Maternal Immunization Against Influenza and RSV: Rationale and Experience

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OBSTETRICAL CONSIDERATIONS FOR USING A VACCINE IN PREGNANT WOMEN*

- High risk for exposure of pregnant woman to disease
- Infection poses a special risk to the mother
- Infection poses a special risk to the fetus
- Vaccine is available, and unlikely to cause harm

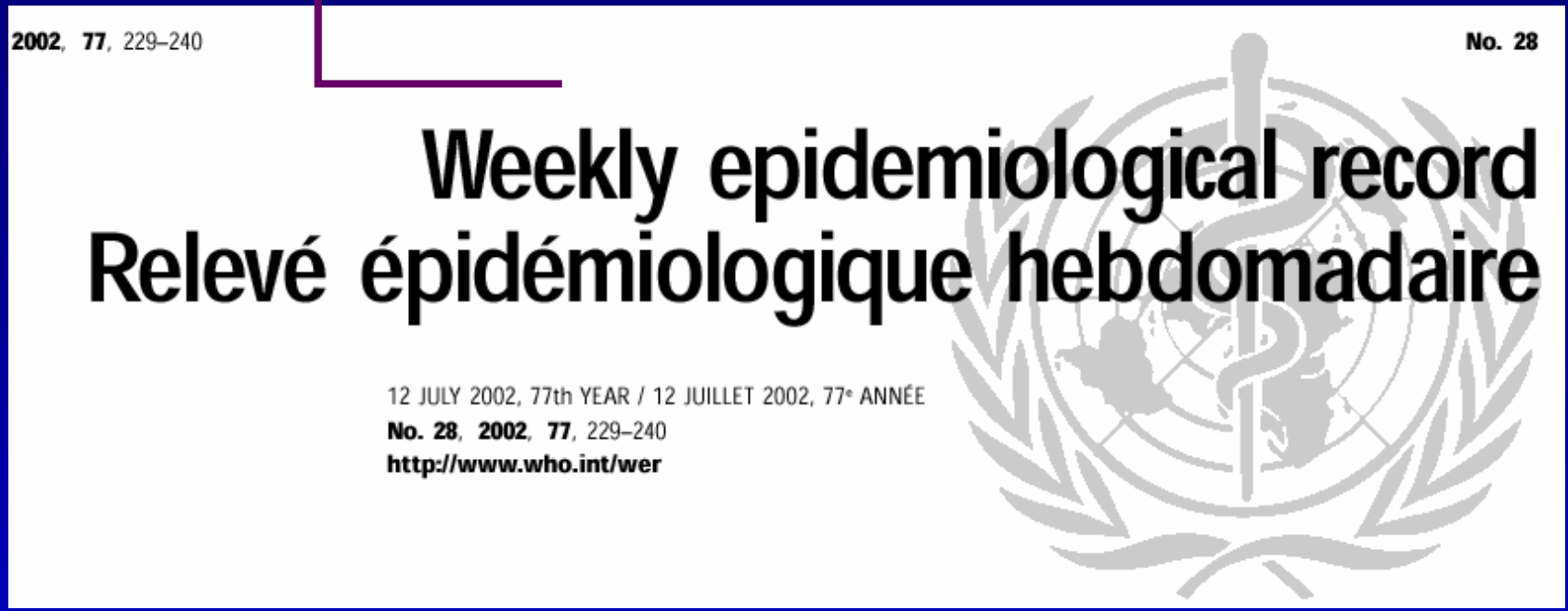
*ACOG Technical Bulletin 1991; 160.

High-risk Adults Considered for Influenza Vaccine, USA*

- Persons aged 50 and older
- Residents of chronic care facilities
- Chronic pulmonary or cardiovascular conditions (including asthma)
- Metabolic diseases (esp. diabetes), renal, hemoglobinopathies, immunosuppression
- For 2004: Healthy children ages 6-24 months and their contacts
- **Women in second or third trimester during flu season**

***MMWR1999; 2000; 2001; 2002; 2004**

Influenza vaccination in 2nd-3rd trimester



Pregnant women who will be in their second or third trimester by the start of the influenza season and who are likely to be exposed are advised to consider vaccination in careful consultation with a competent health care provider.

RISK OF EXPOSURE OF PREGNANT WOMEN TO INFLUENZA

- Overall risk of exposure is high*:
  - Influenza infects ~10% of adults annually
  - Influenza infects up to ~30% of children annually
- Women of childbearing age range have increased exposure to young children, and may have increased rate of exposure compared to general adult population.

*Neuzil and Griffin, Inf Dis Clin N Am 2001;15:123

Historical Reports

- 1918: Mortality associated with infection during pregnancy ~51%, with highest rates in later stages of pregnancy*
- 1957: 50% of women of childbearing age who died of influenza were pregnant; 10% of all influenza deaths that season were in pregnant women (most in latter half of pregnancy)**
- Case reports of complications since then – many in later stages of pregnancy***

* Harris. JAMA 1919;14:978

** Freeman and Barno, Am J Ob Gyn 1959;78:1172; Greenberg et al. Am J Ob Gyn 1958;76:897

*** Neuzil et al Inf Dis Clin N Am 2001;15:123

Excess Rates of Medical Visits for Acute Respiratory Disease Attributable to Influenza per 1,000 Women in Prepaid Medical Care Group (USA)*

Epidemic period	Not pregnant	Pregnant
1975	19.2	-3.4
1976	14.6	13.4
1978	7.4	55.5
1979	5.8	24.0
Combined	10.2	23.7

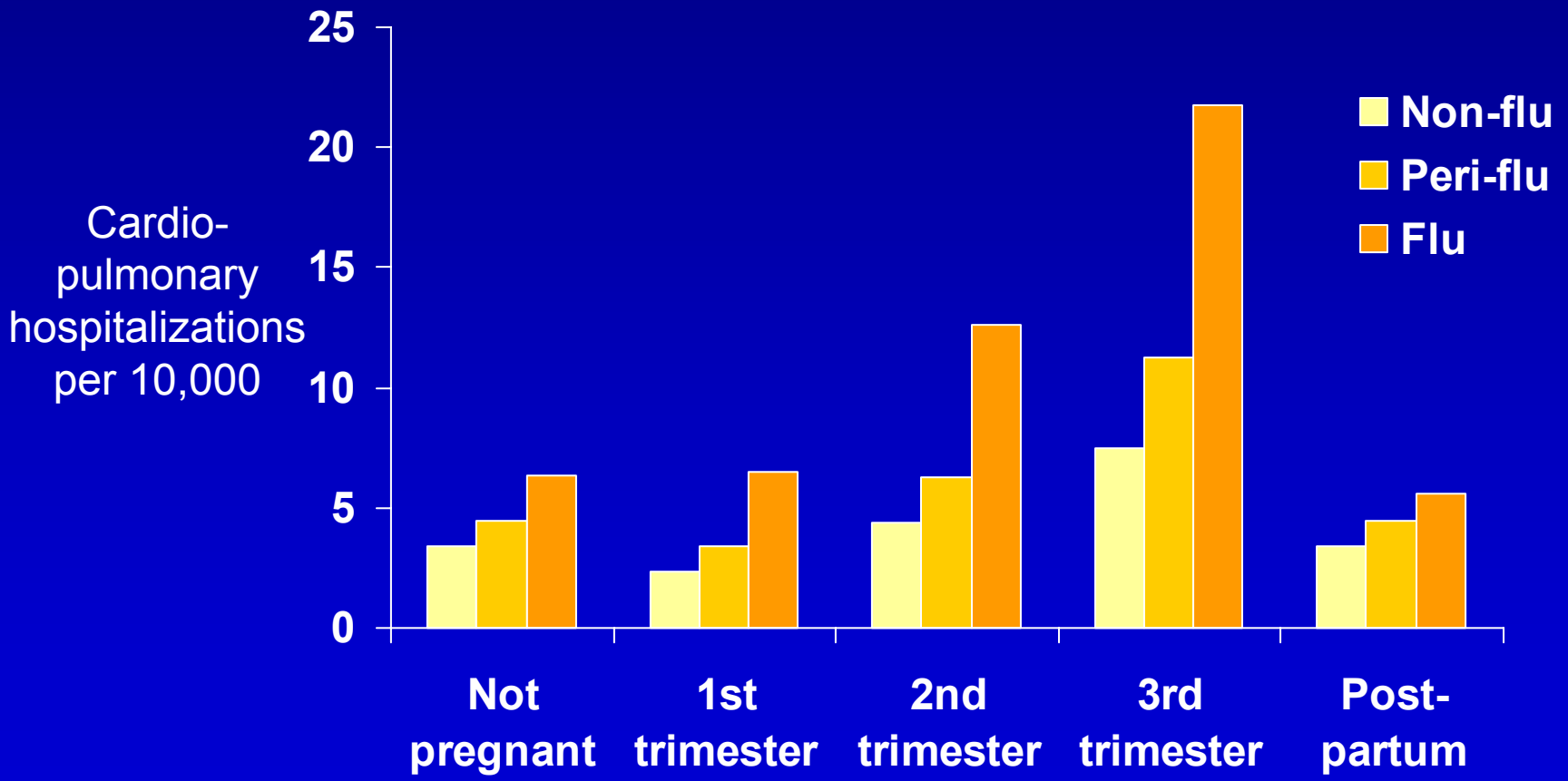
*Mullooly et al. Public Health Reports 1986; 101:205

Influenza-Related Complications in Women Enrolled in Tennessee Medicaid*

- Nested case control study evaluating women ages 15-44 during 17 influenza seasons
- Compared to non-pregnant women the risk of hospitalization increased progressively:
  - 1.4 -fold for gestation weeks 14-20
  - 4.7 -fold for gestation weeks 37-42
- Predict: 25 of 10,000 women in 3rd trimester during flu season will be hospitalized with influenza-related disease

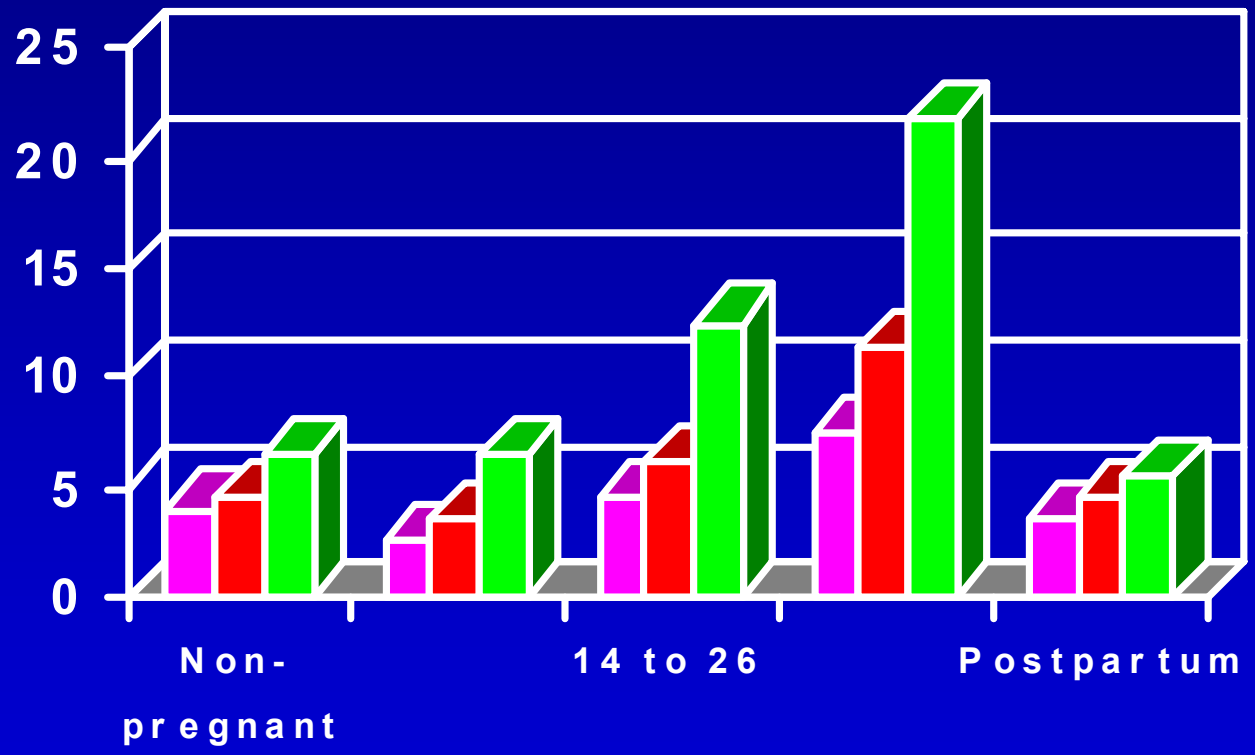
*Neuzil et al, Am J Epi 1998;148:1094

Effect of pregnancy on influenza-related hospitalizations*



Neuzil, et al. NEJM 1996

Pregnancy is a Risk Factor for Hospitalization in Low-Risk Women Ages 15-44 *



*Neuzil et al, Am J Epi 1998;148:1094

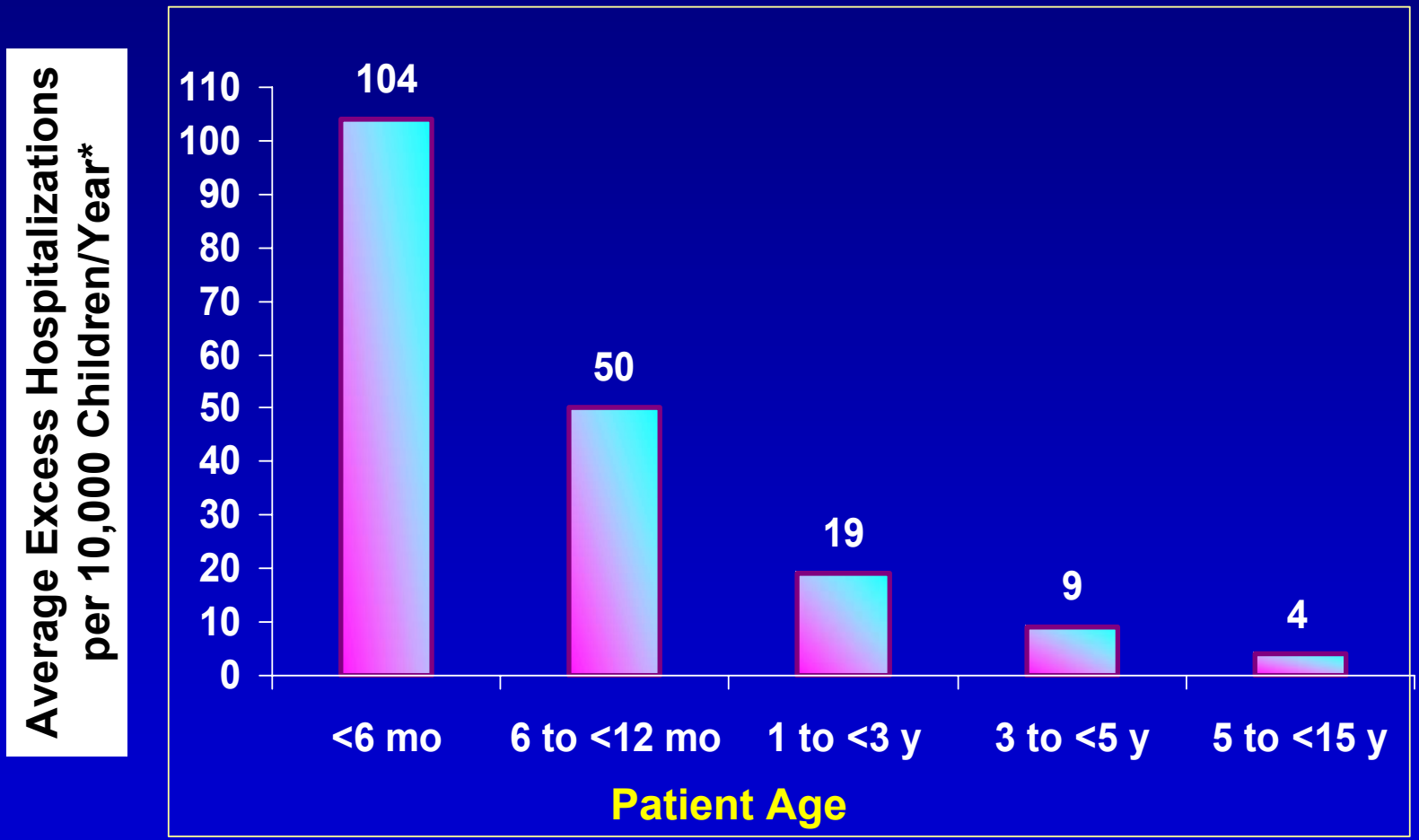
What Is the Effect of Influenza on the Fetus or Newborn?

- In pandemics of 1918 and 1957, pregnancy was interrupted in half of influenza cases complicated by pneumonia.
- Case reports: stillbirths, neonatal deaths associated with maternal infection with influenza.

Jewett JF. NEJM 1974; 291: 256.

Yawn et al. JAMA 1971; 216: 1022.

Excess Hospitalizations per 10,000 Children/Year By Age



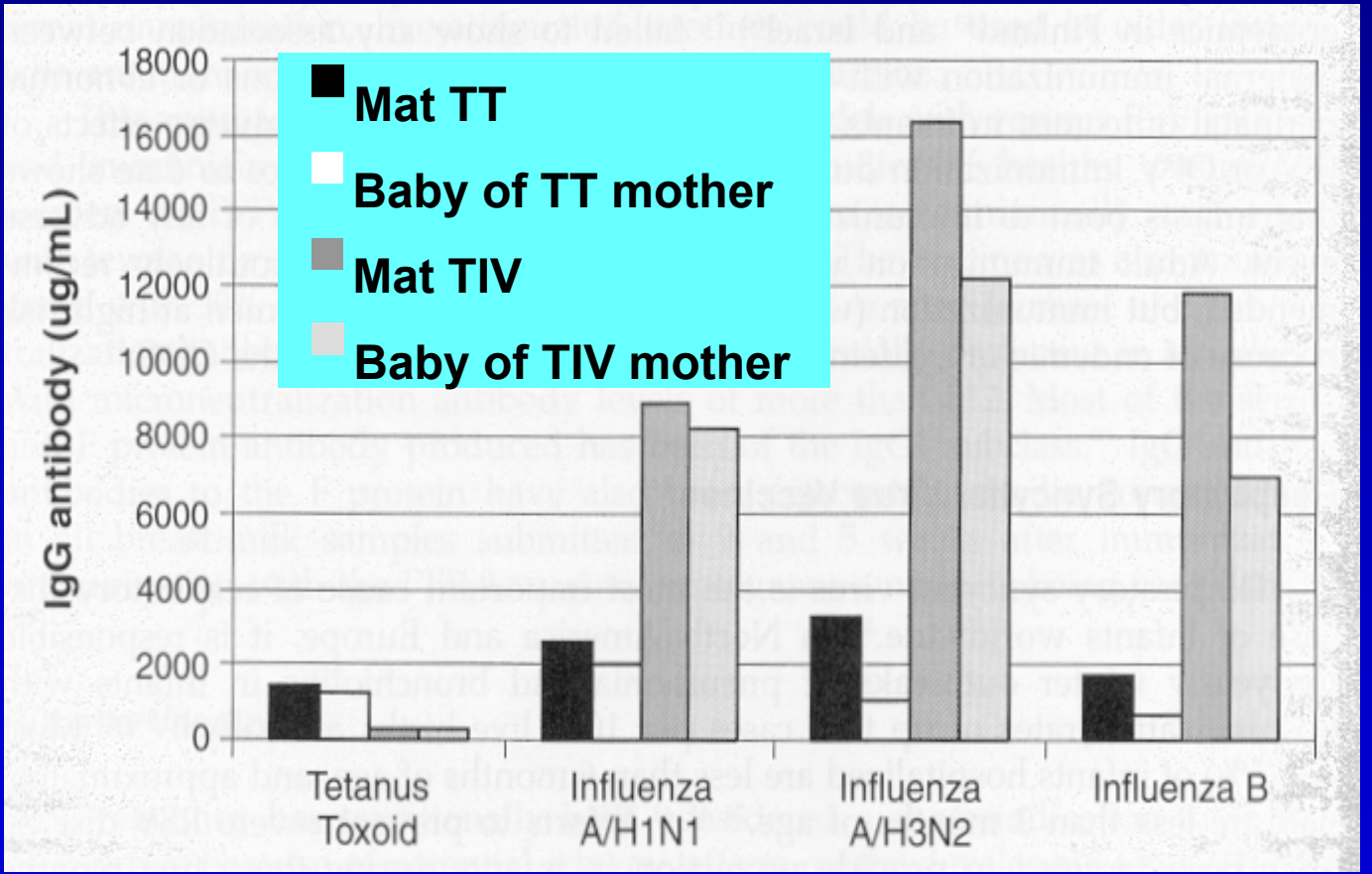
*Values are weighted averages of annual excess hospitalizations for a population of 10,000 persons within the specified age group.

Neuzil KM et al. *N Engl J Med.* 2000;342:225-231.

Transplacentally-acquired Influenza Antibody and Disease in Infants

1. Infants are protected from symptomatic influenza A virus infection by transplacentally acquired antibody (Puck et al, *J Infect Dis* 1980; 142:844-9.)
2. Passive maternal antibody to influenza A/H1N1 delays the onset and decreases the severity of influenza disease in 39 mother-infant pairs.(Reuman et al, *PIDJ* 1987;6:398-403

Influenza IgG Following Maternal Immunization with Influenza Vaccine (TIV) or Tetanus Toxoid (TT)



Englund et al JID 1993; 168:647

Trivalent Inactivated Influenza Vaccine vs. Tetanus Toxoid Vaccine in Pregnant Women*

- Vaccines were safe, well tolerated
- IgG Ab to vaccine antigens present at significantly higher levels in cord and 2 month infant serum samples
- Lymphocyte proliferative responses to vaccine antigens noted in mothers but not in cord or infant lymphocytes.

*Englund, et al. JID 1993;168:647

Why Not Immunize Pregnant Women with Influenza Vaccine?

Risk of ill effects on fetus:

- Fever
- Spontaneous abortions
- Thimerosal
- Developmental sequelae

Collaborative Perinatal Project 1957-1966, USA

- >50,000 immunized pregnant women and their offspring were followed for 7 years in this NIH-sponsored longitudinal study
- Offspring assessed for malformations, learning problems, hearing loss, and cancer
- Vaccines/ # doses:
  - **TRIVALENT INACTIVATED INFLUENZA VACCINE: 2,291**
  - **IPV 18,000; OPV 3,000**
- No significant increase in adverse reactions in mothers or adverse outcomes in infants

Safety of Influenza Vaccine During Pregnancy

- Routinely administered to pregnant women during 1960's
- More recent studies:
  - Heinonen, Collaborative Perinatal Project: 650 children followed x 7 years after their mothers received TIV with normal outcome
  - Deinard: 176 women immunized at all stages of pregnancy, with normal outcome in infants
  - Sumaya; Murray: 135 women received swine flu vaccine; same Ab response as nonpregnant women
  - Englund: 13 pregnant women; min. reactogenicity

Deinard. Am J Ob Gyn 1981;140:240
Sumaya. JID 1979;140:141; Murray et al. J Clin Micro 1979;10:184
Englund et al JID 1993;168:647

Practical Aspects of Influenza Immunization in Pregnancy

- What are the overall benefits of expanding vaccine coverage during pregnancy?
- What are the potential disadvantages?
- How can we engage our obstetrical colleagues in vaccination process?

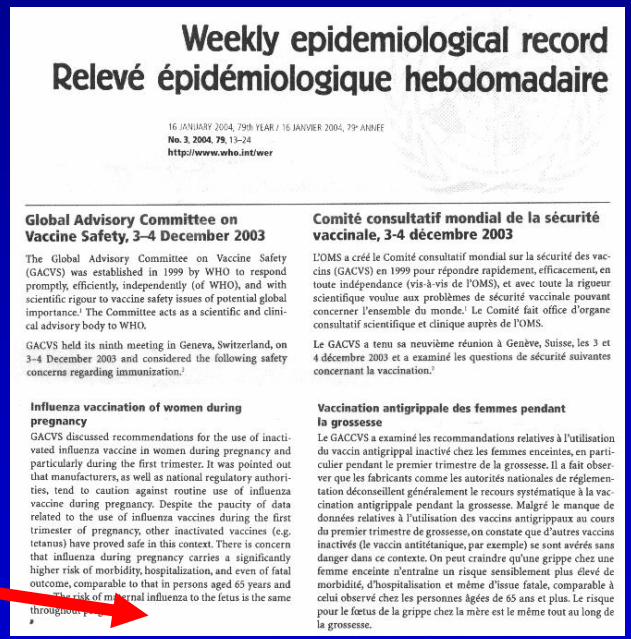
Summary of Available Data

Pregnant women are at increased risk for influenza-related complications.

Increasing vaccine use in pregnancy has the potential to benefit both the woman and her infant.

WHO Global Advisory Committee on Vaccine Safety, Jan. 16, 2004

GAVS concluded that <u>risk-benefit of influenza vaccination during pregnancy, at all stages of pregnancy,</u> should be reconsidered…..



Weekly epidemiological record
Relevé épidémiologique hebdomadaire

16 JANUARY 2004, 79th YEAR / 16 JANVIER 2004, 79e ANNÉE
No. 3, 2004, 79, 13–24
http://www.who.int/wer

Global Advisory Committee on Vaccine Safety, 3–4 December 2003

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 by WHO to respond promptly, efficiently, independently (of WHO), and with scientific rigour to vaccine safety issues of potential global importance.[1] The Committee acts as a scientific and clinical advisory body to WHO.

GACVS held its ninth meeting in Geneva, Switzerland, on 3–4 December 2003 and considered the following safety concerns regarding immunization.[2]

Influenza vaccination of women during pregnancy

GACVS discussed recommendations for the use of inactivated influenza vaccine in women during pregnancy and particularly during the first trimester. It was pointed out that manufacturers, as well as national regulatory authorities, tend to caution against routine use of influenza vaccine during pregnancy. Despite the paucity of data related to the use of influenza vaccines during the first trimester of pregnancy, other inactivated vaccines (e.g. tetanus) have proved safe in this context. There is concern that influenza during pregnancy carries a significantly higher risk of morbidity, hospitalization, and even of fatal outcome, comparable to that in persons aged 65 years and [illegible] risk of maternal influenza to the fetus is the same throughout [illegible]

Comité consultatif mondial de la sécurité vaccinale, 3-4 décembre 2003

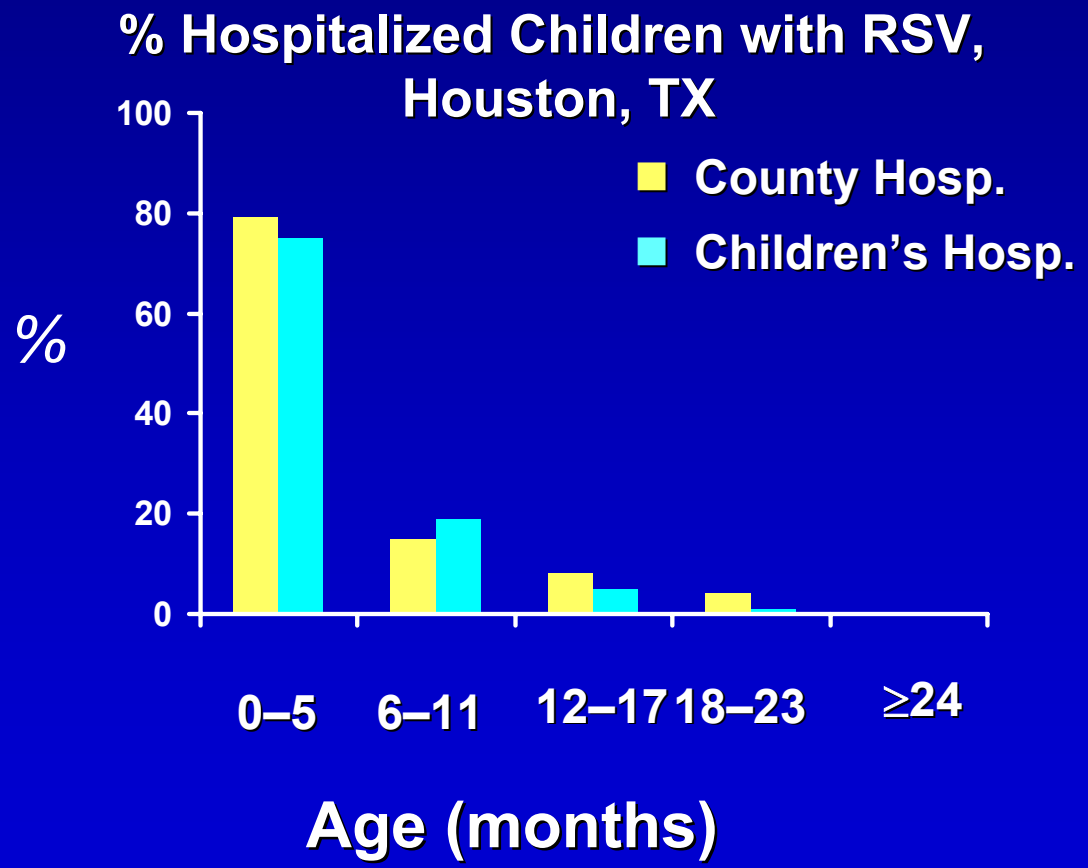
L'OMS a créé le Comité consultatif mondial sur la sécurité des vaccins (GACVS) en 1999 pour répondre rapidement, efficacement, en toute indépendance (vis-à-vis de l'OMS), et avec toute la rigueur scientifique voulue aux problèmes de sécurité vaccinale pouvant concerner l'ensemble du monde.[1] Le Comité fait office d'organe consultatif scientifique et clinique auprès de l'OMS.

Le GACVS a tenu sa neuvième réunion à Genève, Suisse, les 3 et 4 décembre 2003 et a examiné les questions de sécurité suivantes concernant la vaccination.[2]

Vaccination antigrippale des femmes pendant la grossesse

Le GACCVS a examiné les recommandations relatives à l'utilisation du vaccin antigrippal inactivé chez les femmes enceintes, en particulier pendant le premier trimestre de la grossesse. Il a fait observer que les fabricants comme les autorités nationales de réglementation déconseillent généralement le recours systématique à la vaccination antigrippale pendant la grossesse. Malgré le manque de données relatives à l'utilisation des vaccins antigrippaux au cours du premier trimestre de grossesse, on constate que d'autres vaccins inactivés (le vaccin antitétanique, par exemple) se sont avérés sans danger dans ce contexte. On peut craindre qu'une grippe chez une femme enceinte n'entraîne un risque sensiblement plus élevé de morbidité, d'hospitalisation et même d'issue fatale, comparable à celui observé chez les personnes âgées de 65 ans et plus. Le risque pour le fœtus de la grippe chez la mère est le même tout au long de la grossesse.

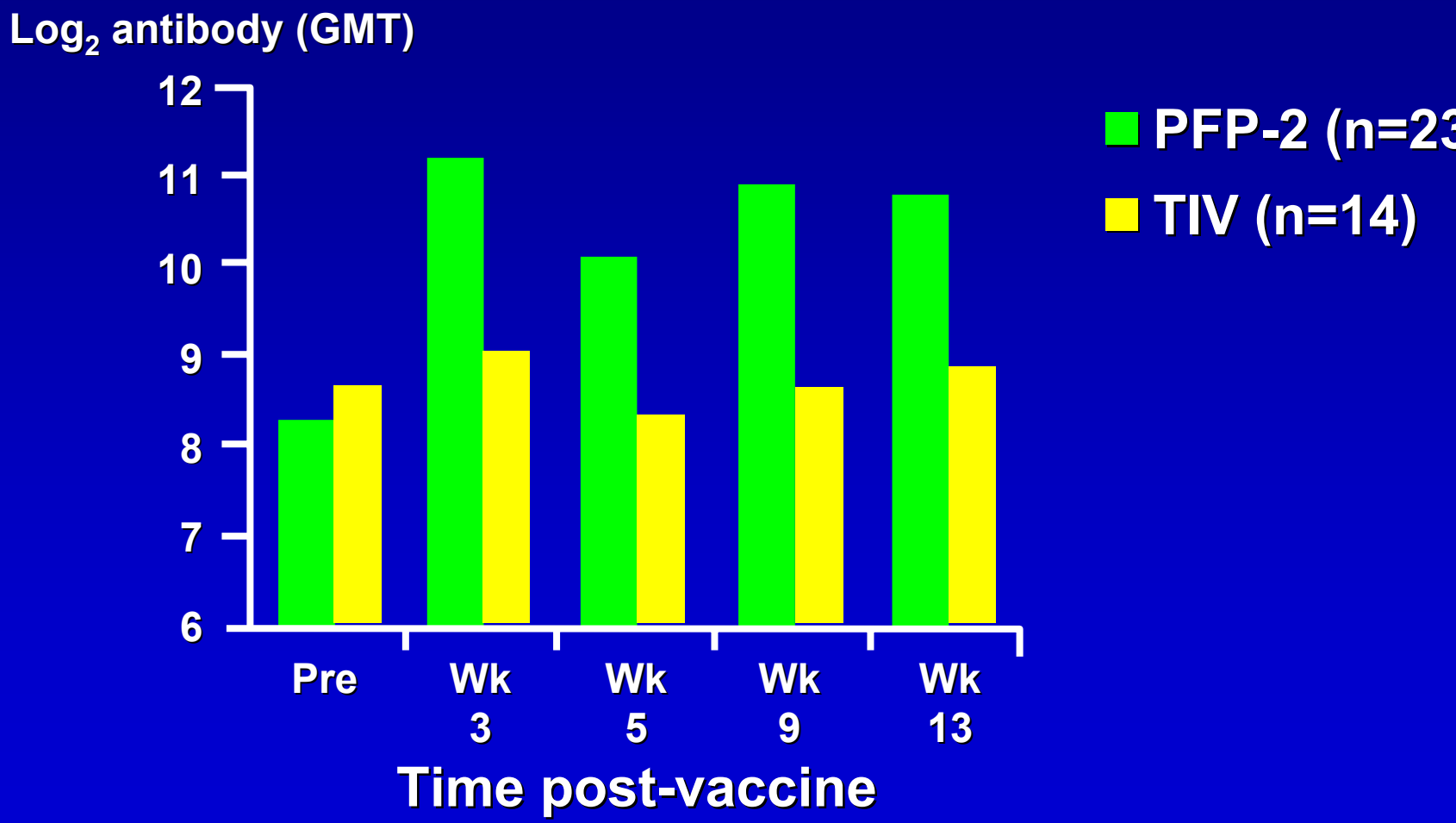
RSV: Most Important Respiratory Disease in Young Infants



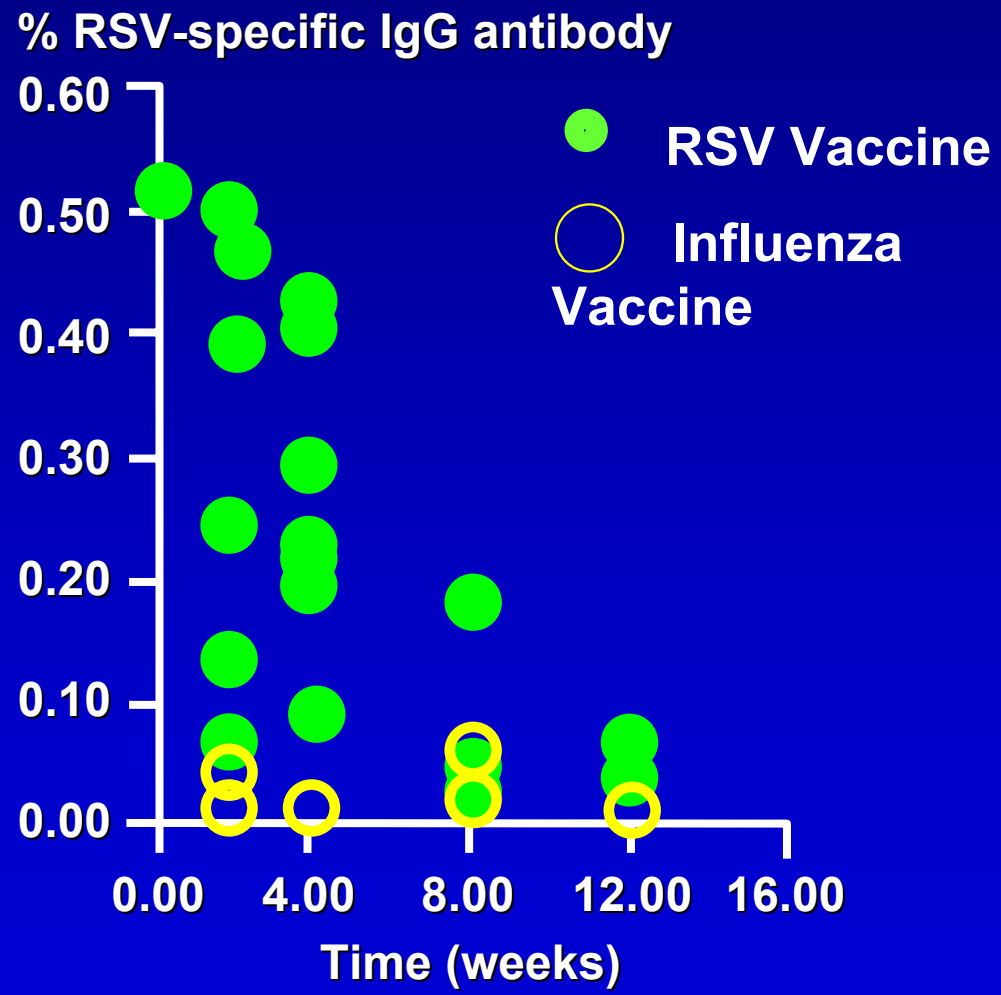
Maternal Immunization with RSV Vaccine to Prevent RSV Disease in Infancy

- Most urgent need for protection against RSV is during first months of life, when vaccines are poorly immunogenic
- >75% of hospitalization for significant RSV disease occurs in full term, healthy infants: target population
- Clinical studies with RSV subunit vaccinesdemonstrate good immunogenicity and lack of reactogenicity in postpartum women
- Teratogenicity: Potential teratogenicity of PFP vaccine has been studied in animal model has been looked for and not foundl

IgG anti-F protein Following Post-Partum RSV PFP-2 Vaccine



The Role of Breast Feeding:
Breast milk IgG following RSV PFP-2 or TIV in postpartum women



The Little Madonna,

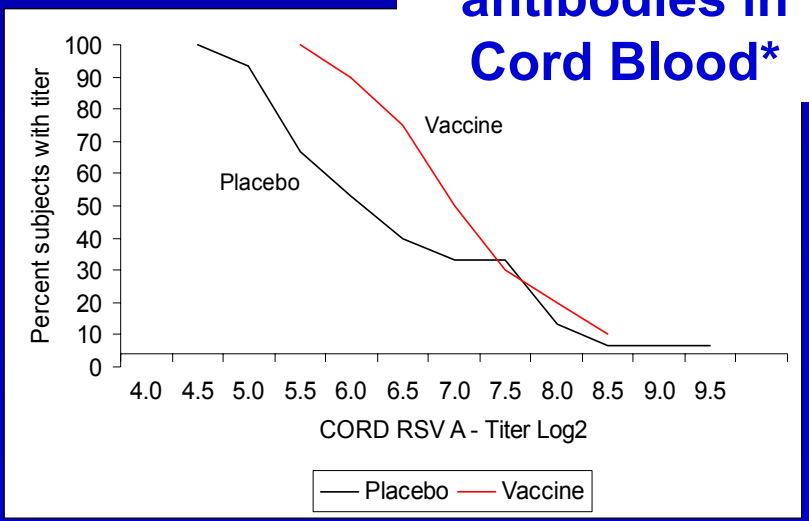
da Vinci 1452-1519

RSV VACCINE vs PLACEBO IN PREGNANT WOMEN*

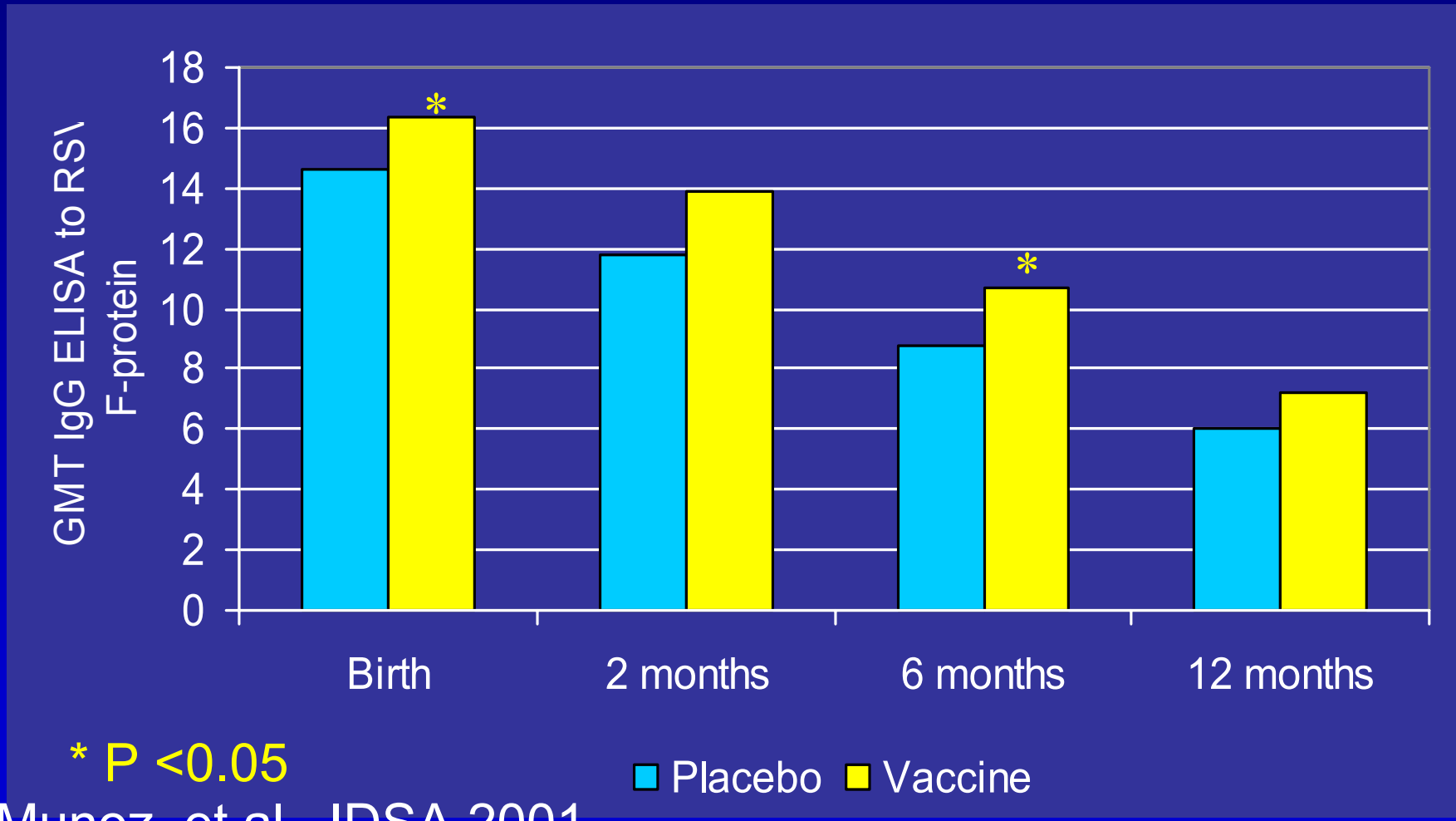
- Primary Endpoints:
  - Safety in healthy women in the 3rd trimester of pregnancy and their offspring
  - Effect of vaccine induced-antibody on primary RSV disease in infants
- Secondary Endpoints:
  - Immunogenicity
  - Efficiency of antibody transfer
  - Persistence of antibody in infants
  - Breast milk antibody

*Munoz et al. IDSA 2001 (Abstr)

RSV-A Neutralization antibodies in Cord Blood*



GMT of IgG ELISA antibody to RSV-F Protein in INFANTS*



* P <0.05

*Munoz, et al. IDSA 2001