Immunogenicity of Measles Vaccine in Infants with and without Passive Antibodies

Hayley Gans, M.D.
Stanford University School of Medicine
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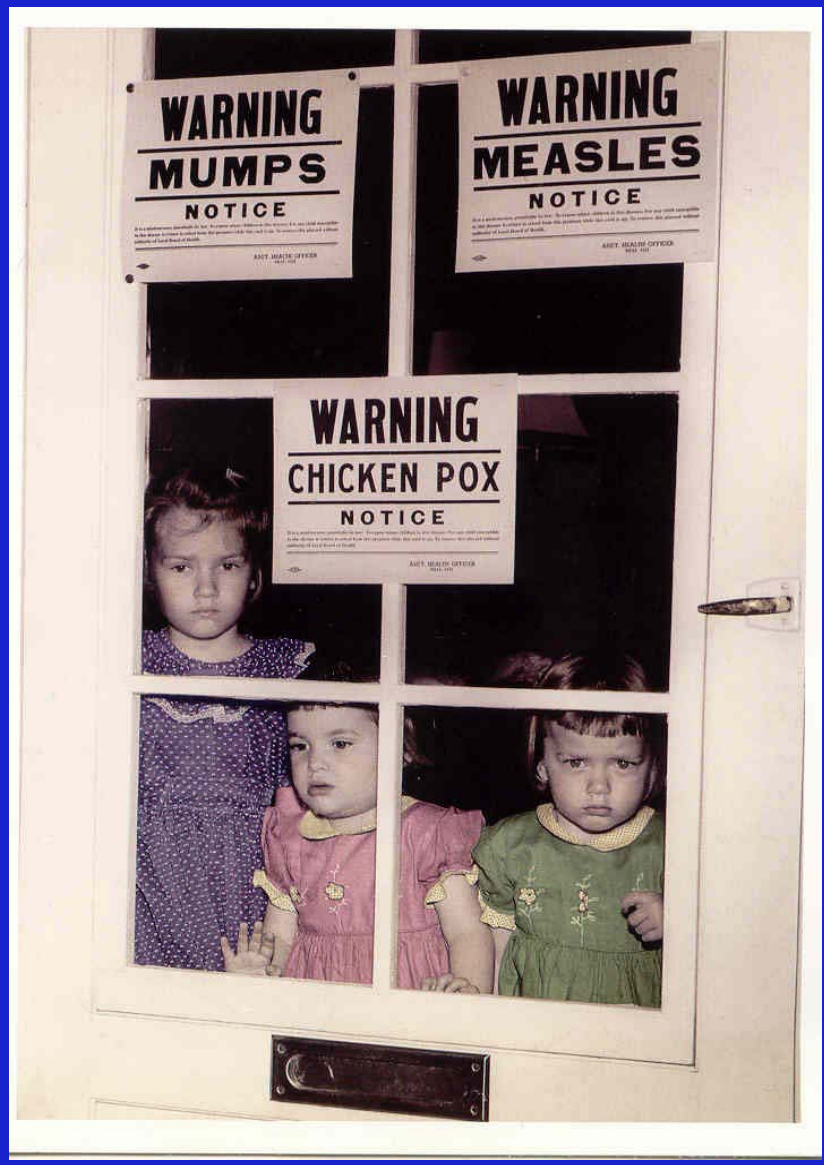
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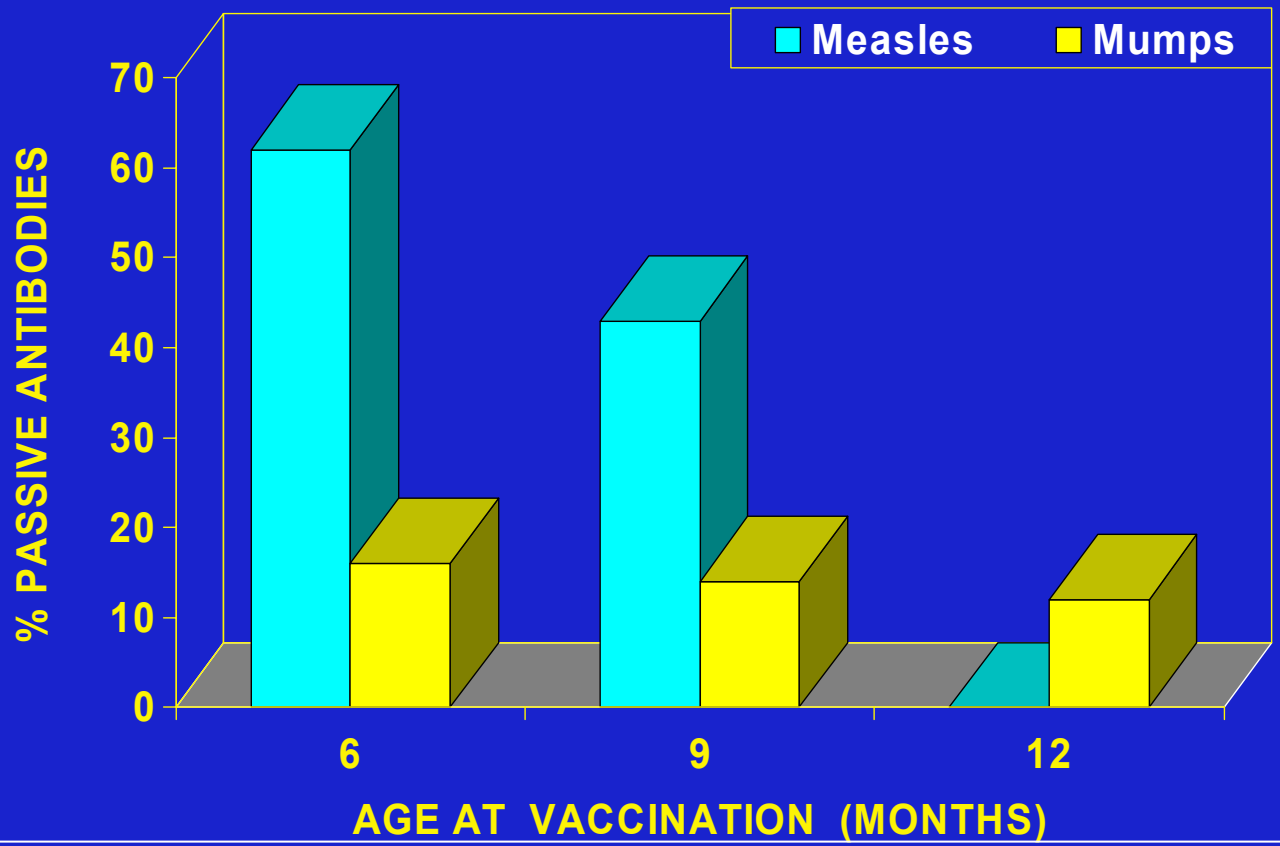
Background

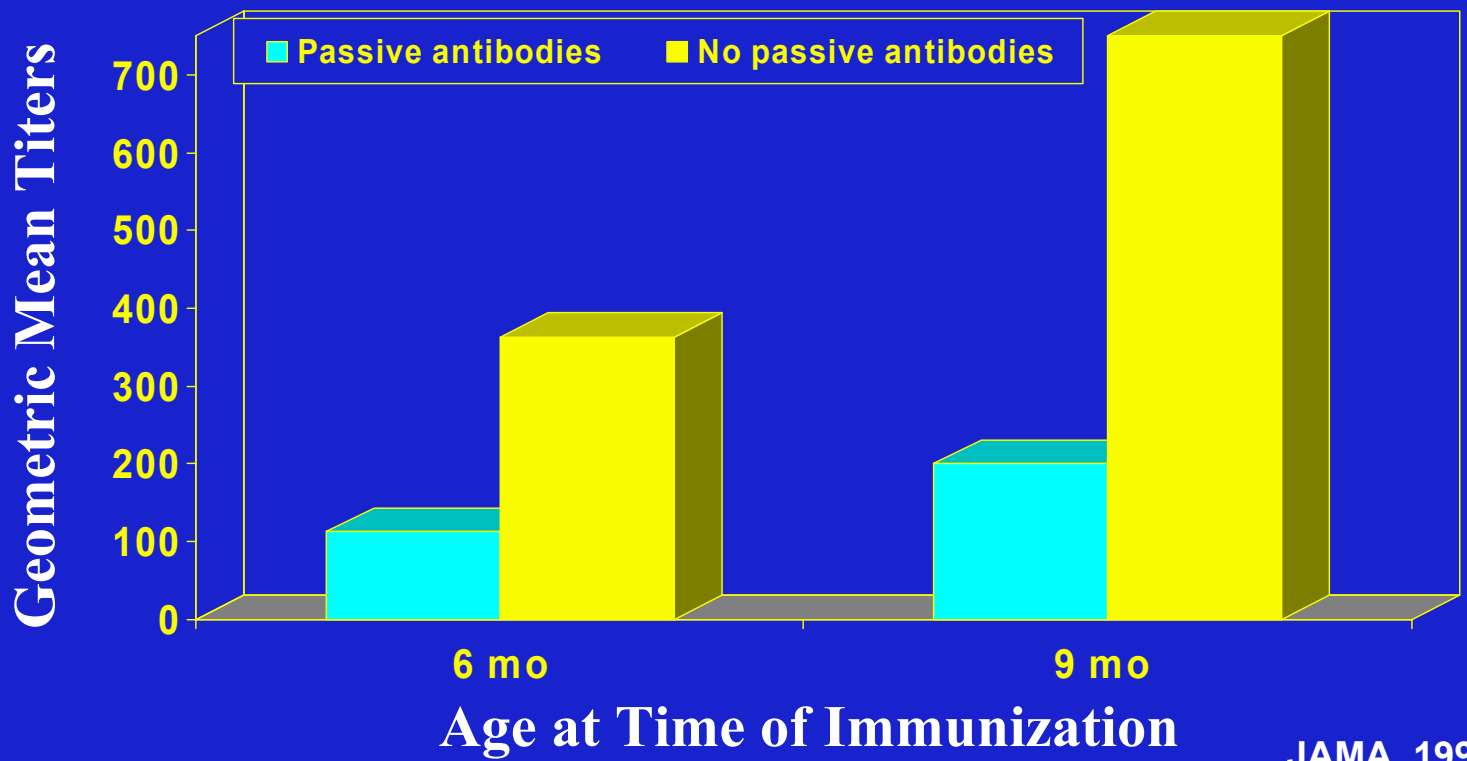
- **Live attenuated measles vaccine**
  - 7-8 million measles-associated deaths/year before 1963
  - 90 million measles cases prevented/year by vaccination
- **Need for measles immunization of infants <12 months**
  - 800,000 deaths/year, most are infants <12 months
  - Early loss of passive antibodies in infants of vaccinated mothers in developed countries
- **Measles immunization before 12 months**
  - **Historical concerns**
    - **Interference from passive antibodies**
    - **Effect on response to re-vaccination**
  - **Current concerns**
    - **Interference from passive antibodies**
    - **Developmental limitations of infant immune system**

Percentage of Infants with Passive Antibodies to Measles or Mumps before Immunization



Decreased presence of passive antibodies in infants born to mothers with vaccine induced measles immunity.

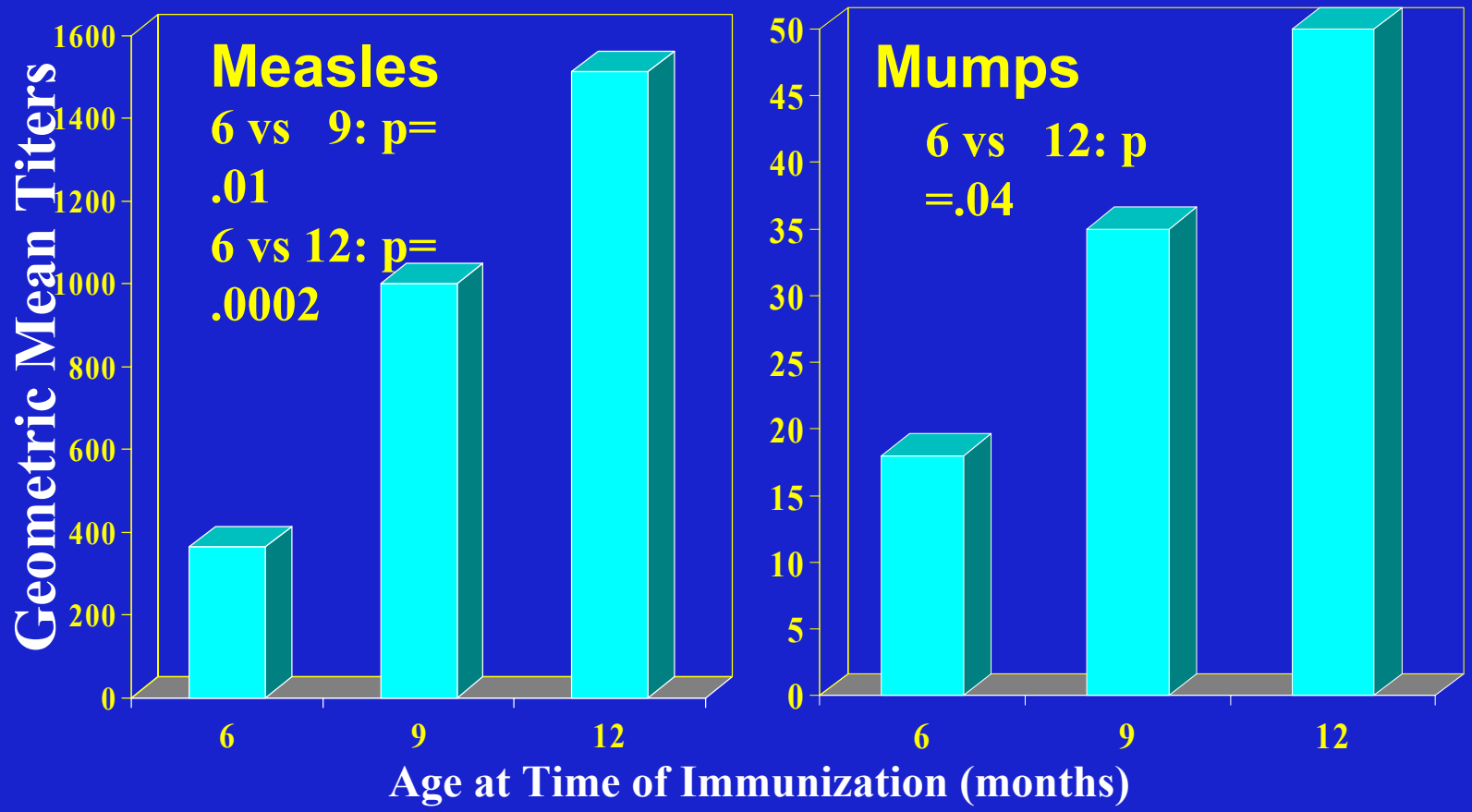
Effect of Passive Antibodies on Geometric Mean Titers after Measles Immunization at 6 or 9 Months



JAMA, 1998; JID 2001

6 month olds have low GMTs with OR without passive antibodies.
9 month olds develop high GMTs IF vaccinated in the absence of passive antibodies.

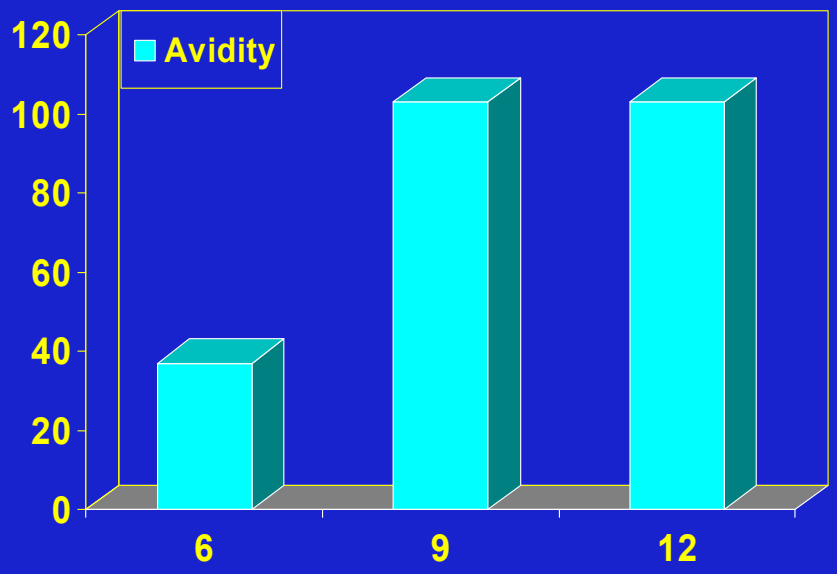
Geometric Mean Titers after Measles or Mumps Immunization of Infants with No Passive Antibodies



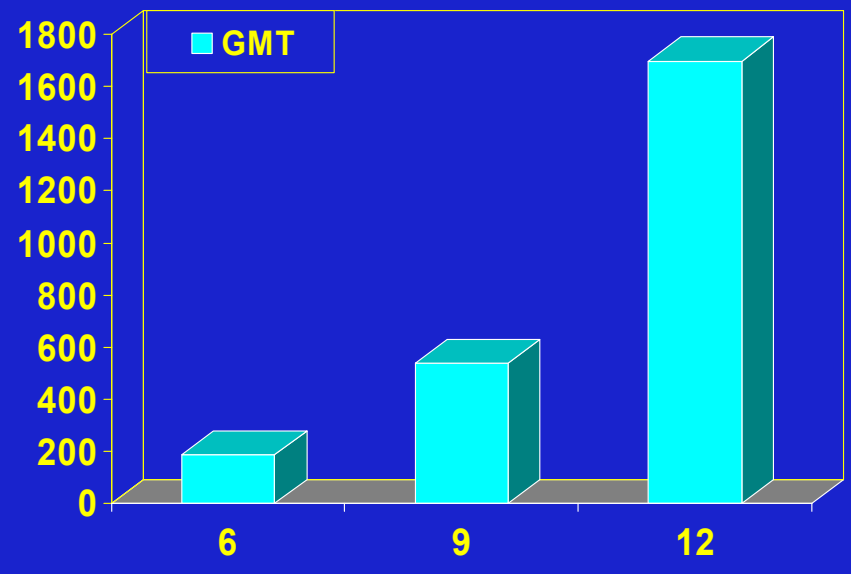
Pattern of low measles GMT in 6 month olds without passive antibodies was confirmed with mumps

Quality of humoral response 12 weeks after primary measles immunization

6 vs. 9 and 12 mo; P<.01



6 vs. 12 mo; P<.001



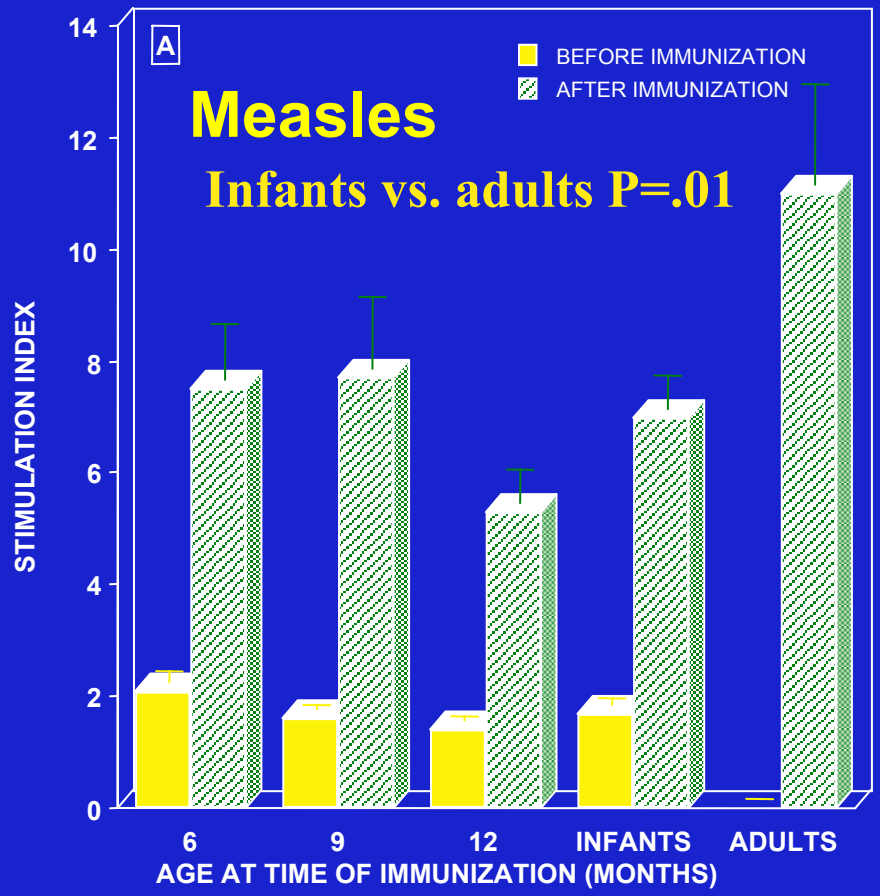
6 month olds have diminished capacity to produce high avidity antibodies 12 weeks after primary measles immunization.
Correlation between GMT and avidity at 6 mo
This maturational defect appears to normalize by 9 months of age.

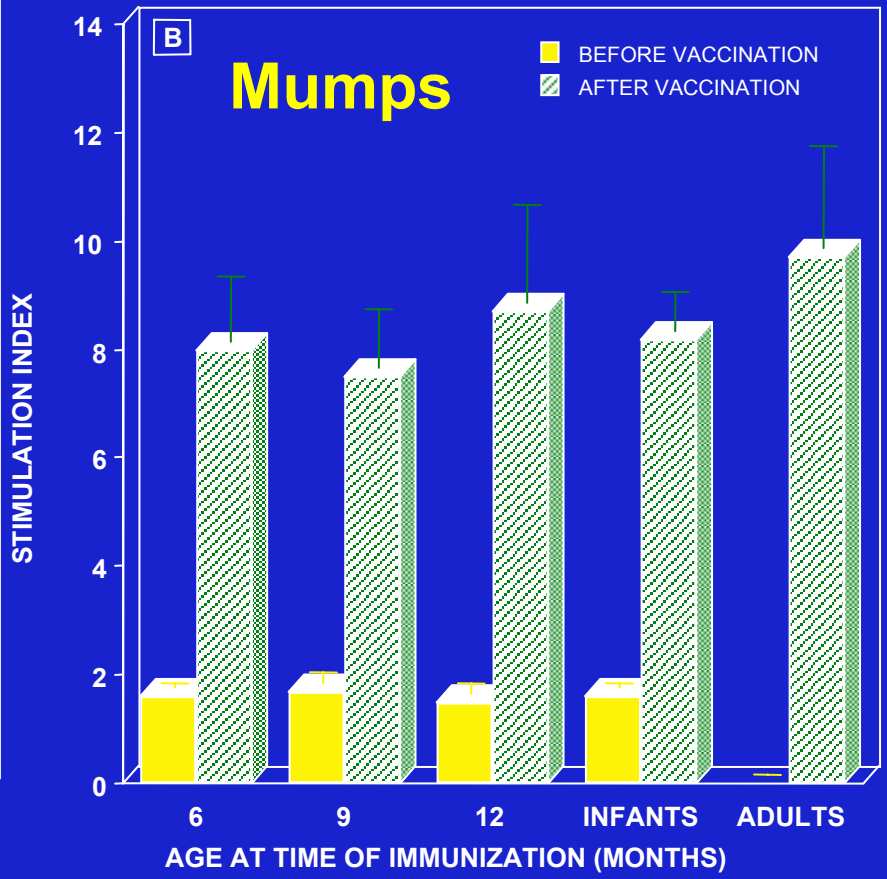
Summary: Humoral Immunity

- **6 months:**
  - **Humoral responses were low**
    - Measles vaccine
      - Passive antibody interference
      - Maturational deficiencies
      - Limitation in production of high avidity antibodies
    - Mumps vaccine
      - Maturational deficiencies
- **9 months**
  - **Humoral responses were low**
    - Measles vaccine
      - Passive antibody interference

Confirms passive antibody interference which appears to be antigen specific
Inherent B cell "deficiency" as general antiviral phenomenon

Cellular Immunity to Measles and Mumps: T cell Proliferation Before and After Immunization

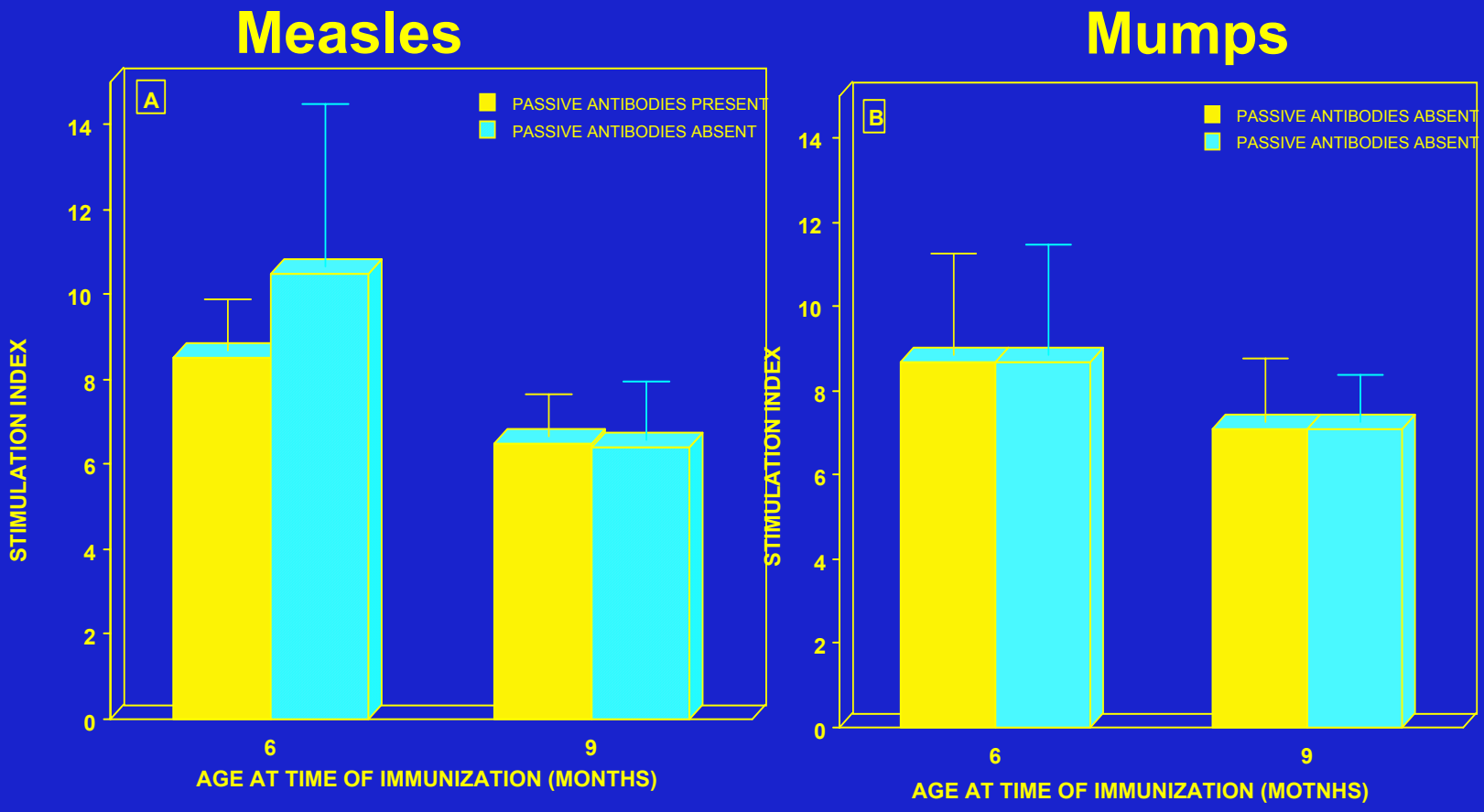




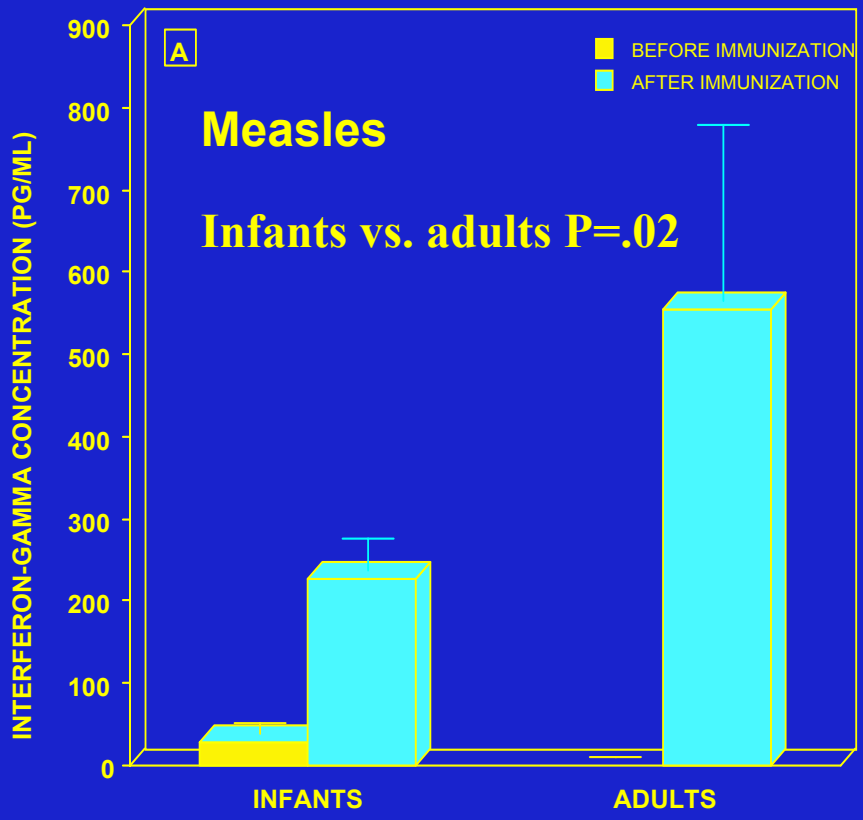
6 mo olds T cell proliferation responses to measles and mumps equal to those of 9 and 12 mo olds.

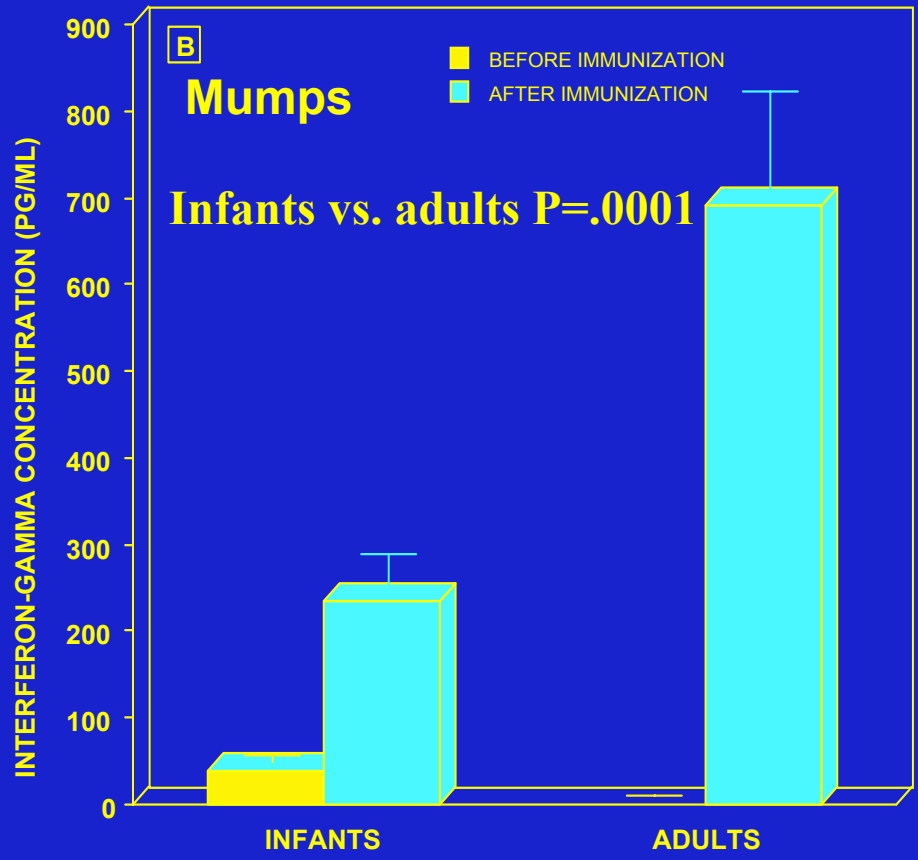
Infants had lower T cell proliferation compared to adults after measles vaccination

Induction of CD4 T Cell Proliferation to Measles and Mumps: No Passive Antibody Interference



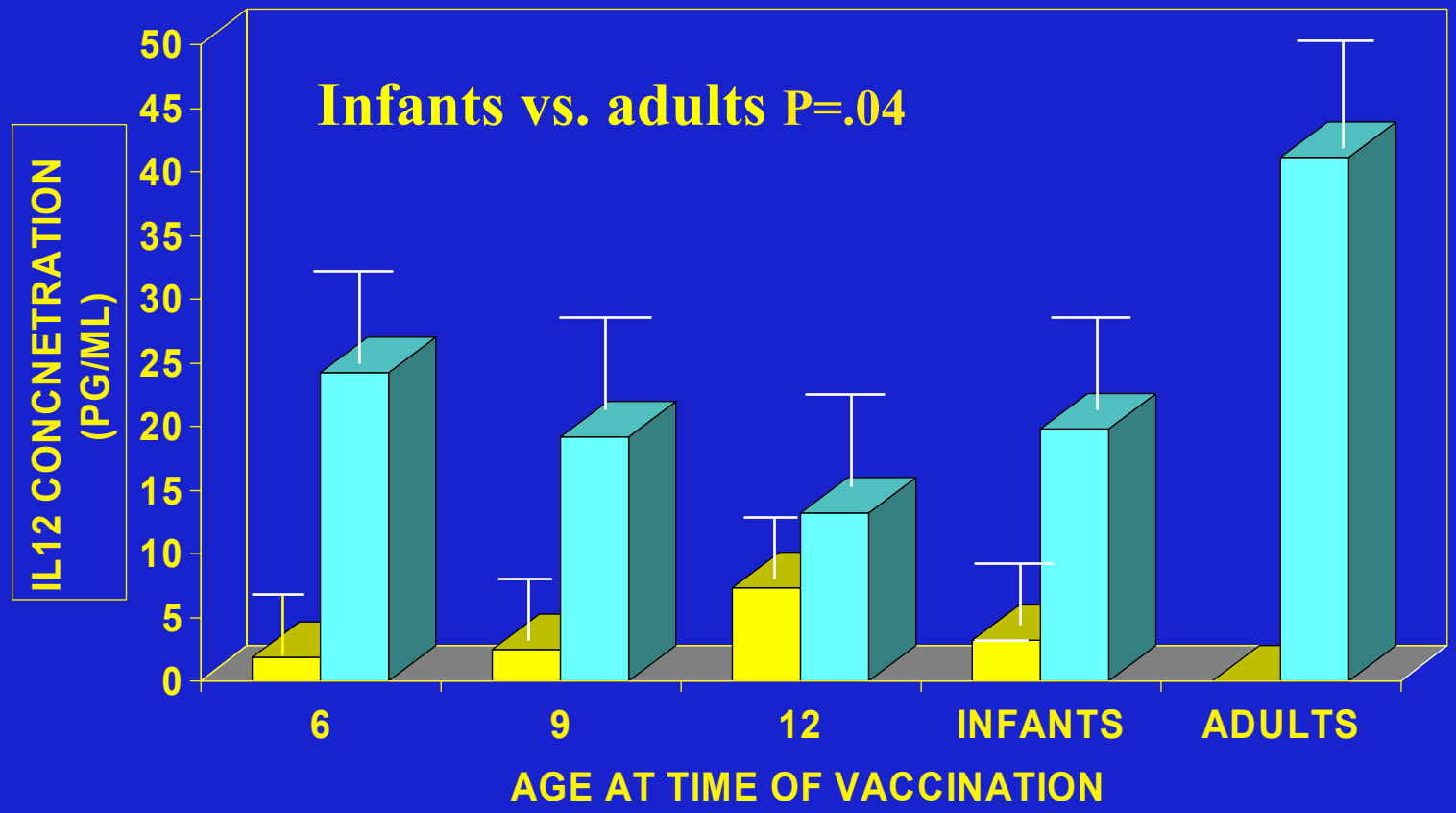
Interferon-γ Release by PBMC Stimulated with Measles or Mumps Antigen: Before and After Immunization





Infant T cells showed limited production of IFNγ after measles and mumps vaccination compared with adults

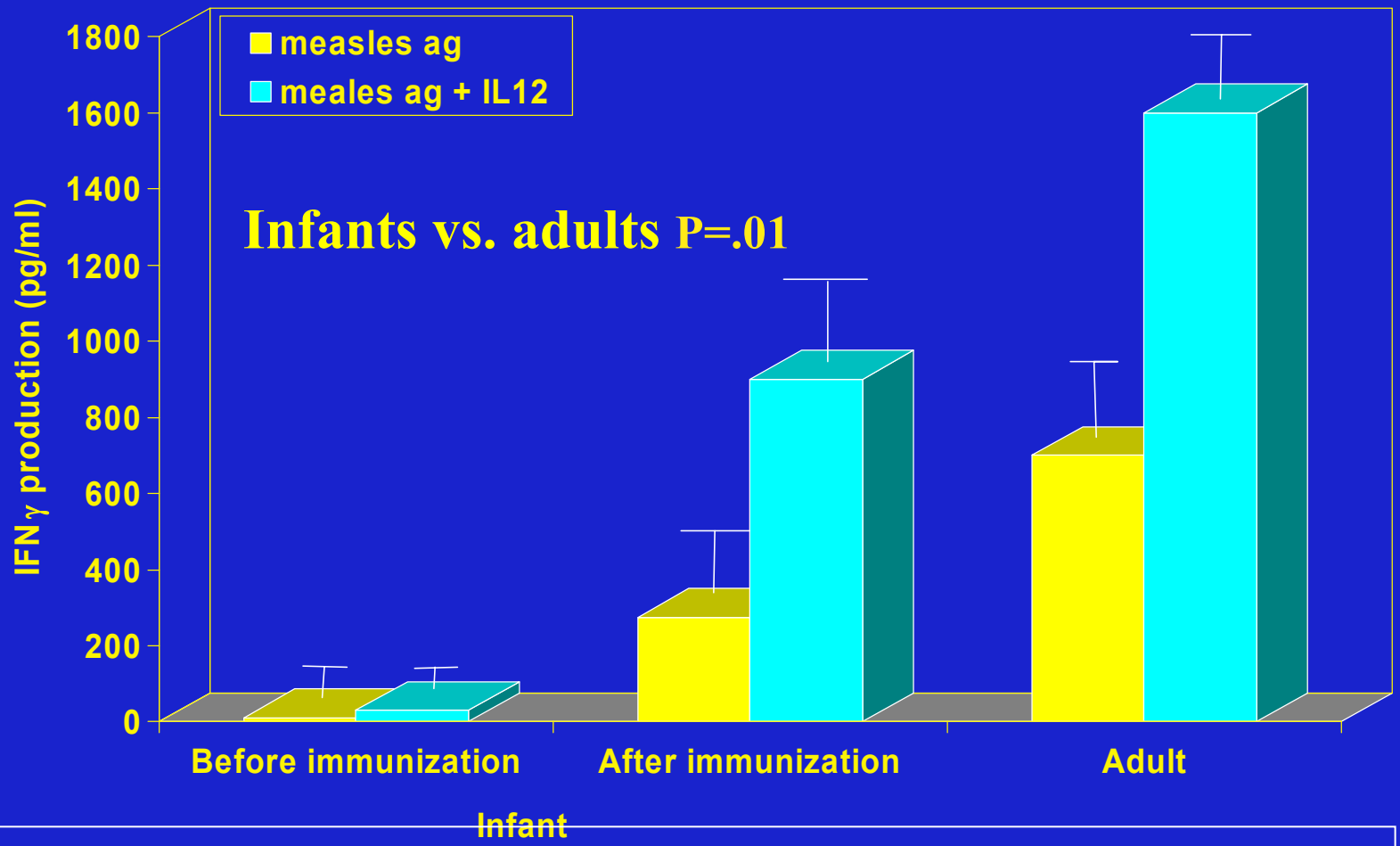
IL-12 release by PBMC stimulated with measles antigen: Before and after measles immunization



J of Immunol, 1999

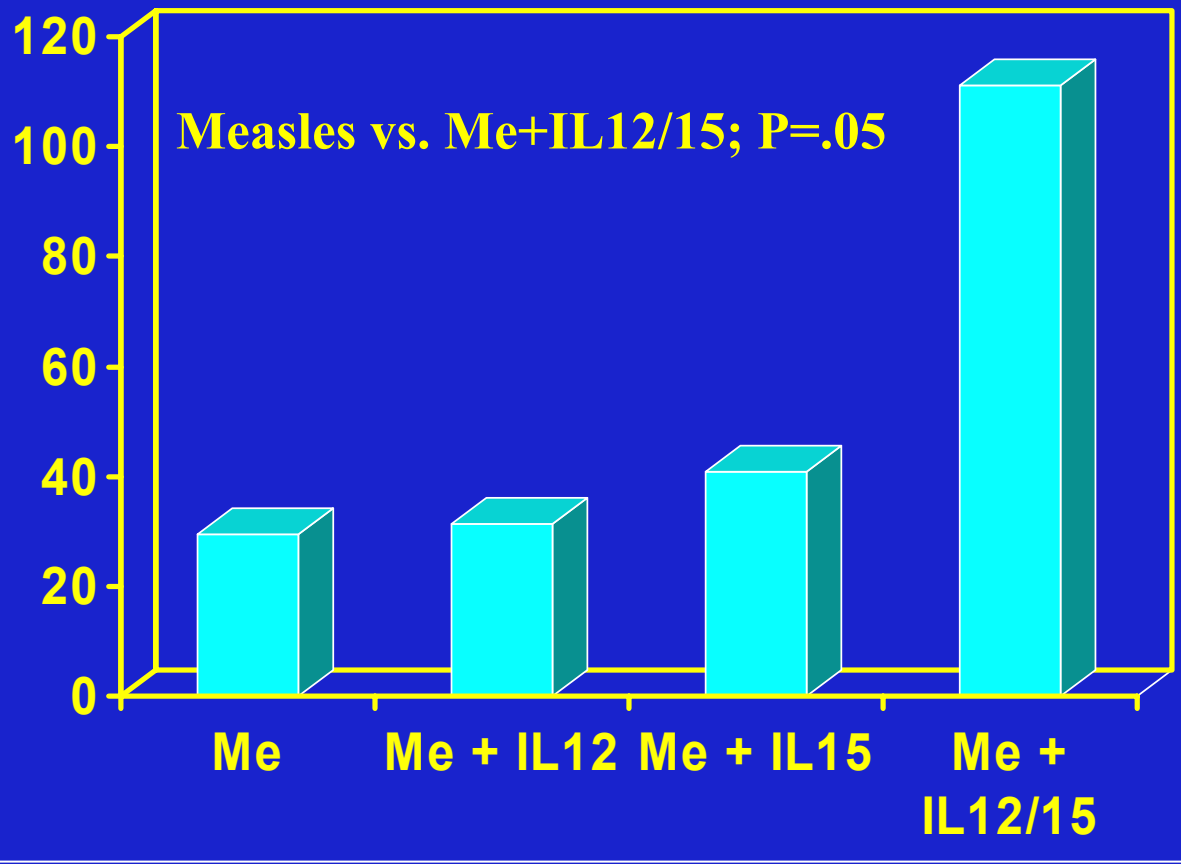
Infant T cells showed limited production of IL-12 after measles vaccination compared to adults <u>BUT</u> no age-related differences

rIL12 Effect on IFN-γ Release by PBMC Stimulated with Measles Antigen



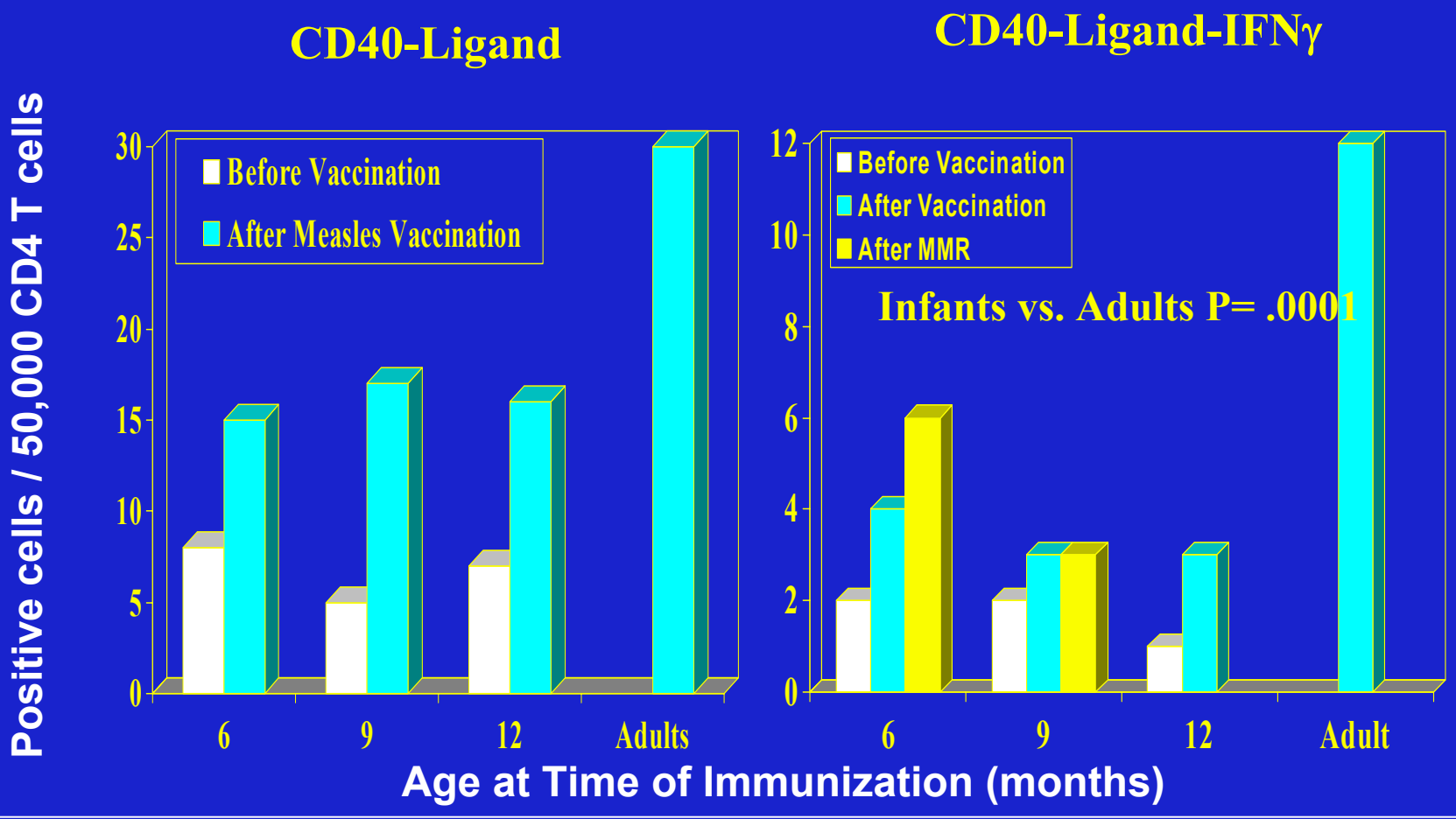
Infant T cells showed limited production of IFN-γ in response to rIL12 compared to adults

rIL12 and rIL15 effect on T cell proliferation 12 weeks after Measles Immunization in Infants



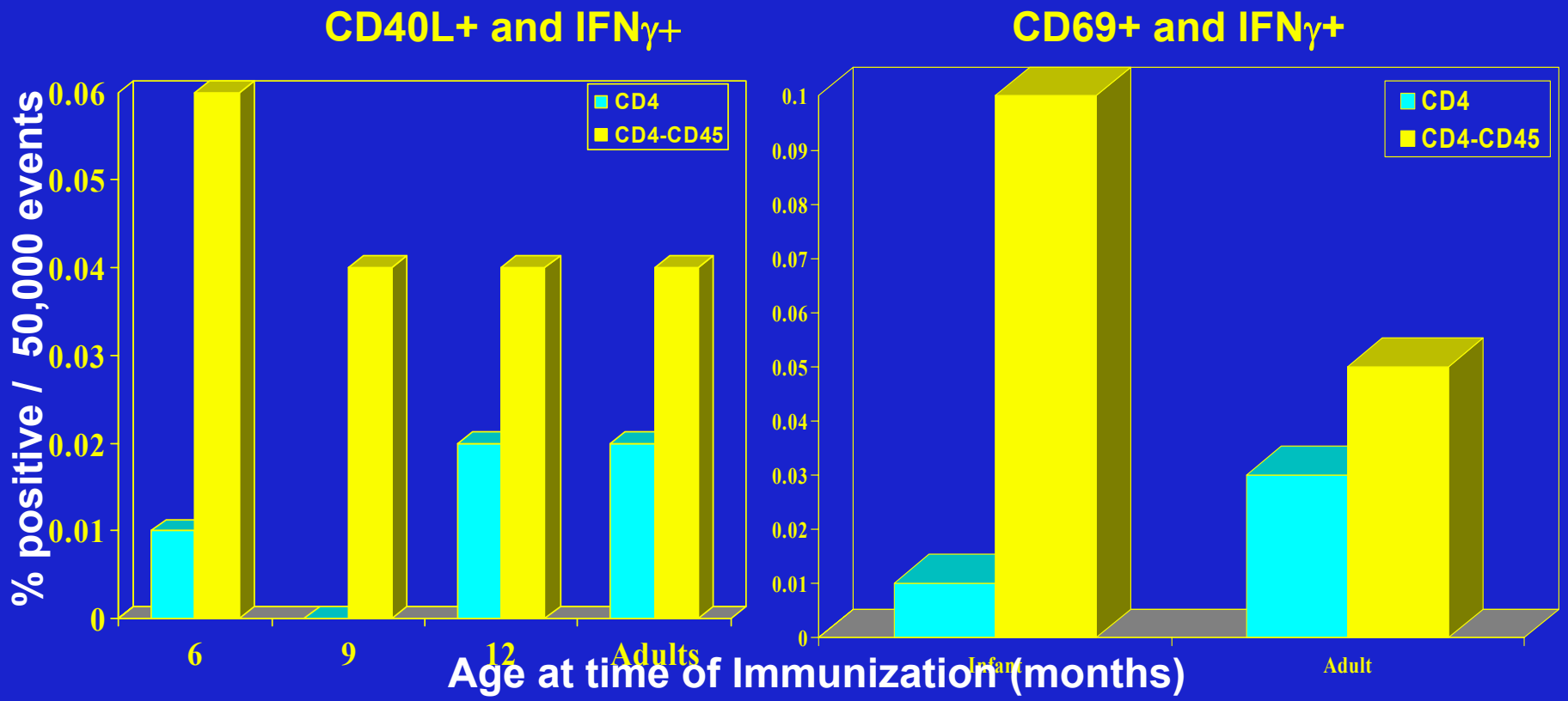
Correction of proliferation "defect" in infants but not adults after measles immunization with the addition of both rIL12 and rIL15

Frequency of CD4 T cells expressing CD40-Ligand and CD40L-IFN-γ after Measles Stimulation



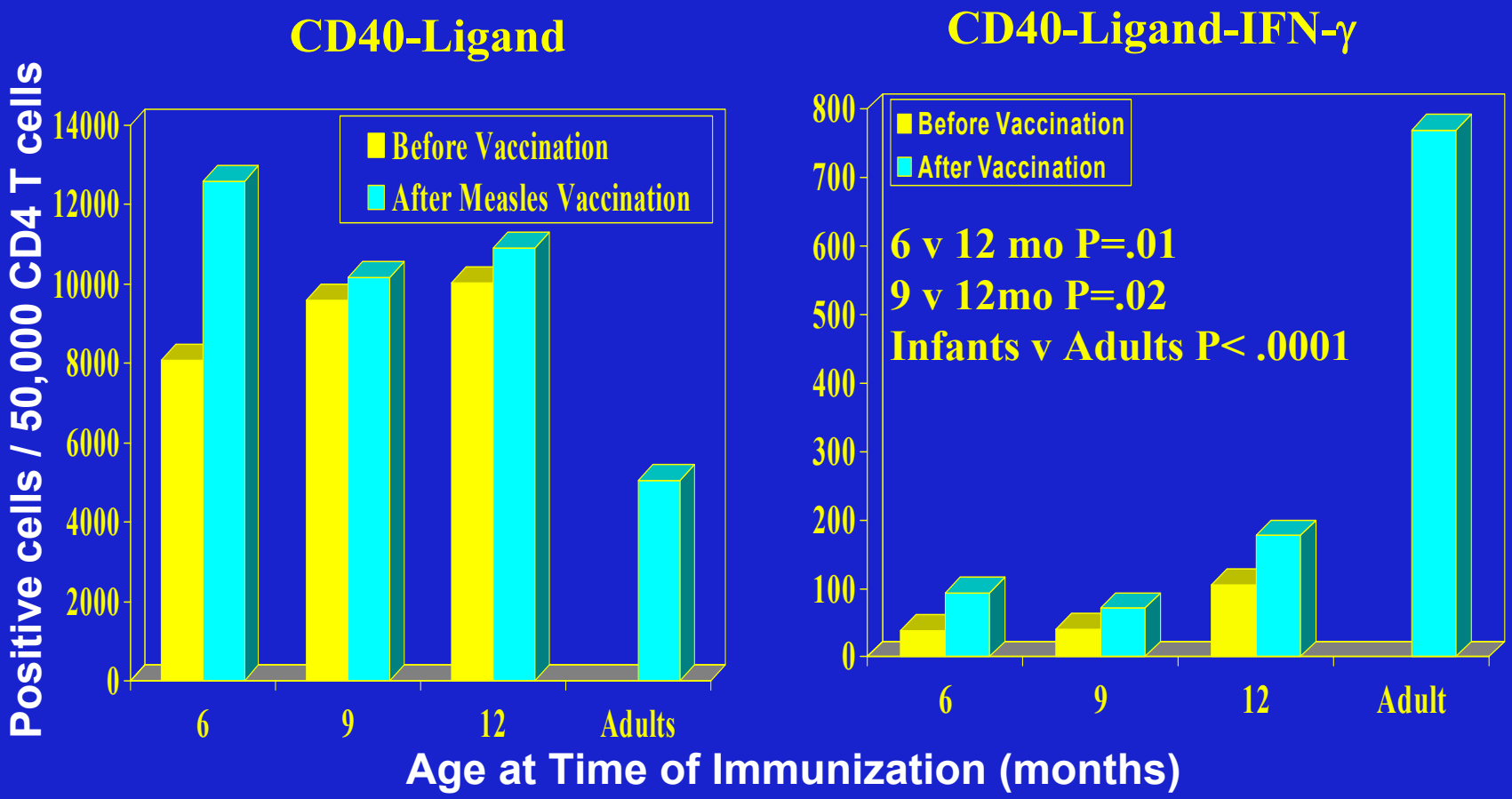
No age-related limitation in measles-specific CD4+T cells that up-regulate CD40-Ligand and produce IFN-γ.
Infants can up-regulate CD40-L at comparable rates to adults but fewer of these cells produce IFN-γ

Frequency of Total CD4 T cells versus CD45RO+ CD4 T cells expressing CD40-L or CD69 and IFN-γ after Measles Stimulation



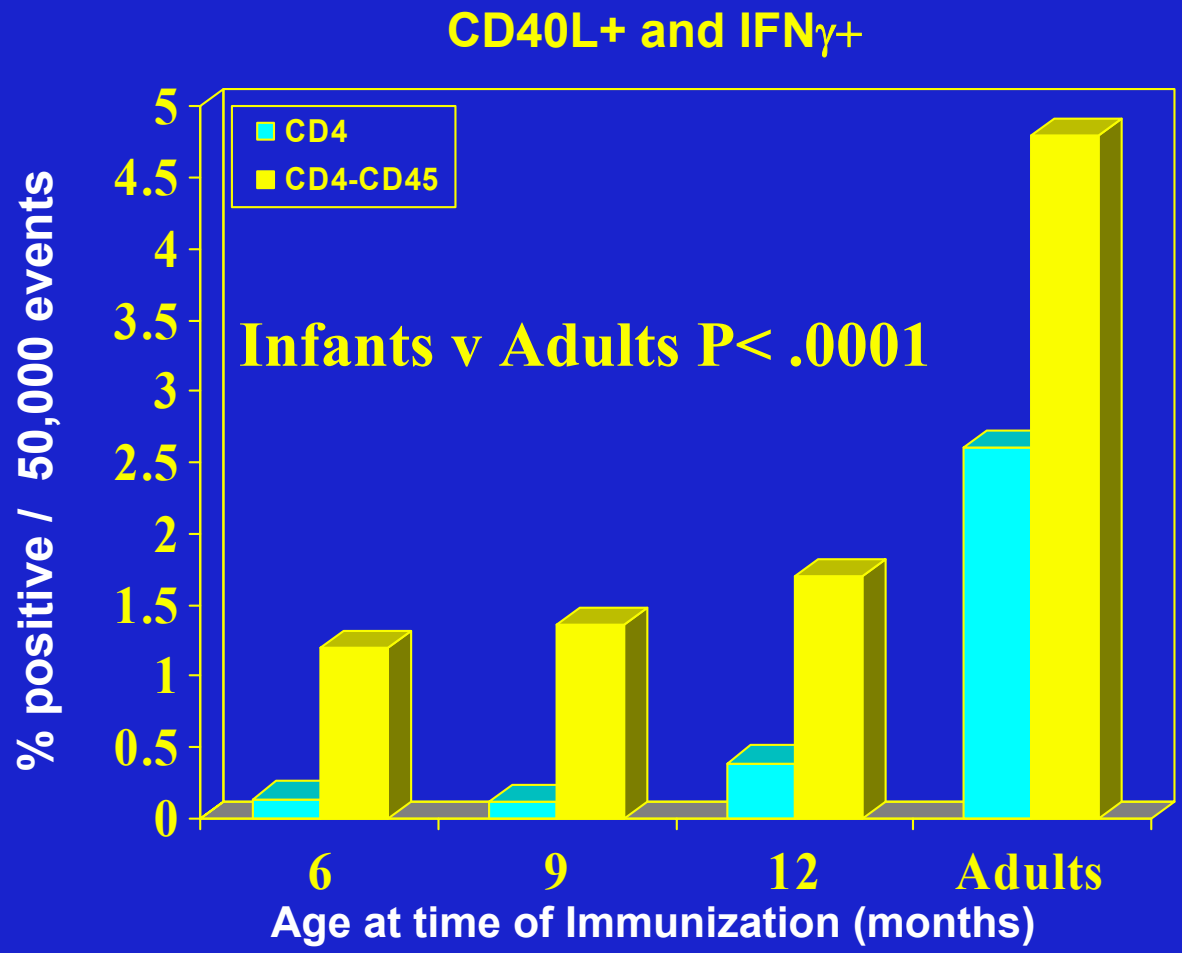
Frequencies of measles-specific memory CD4 T cells that are CD40-L+ or CD69+ and IFN-γ + are equivalent in infants and adults.

Frequency of CD4 T cells expressing CD40-Ligand and CD40L-IFN-γ after SEB Stimulation



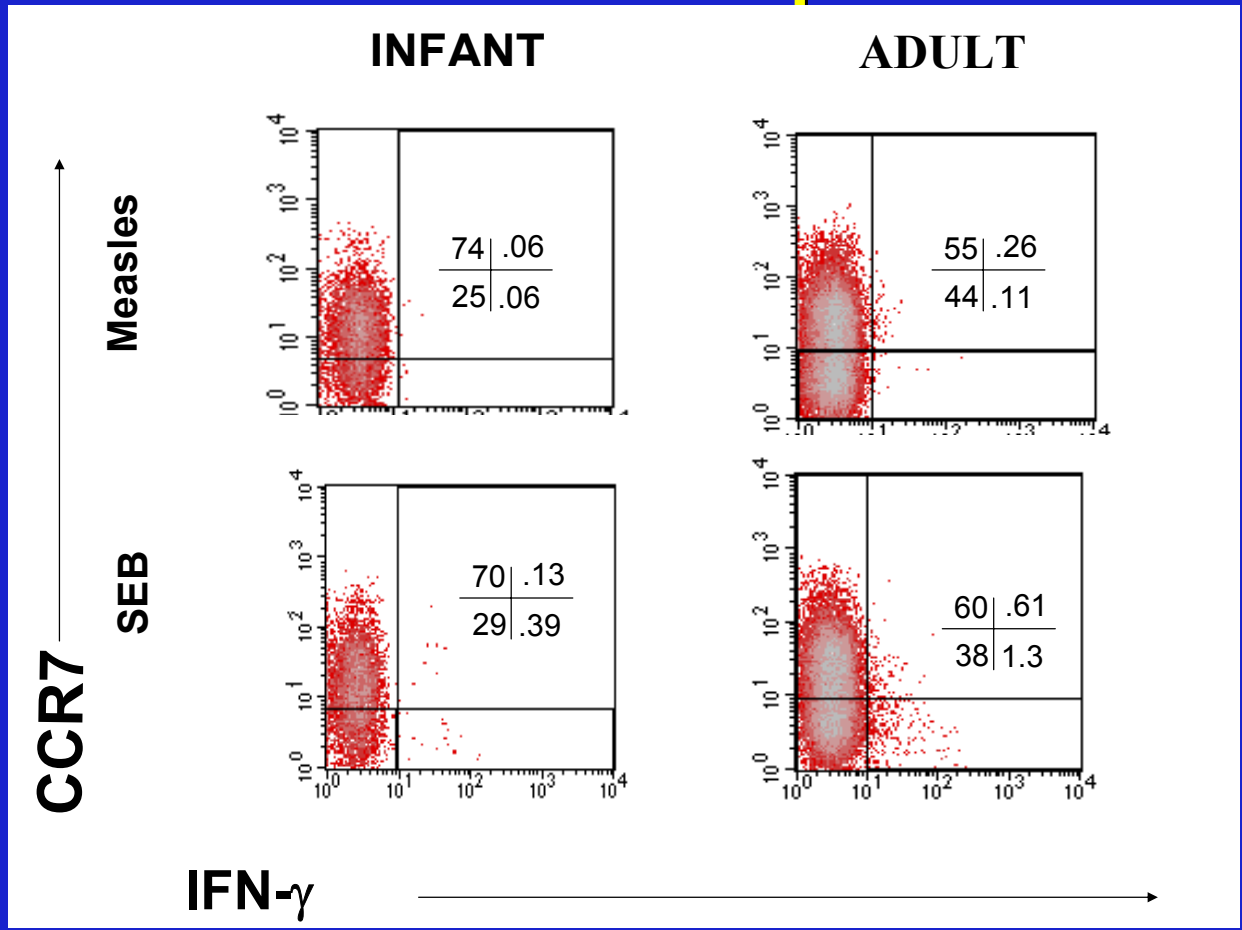
6 and 9 mo demonstrate limitation in CD4 T cells that up-regulate CD40-Ligand and produce IFN-γ after maximal stimulation.
Infants can up-regulate CD40-L at comparable rates regardless of age and to adults but fewer of these cells produce IFN-γ.

Frequency of Total CD4 T cells versus CD45RO+ CD4 T cells expressing CD40-L and IFN-γ after SEB Stimulation



Frequencies of memory CD4 T cells that are CD40-L+ and IFN-γ + are lower in infants compared to adults in response to maximal stimulation.

Frequency of CD4+ memory T cells in relation to CCR7 expression



Frequencies of memory CD4+ T cells that are CCR7- and IFN-γ + are lower in infants compared to adults in response to measles and maximal stimulation.

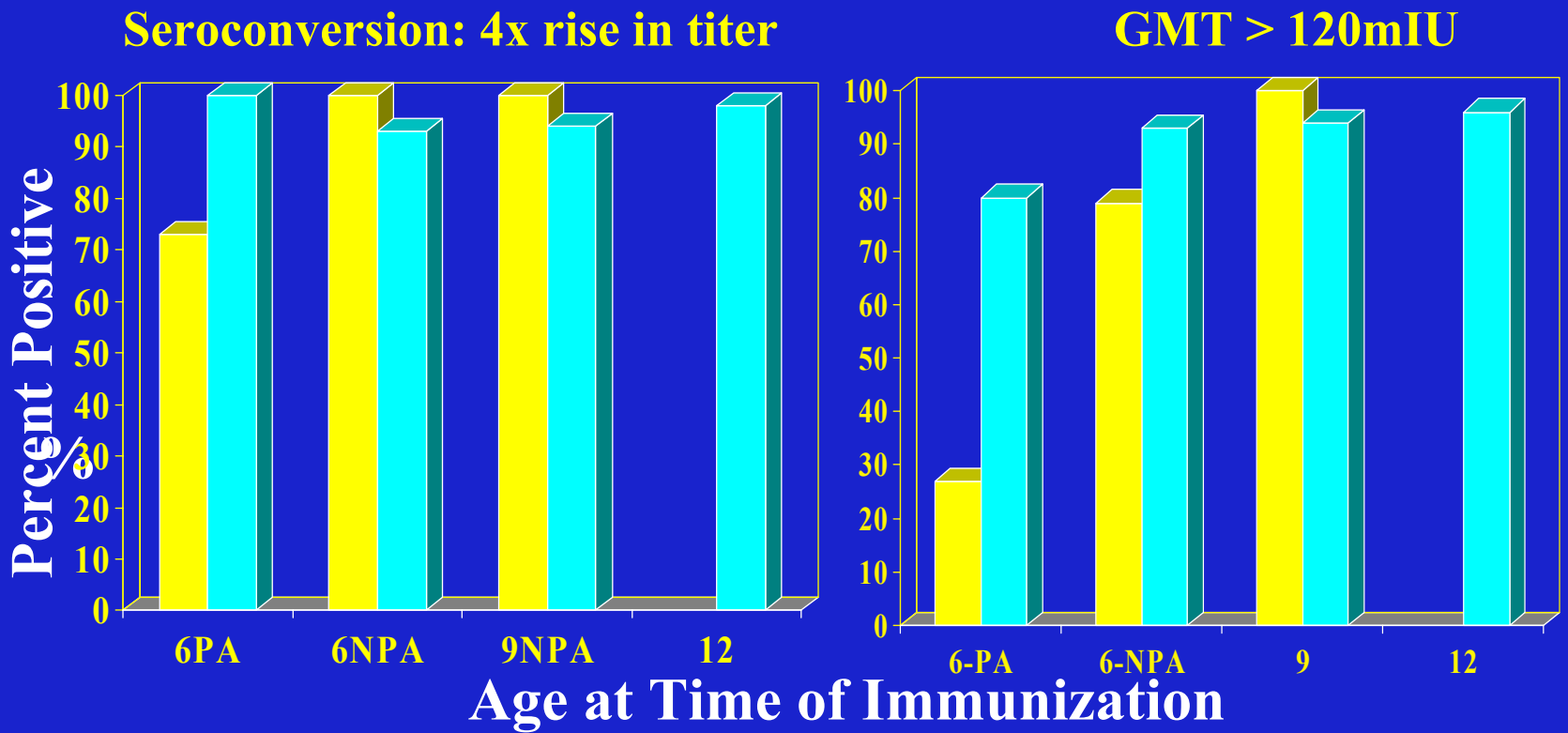
Summary: Cell Mediated Immunity

- **Infant response**
  - **No antigen-specific age-related differences**
    - T cell proliferation
    - IFN-γ, IL-12 production
  - **Age-related limitation after maximal stimulation**
    - RCF of T cells that are able to secrete IFN-γ
  - **No passive antibody effect**
    - T cell proliferation
    - Cytokine production

Summary: Cell Mediated Immunity

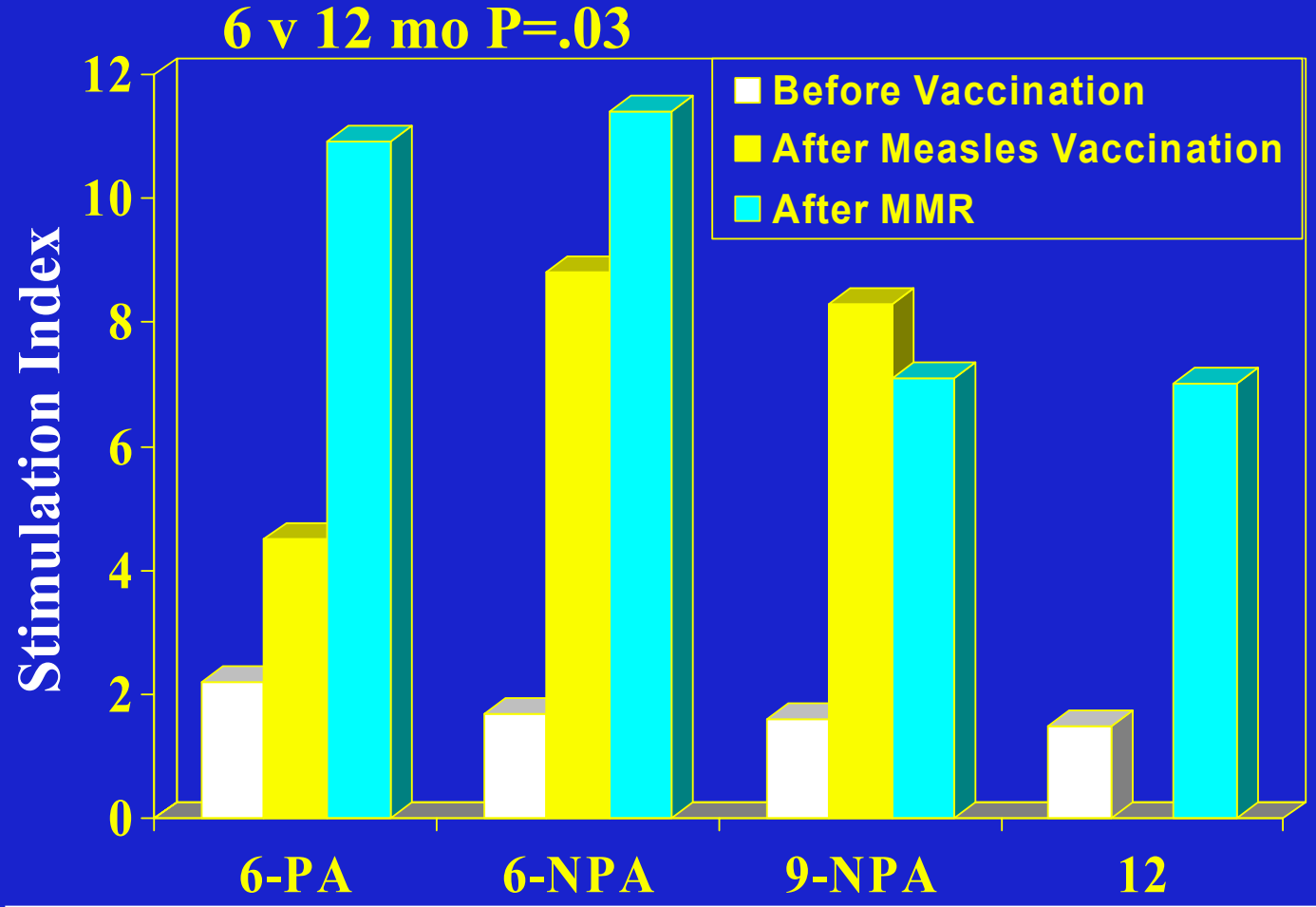
- **Differences between infants and adults**
  - Lower CD4+ T cell proliferation, IFN-γ and IL-12
  - T cells produced limited IFN-γ in response to measles and exogenous IL-12
  - Correction of proliferative defect after measles immunization when IL-12 and IL-15 are added to measles
  - Infant T cells upregulate CD40L in response to measles antigen and SEB, but show a relative inability to produce IFNγ which is only partially corrected when the memory population is evaluated
  - The majority of infant memory cells reside in the CCR7-high population and CCR7-low T cells demonstrate a limited effector function

Humoral Immunity in 6 and 9 Month Old Infants after One and Two Doses of Measles Vaccine:



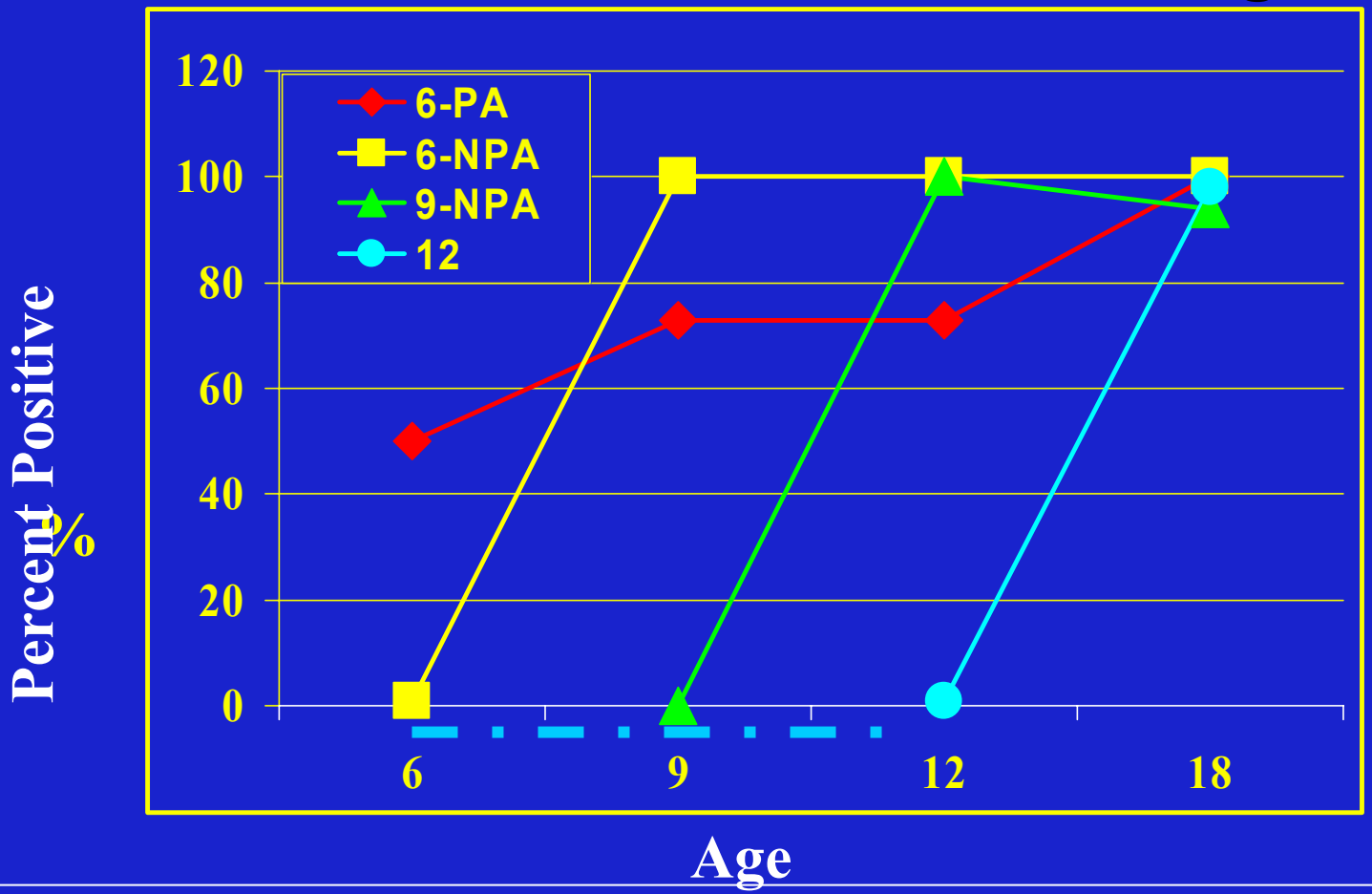
Maturational limitations seen in 6 mo old infants after first measles dose do not restrict adequate responses to MMR given at 12 months
Passive antibodies do not restrict seroconversion of 6 mo old infants after MMR <u>but</u> fewer infants have GMT > 120mIU

Cellular Immunity in 6 and 9 mo Old Infants after One and Two Doses of Measles Vaccine:



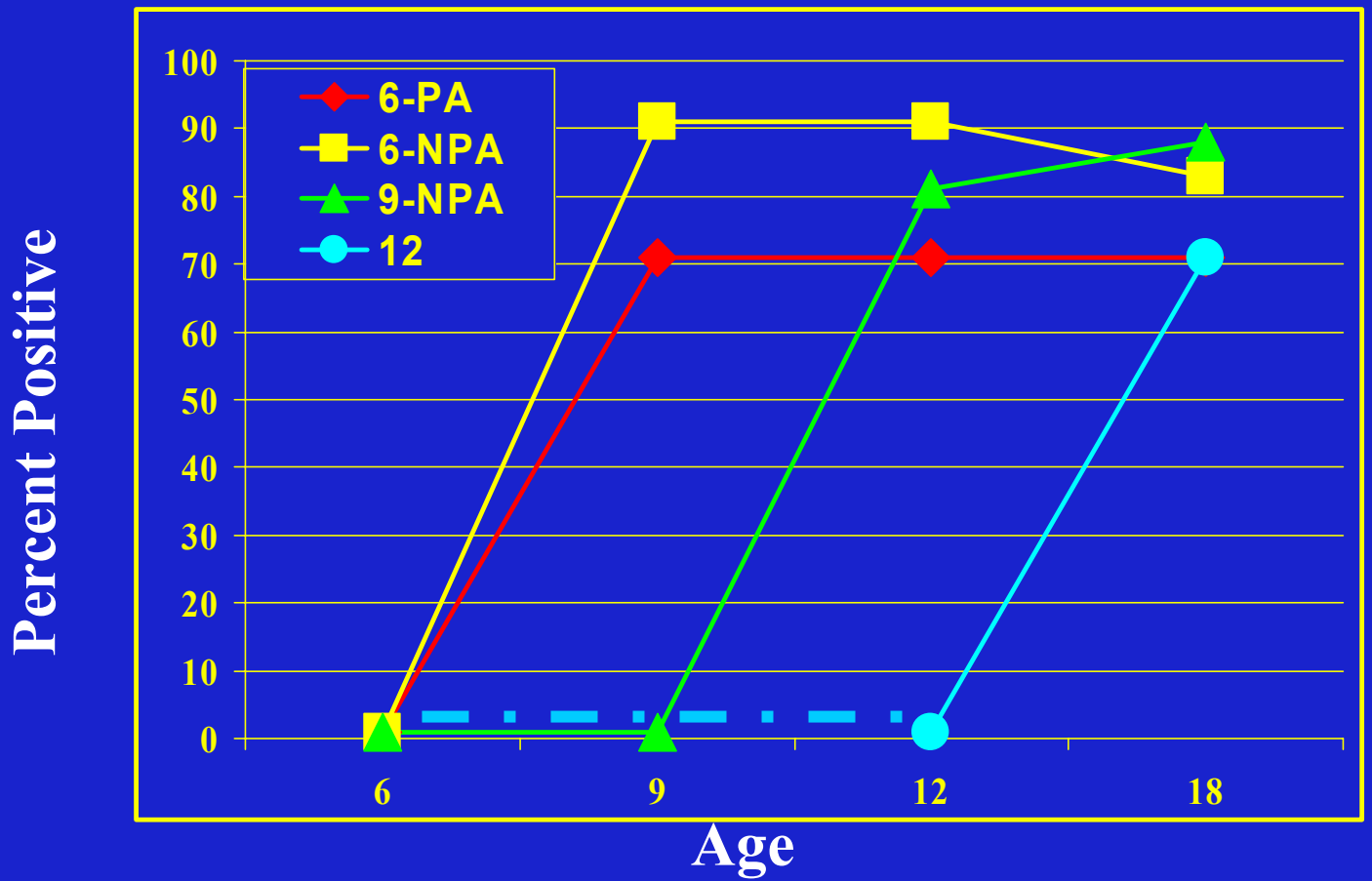
Higher SI in infants given two dose regimen at 6 months and a second dose at 12 months versus single dose at 12 months

Percentage of Infants with Measles Antibodies in Relation to Vaccine Regimen



Adequate humoral responses in infants without passive antibodies allows them to avoid a period of measles susceptibility

Percentage of Infants with Measles Cellular Immunity in Relation to Vaccine Regimen



Adequate T cell immunity in all infants regardless of passive antibodiesmay allow them to avoid a period of measles susceptibility

Summary: Early Two-dose Regimen

- **In the absence of passive antibodies**
  - 6 month olds
    - **respond well to a second dose - no difference from 9 month olds after second dose**
  - 9 month olds
    - **humoral and cellular immunity equal to 12 month olds**
    - **GMT is higher after second dose than after a single MMR at 12 months.**
- **In the presence of passive antibodies**
  - 6 month olds
    - **Seroconversion rates equal to other groups after second dose**
    - **GMT and percentage with titer >120 after second dose are lower**
    - **higher T cell responses**
  - All infants
    - **Induction of Measles-specific CD4+ T cell responses**

Measles-specific CD4 T cells may provide adaptive immunity that modulates disease severity even when the humoral immune response is limited.

6 and 9 mo infants vaccinated in the absence of passive antibodies benefited with both humoral and cell mediated immunity and avoided a period of susceptibility

Infants immunized in the presence of passive antibodies probably avoided a period of susceptibility at least to measles in the severe form

Acknowledgments

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