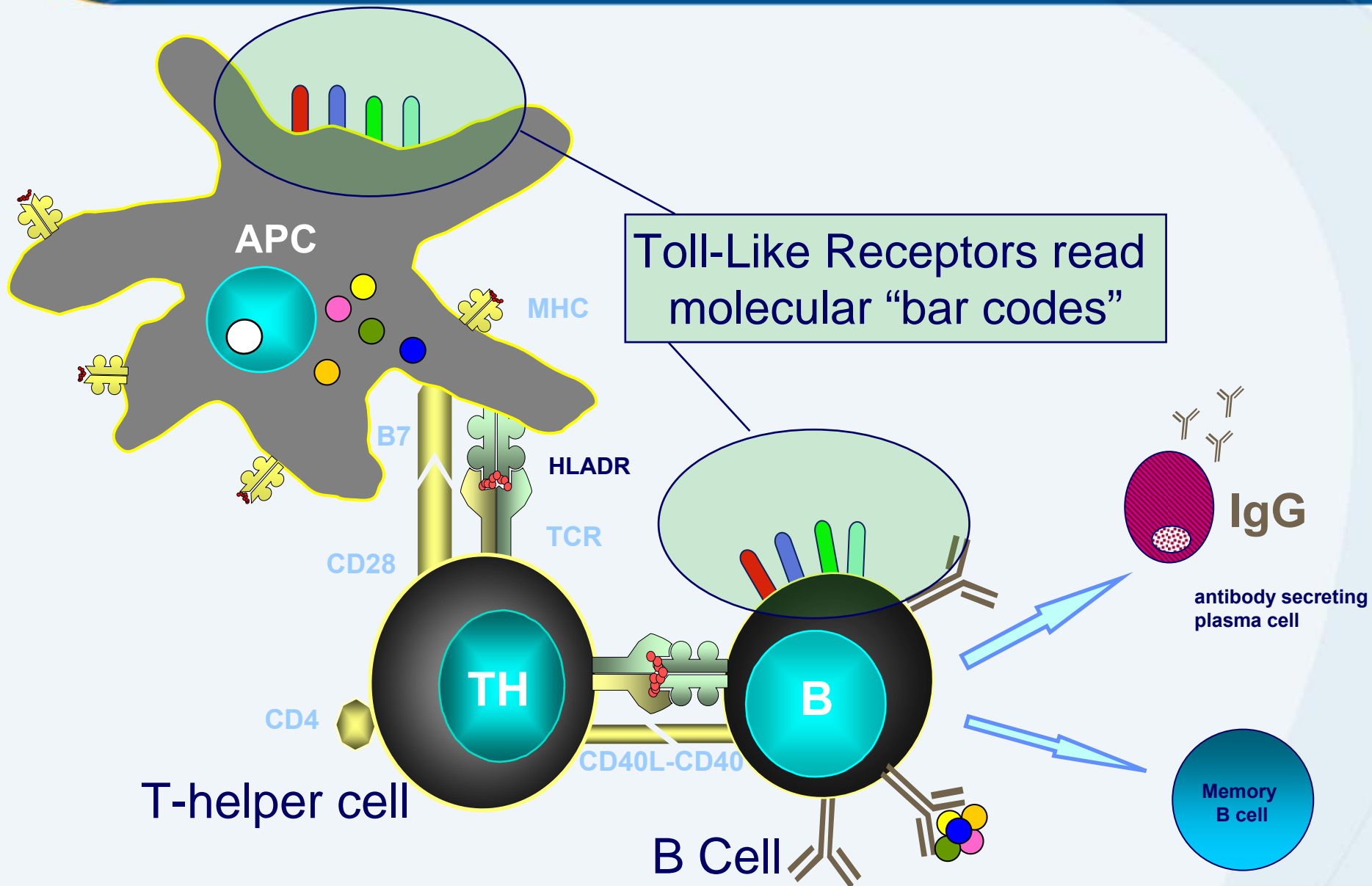
Overview of Immune Responses

Innate responses

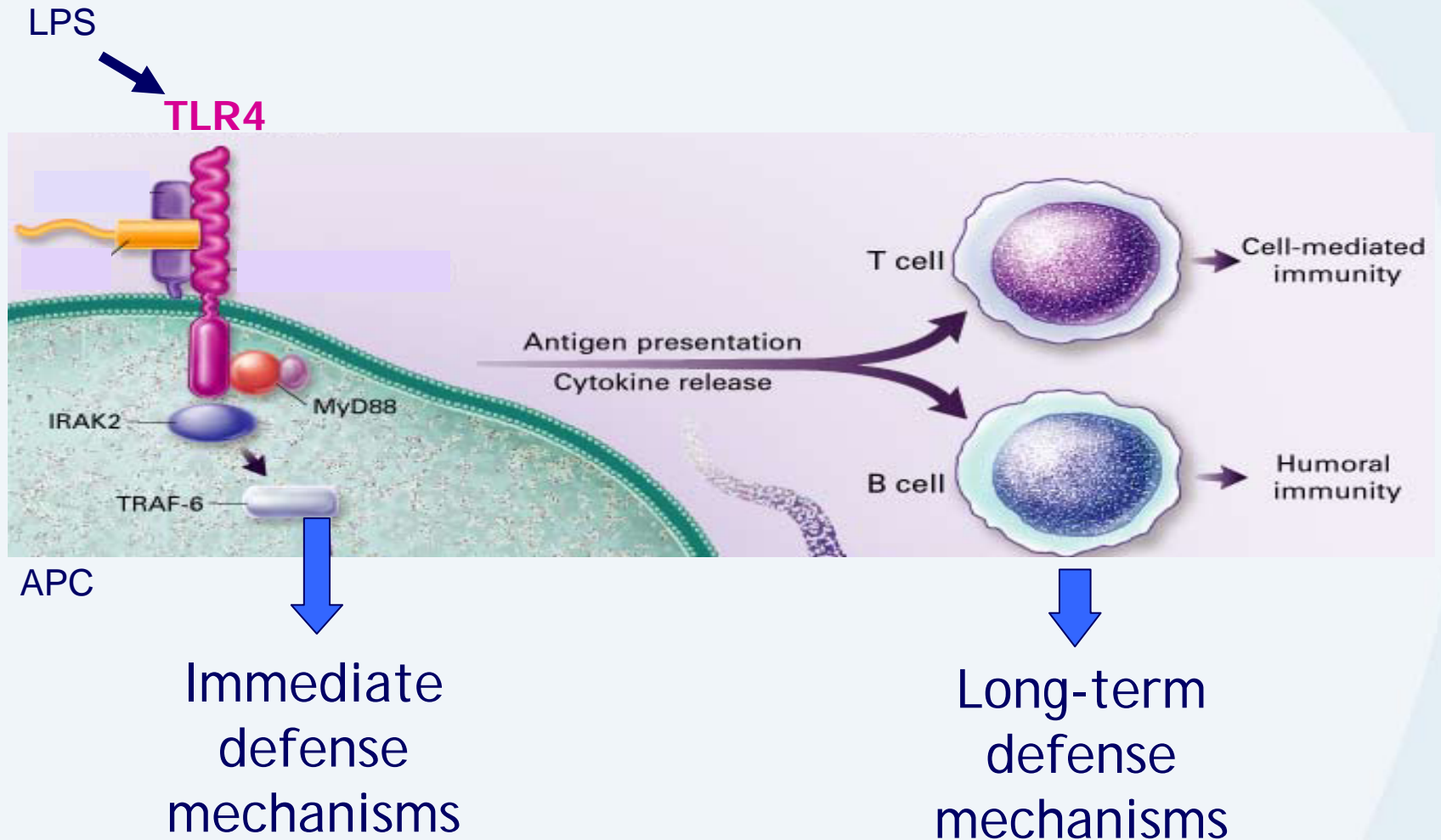
Adaptive responses



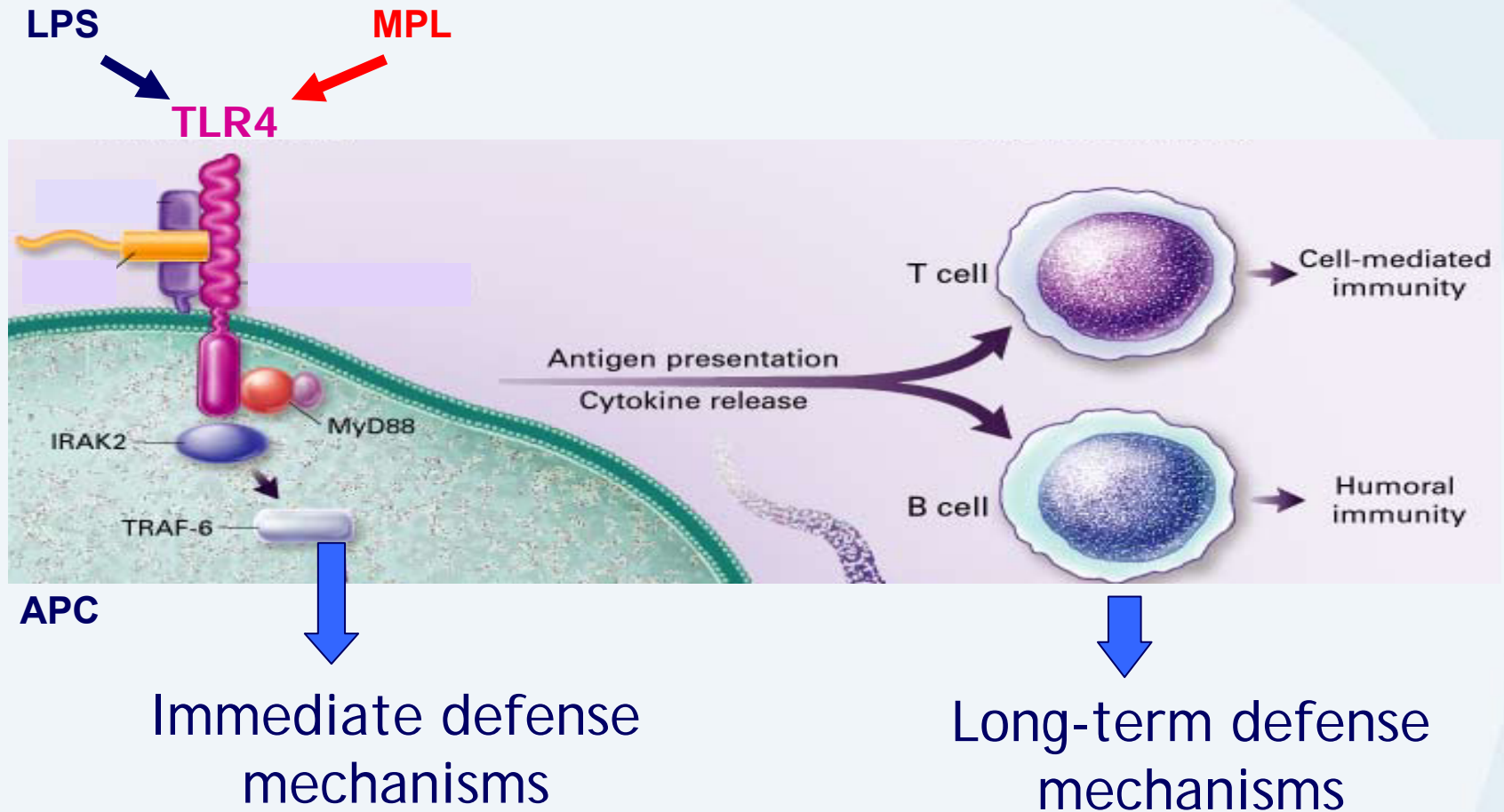
The Role of Antigen Presenting Cells



The Role of TLR4 in Immune Activation



MPL Mode of Action



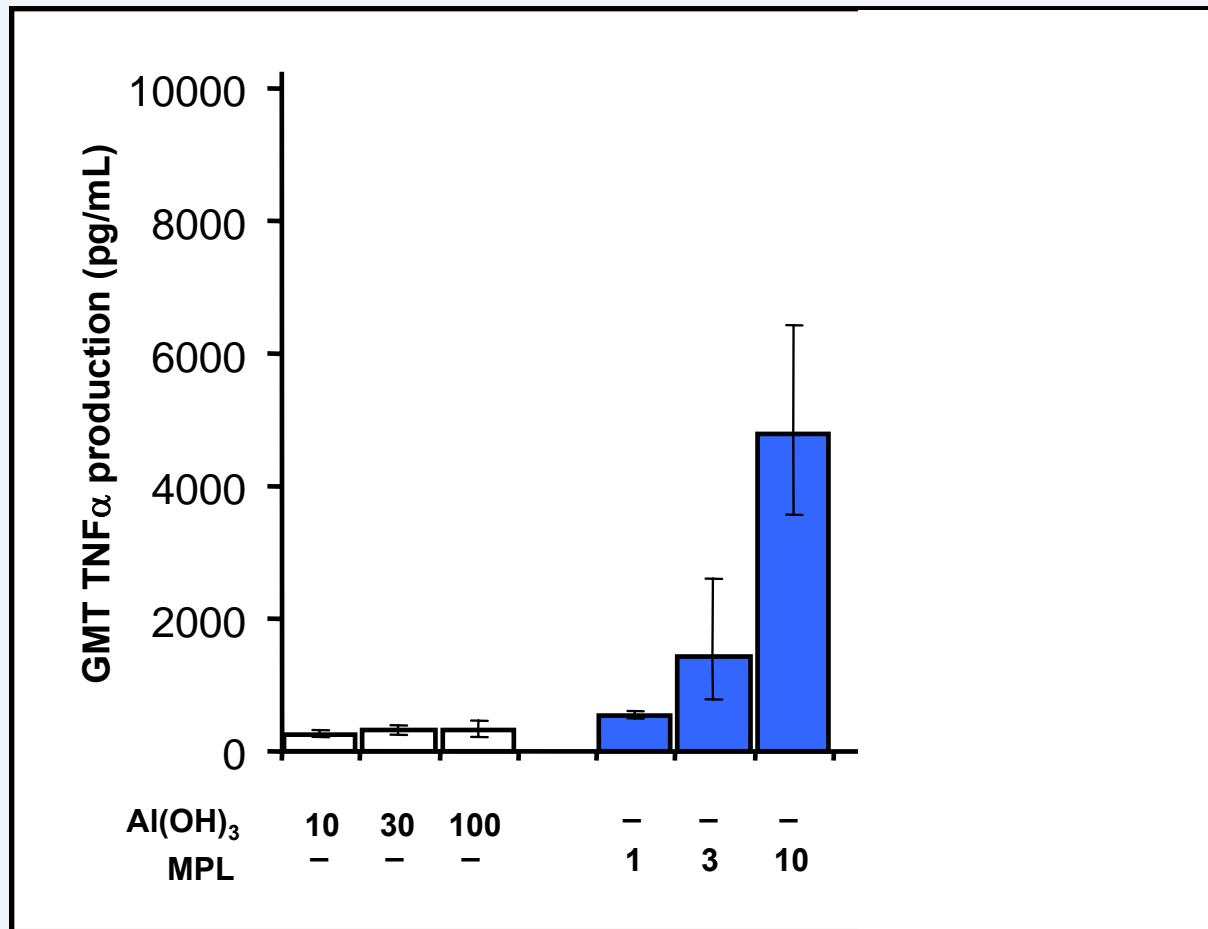
Predicted Effect of AS04 in HPV16/18 Vaccine

- Based on current immunological knowledge and mode of action of MPL, **predicted effect of AS04 is to activate Antigen Presenting Cells**, leading to :
 1. Activation of Innate Immunity – 1st line of defense non specific & no memory
 2. Activation of adaptive Immune responses – 2nd line of defense antigen specific & immune memory:
 - HPV16 & 18 antibodies
 - HPV16 & 18 memory responses

AS04 & Innate Immunity – *In vitro* data

Cytokine Secretion

TNF α production by U937 monocytic cell line



HPV16/18 AS04 - Immune Profile

- **High levels of Immunity**

- Antibody titers
- B cell memory



- **Sustained antibody levels**

- Total antibodies
- Neutralizing antibodies



- **Antibodies at site of infection**

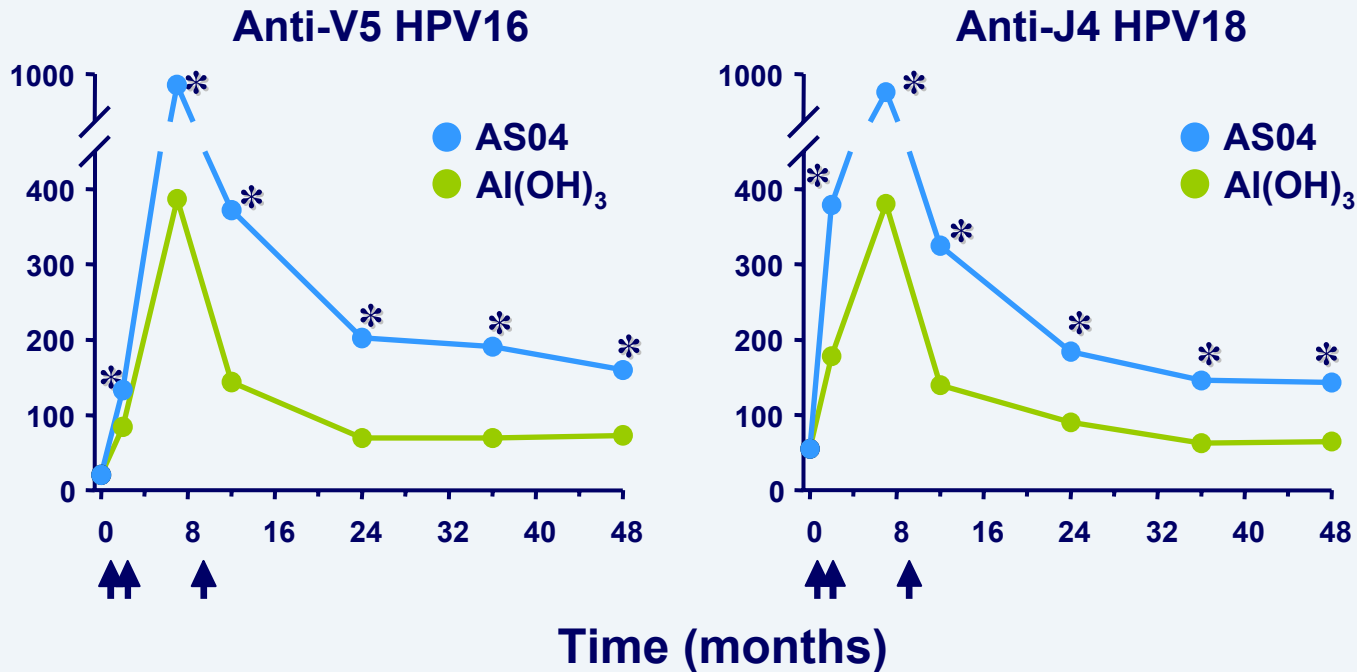


- **High antibody levels in a broad age range**



GSK HPV Vaccine: AS04 vs Aluminum Hydroxide Phase II Clinical Data

Induction of neutralizing antibodies



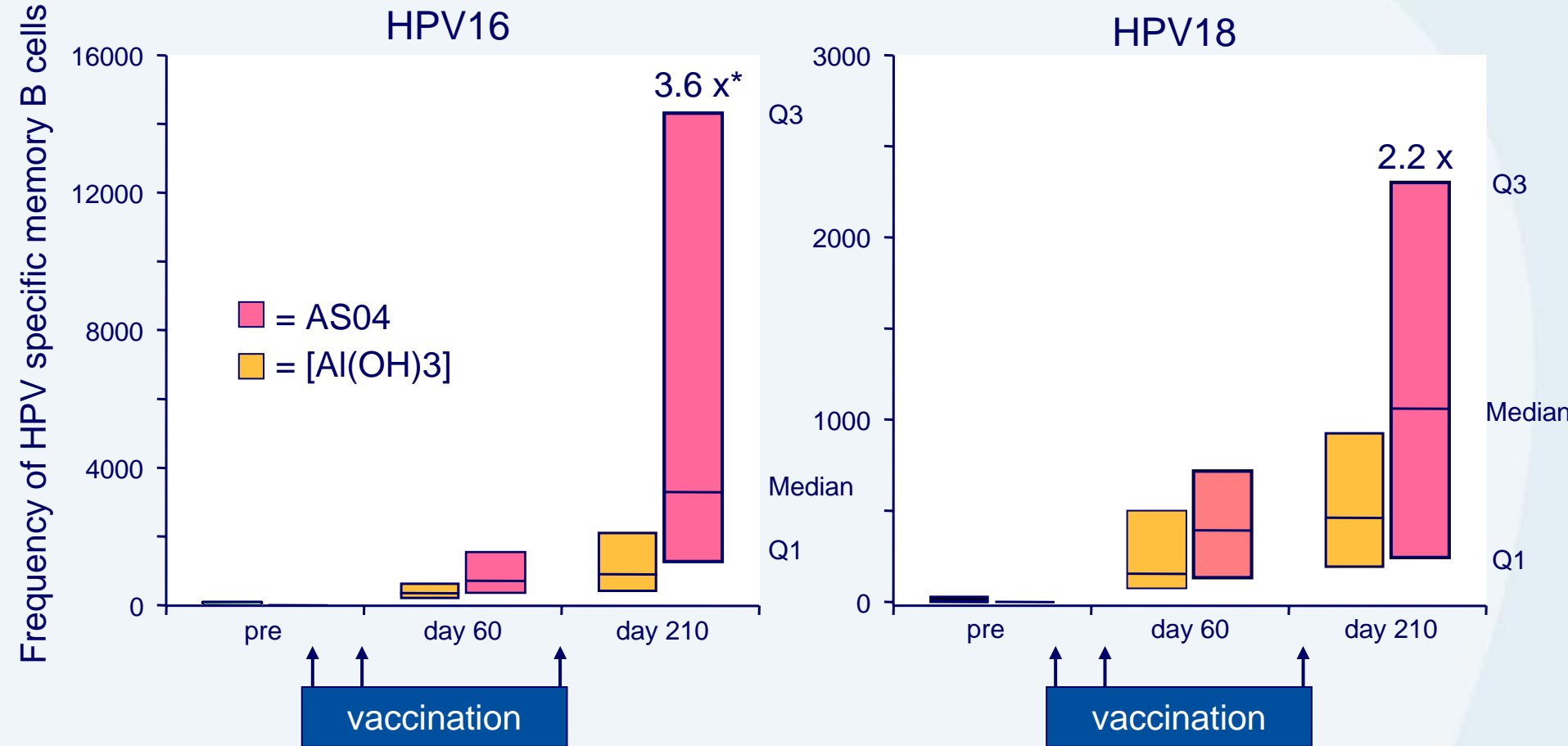
Enhanced and Sustained Immunogenicity Over 4 Years

* Statistically significant²⁰⁰⁶

Comparator is GSK vaccine formulated with Al(OH)₃

GSK HPV Vaccine: AS04 vs Aluminum Hydroxide Phase II Clinical Data

Memory B Cell Responses



Comparator is GSK vaccine formulated with Al(OH)₃

HPV16/18 AS04 - Immune Profile

- **High levels of Immunity**

- **Antibody titers**
- **B cell memory**



- **Sustained antibody levels**

- **Total antibodies**
- **Neutralizing antibodies**



- **Antibodies at site of infection**



- **High antibody levels in a broad age range**

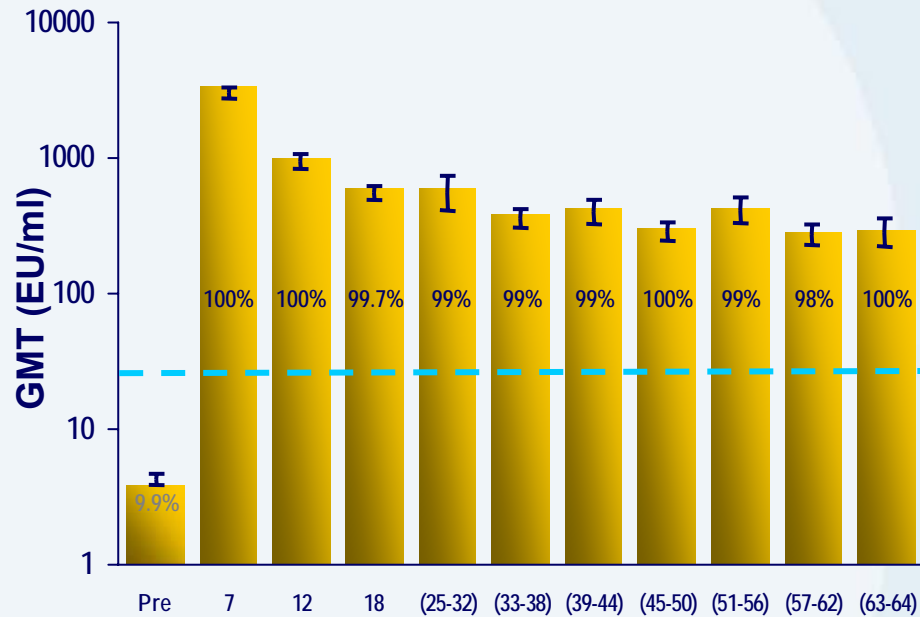
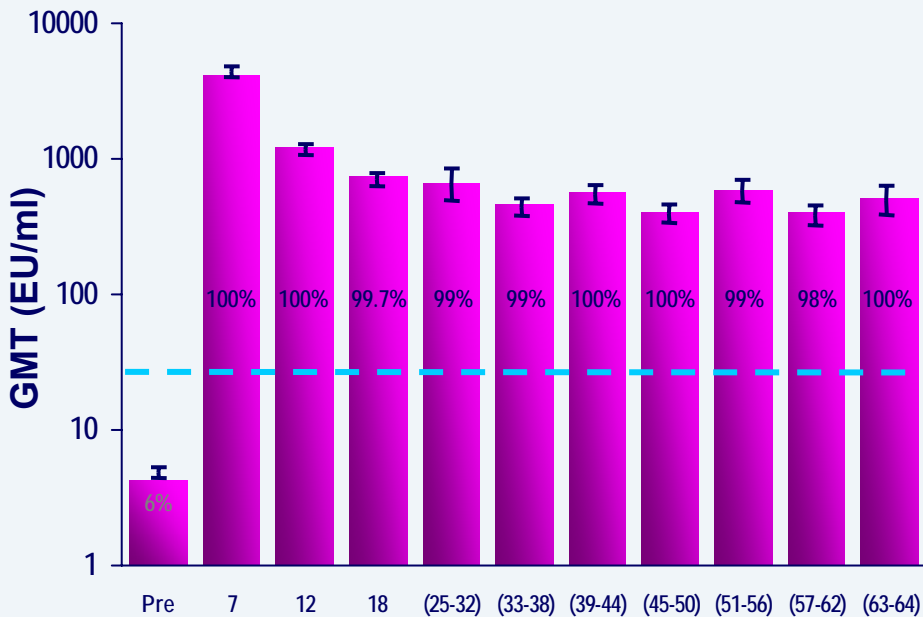


HPV-001/007: Strong & Durable Immune Response up to 5.5 years

Total Antibodies (ELISA)

HPV-16

HPV-18



HPV-001

HPV-007

HPV-001

HPV-007

Follow up time (Months)

Follow up time (Months)

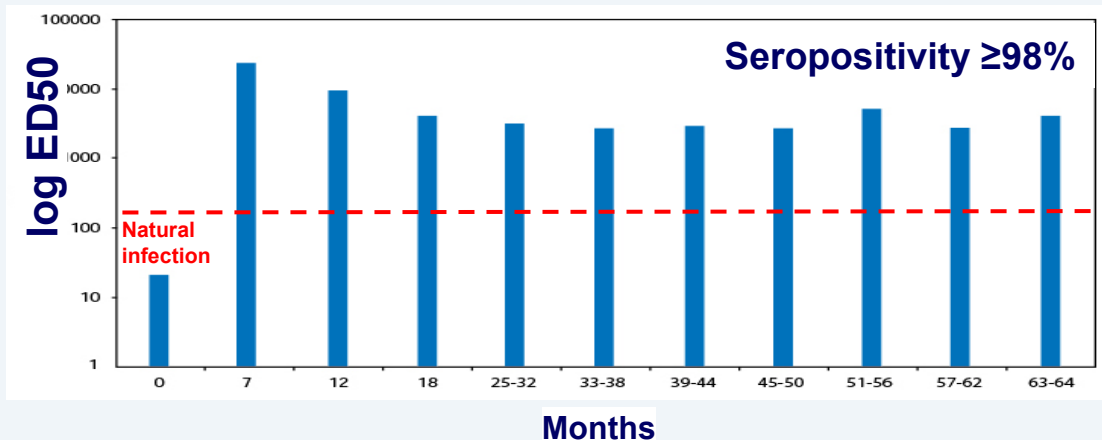
--- Natural Infection

Titers determined on HPV16/18 ELISA positive/ DNA negative subjects

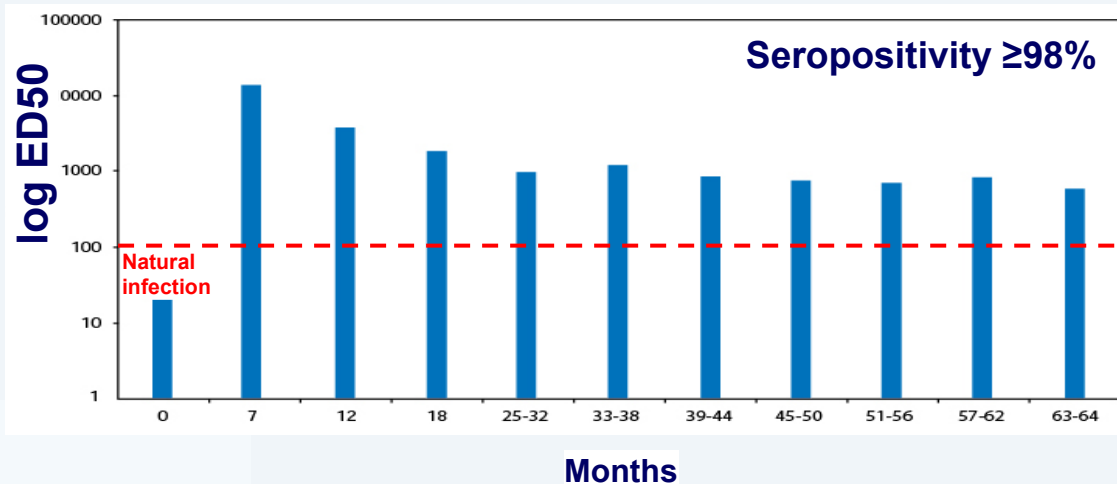
HPV-001/007: Strong & Durable Immune Response up to 5.5 years

Neutralizing Antibody Responses

Anti-HPV-16



Anti-HPV-18



HPV 16 & 18
~10 fold biologically active higher titers as compared to natural infection

--- Natural Infection

HPV16/18 AS04 - Immune Profile

- **High levels of Immunity**

- Antibody titers
- B cell memory



- **Sustained antibody levels**

- Total antibodies
- Neutralizing antibodies



- **Antibodies at site of infection**



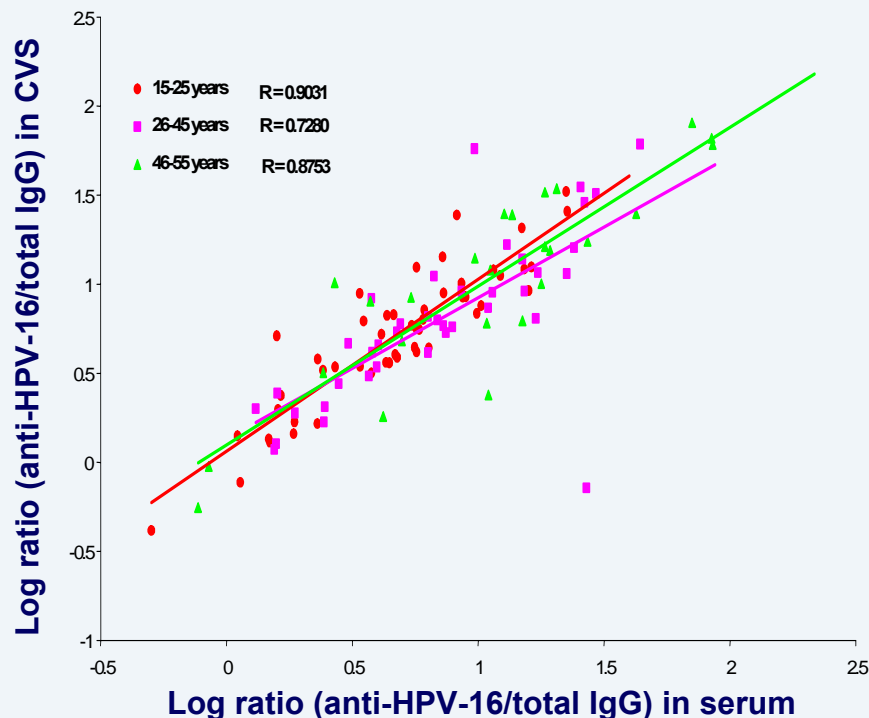
- **High antibody levels in a broad age range**



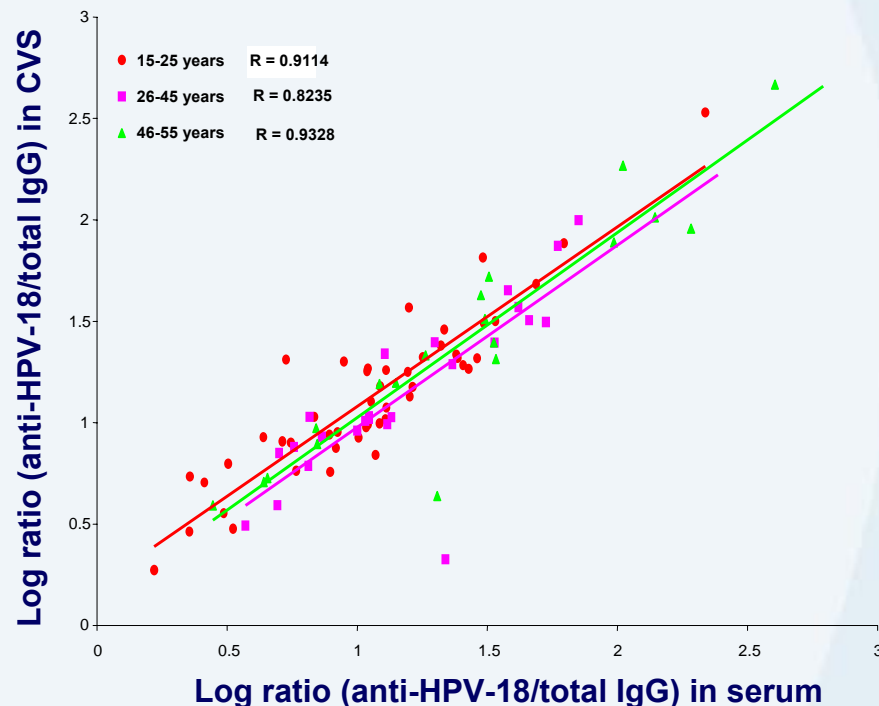
Correlation Between Serum & Cervical Mucosa Antibody Levels

HPV-014 - women 15-55 yrs M24

Anti-HPV-16



Anti-HPV-18



Best guarantee of immune protection is having antibodies at the site of infection

HPV16/18 AS04 - Immune Profile

- **High levels of Immunity**

- **Antibody titers**
- **B cell memory**



- **Sustained antibody levels**

- **Total antibodies**
- **Neutralizing antibodies**



- **Antibodies at site of infection**



- **High antibody levels in a broad age range**



Immunobridging

Girls
10-14
years

HPV-012

Immunobridge

Women
15-25
years

HPV-001/007

HPV-008

*Efficacy demonstrated
up to 5.5 years post first
vaccination*

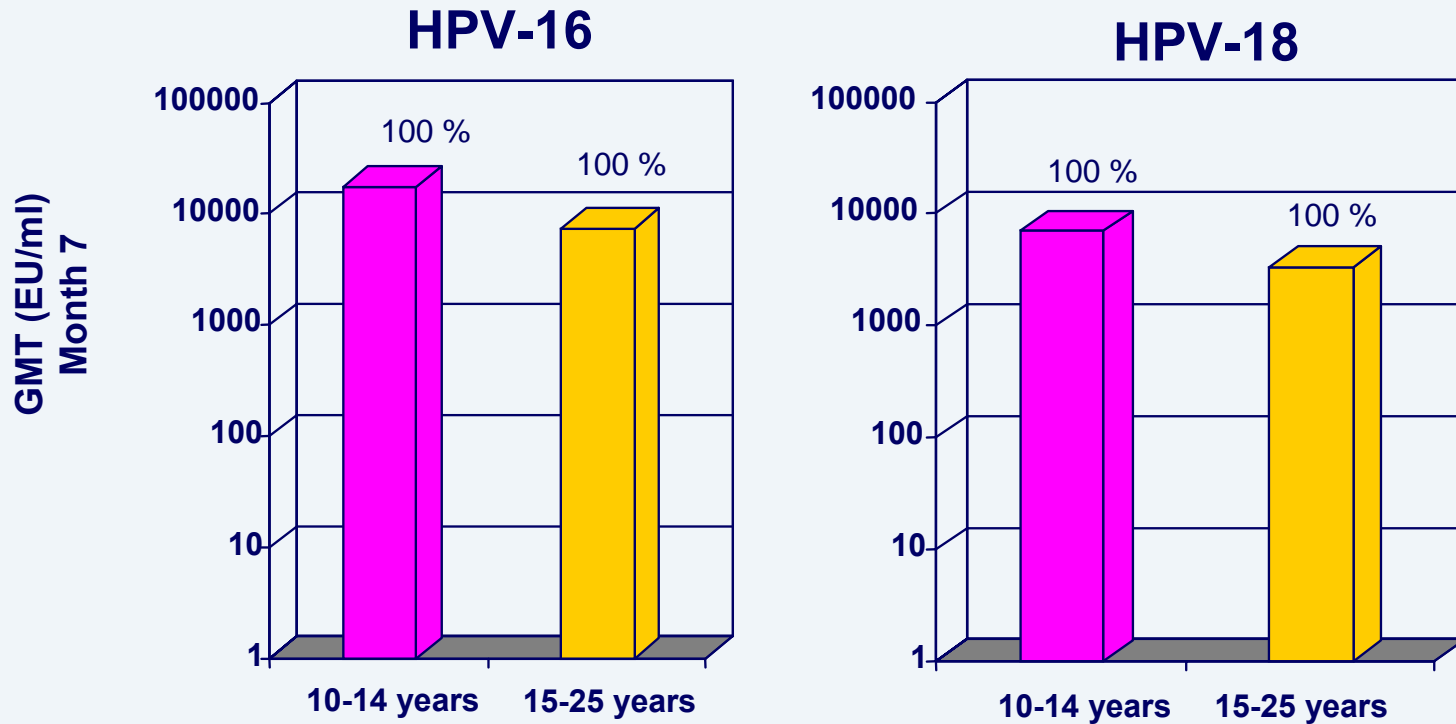
Women
26-55
years

HPV-014

Immunobridge

Immunobridge to the Younger Age Group (10-14 yrs)

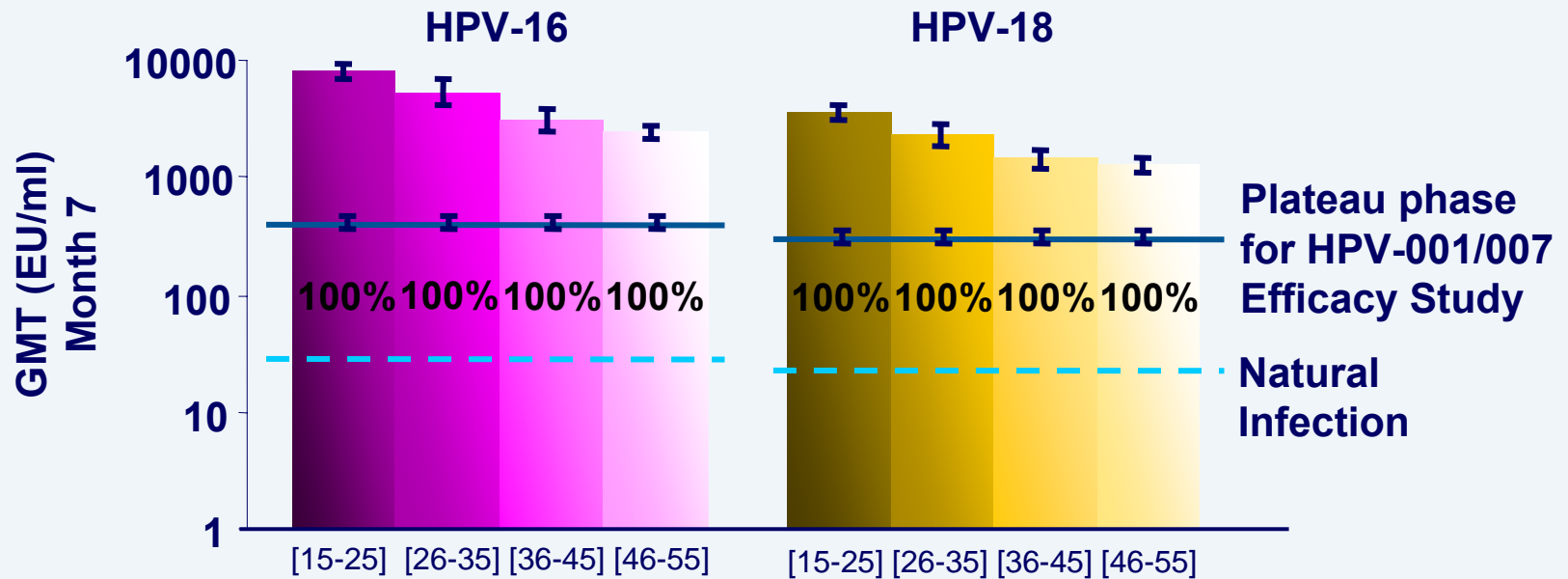
**HPV-012: Blinded, randomized, multicenter study in Europe
N=532 (15-25 years); 150 (10-14 years)**



Non-inferiority of the immune response was demonstrated for the 10-14 years group

Immunobridge to the Older Age Group (26 yrs and older)

HPV-014: Open, age-stratified multicenter study in Europe, N= 666



ATP cohort, Seronegative at entry

Non-inferiority of the immune response was demonstrated for both the 26-45 and 46-55 years age groups

Conclusions

- AS04 has been designed to enhance immunogenicity and increase duration of protection through activation of innate & adaptive immunity
- Clinical data substantiate the prediction of enhanced and sustained neutralizing antibody levels
- High antibody titers against HPV16 **and** HPV18 in a broad age range (10-55 yrs)
- Antibody detection at the level of the cervix
- Sustained antibody responses and memory B-Cell

High and sustained levels of high quality immunity as a basis for long term protection against cervical cancer