ESCMID Postgraduate Education Course
Infectious Diseases in Pregnant Women, Fetuses and Newborns
Bertinoro, Italy 3 – 7 October 2010

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Disclosures: Consultant to Merck. Research support from Sanofi Pasteur. Partial interest in a relevant patent.

Objectives

- Rationale for CMV vaccine development
- Vaccines that have reached clinical trials
- Results of clinical trial aimed at prevention of maternal infection
- Future directions

Rationale for CMV vaccine development

- Public health importance of congenital CMV infection
- Difficulty preventing maternal infection by limiting exposure
- Immunity protects from disease

Estimate of Congenital CMV Disease Burden in U.S.

Based on rates from Dollard et al, Rev Med Virol 17:355, 2007

Live births, 2004	4.1 million
Congenital CMV cases (0.7%)	28,700
Symptomatic at birth (12.7% cases)	3,645
Symptomatic with sequelae (50%)	1,822
Asymptomatic with sequelae (13.5%)	3,382
Total per year with sequelae	5,204

Brain disease in children: congenital CMV infection vs H. flu b meningitis (Prevaccine) in the U.S.

Event, cases/yr	Congenital CMV	H.flu b meningitis
Infections	40,000	10,000
Deaths	280	500
Hearing loss	4,800	1,000
IQ < 70	2,350	100
Cerebral palsy	900	200

IOM Report: "quantitative model for prioritizing vaccine development."*

- Reviewed 26 conditions with potential for vaccine prevention
  - Public health importance for U.S.
  - Vaccine possible within 20 years
- Cost-effectiveness analysis
- Grouped candidate vaccines, Levels I-IV, from highest to lowest, based on cost and QALY saved
- CMV vaccine given to 12 year olds, ranked Level I, saves money and QALYs

***Vaccines for the 21st Century: A Tool for Decisionmaking, www.nap.edu/html/vacc21**

Annualized $ saved per vaccine

Assumptions: 100% efficacy and use; 0$ development cost

Vaccine	Billions $/yr saved
CMV	4.0
HPV	0.53
HCV	0.18

***Vaccines for the 21st Century: A Tool for Decisionmaking, www.nap.edu/html/vacc21**

Non-vaccine prevention of CMV infection?

- Infection is subclinical with chronic viral shedding for months to years.
- Source of infection for mothers is likely to be family member or other intimate contact that cannot be avoided
  - Spouse or sex partner
  - Child
- No clear public health message for prevention by limiting exposure

Rates of congenital CMV infection according to maternal antibody status at previous delivery

Fowler, Stagno, Pass, JAMA 289:1008, 2003

Maternal Group	N	Cong CMV	%
Immune	2,844	29	1.0*
Nonimmune	553	18	3.26

* RR = 0.31 (95% CI, 0.18-0.56)

Immunity and Protection from CMV Disease (gross over simplification)

- Humoral immunity (antibody)
  - Antibody to envelope glycoproteins neutralizes virus
  - Key targets: gB, gH, gM/gN
- Cellular immunity
  - CD8 CTL – control of virus replication in the host
  - CD4 memory, cytokine production
  - Key targets for CTL: pp65, IE1

Challenges for CMV Vaccine Development

- Large, complex virus
  - ~20 X the genetic material of HIV
  - Able to evade, subvert or mimic host response
- Chronic infection in normal host in the face of humoral and cellular immune response
- Reinfections occur in immune hosts
- Highly variable viral genome

Preconceived Conclusion:
Vaccine prevention will not be possible.

CMV vaccines that have entered clinical trials to date:

- Live CMV vaccines
  - Towne CMV*
  - Towne/Toledo chimeras*
- Vectored vaccines
  - Avian pox virus vector
  - Alphavirus vector, gB, pp65, IE1*
- Plasmid DNA vaccine
  - gB, pp65, IE1 as mono-, bi- or trivalent vaccine*
- Subunit recombinant protein
  - gB/MF59*
  - gB/HSVgD2
- Peptide vaccines
  - Pp65-A*0201
  - Pp65-pan HLA-DR-binding epitope

*Results of clinical trials will be discussed.

CMV vaccines

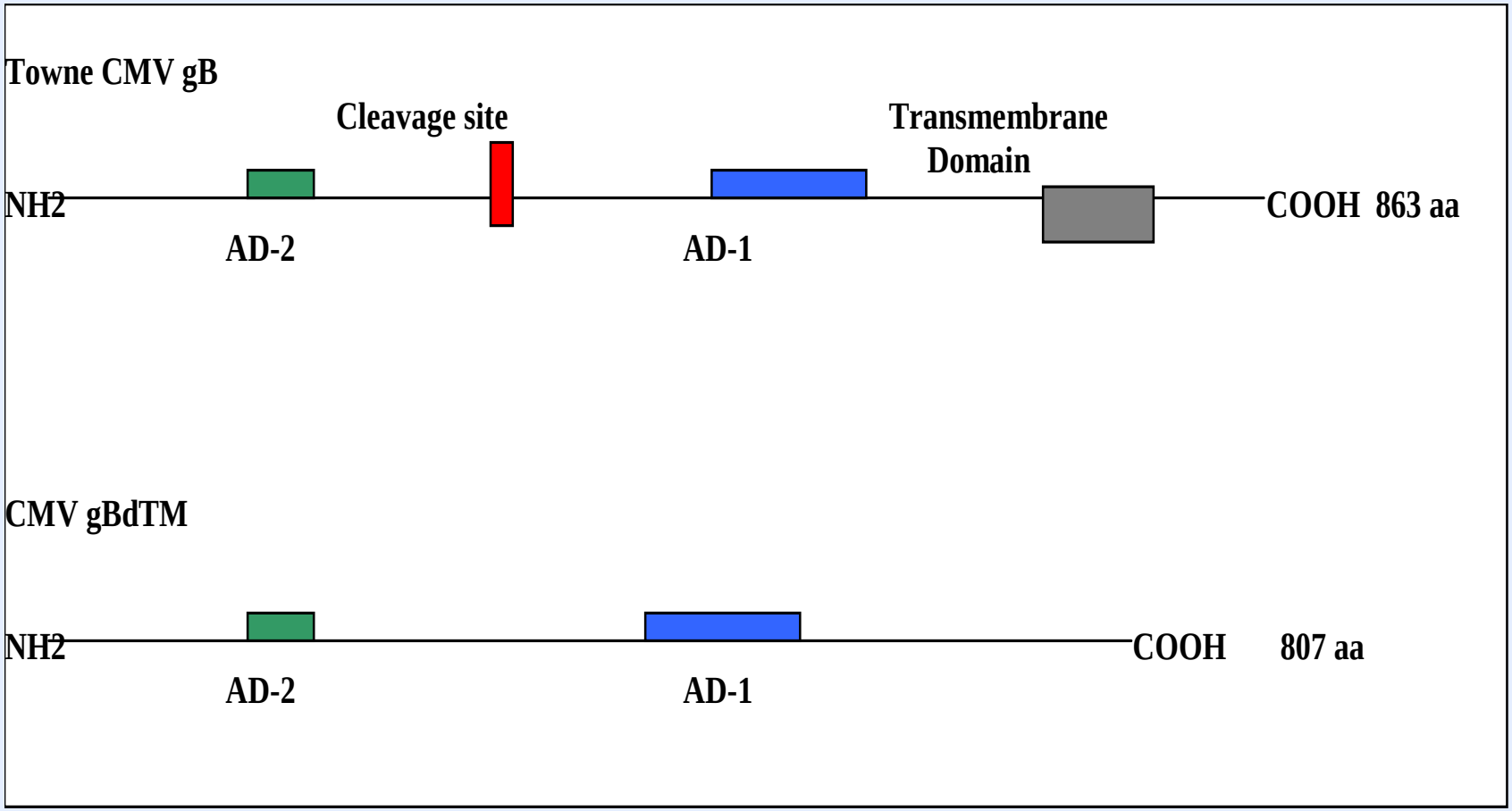
That have clinical trials reported up to 2010

Vaccine/Format	Antigens	COMPANY	DEVELOPMENT
alphavirus vectored	pp65, gB, IE1	AlphaVax Novartis	Phase I trial completed
Avian pox virus vector (ALVAC)	pp65, gB	sanofi pasteur	Phase I trials completed
Live virus	Chimeric virus	MedImmune (Astra Zeneca)	Phase I trial completed
DNA/plasmid	pp65, gB, IE1	Vical	Phase I trial completed
Live attenuated virus	Towne CMV	Vical	Multiple trials completed
Subunit, recomb protein	gB	sanofi pasteur	Multiple phase I and II trials completed
Subunit, recomb protein	gB	GSK	Phase I trial completed
Lipopeptide with adjuvant	Pp65-A*0201	City of Hope NCI	Phase I trial underway

Rationale for CMV gB as vaccine component

- Abundant envelope glycoprotein
- Important target of neutralizing antibody
- Antibody to gB in 100% post-infection
- Stable antigenic domains with little inter-strain heterogeneity
- Important biologic role: attachment, entry, cell to cell transmission
- Active and passive immunization with gB in animals protects against challenge
- In guinea pig model, maternal immunization with gB protects fetus

CMV gBdTM: Deletion of transmembrane portion of Towne CMV gB and loss of cleavage site - vaccine antigen



Findings from Chiron Sponsored Clinical Trials with CMVgB/MF59, 1994-1998

- No significant safety concerns, > 700 immunized
- Highly immunogenic
  - neutralizing antibody
  - high levels of gB antibody
  - persistent CD4 response
- More immunogenic with MF59 than alum
- Optimal antigen dose: 5 - 30μg
- 0,1 and 6 month schedule best of those tested
- Highly immunogenic in young children

CMV gB vaccine with MF59 adjuvant: A brief history

- Initially developed at Chiron early 1990s
- Multiple phase I and II clinical trials completed 1994-1998
- NIAID supported phase II efficacy trial at UAB, opened 1999
- Vaccine antigen acquired by Aventis Pasteur (now Sanofi Pasteur), 2000

Settings with High Incidence of CMV Infection Among Women of Childbearing Age

Study	Setting	Seroconver/yr, %
Adler, 1989	Day care workers	11
Pass, 1990	Day care workers	20
Murph, 1991	Day care workers	7.9
Pass, 1986	Day care parents	15
Chandler, 1985	STD clinic	37
Sohn, 1989	Teen clinic	34
Fowler, 2004	Postpartum women	5.9

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Clinical Trial of Recombinant CMV gB Vaccine in Postpartum Women

- Vaccines:
  - CMV gB, 20 µg (Sanofi Pasteur) with MF59 (Novartis)
  - Saline placebo
  - Schedule: 0, 1, and 6 months
- Population: Healthy CMV seronegative women within 12 months of birth of a newborn
- Screening on post-partum wards
- Study sites:
  - UAB, Birmingham
  - UA College of Community Health Sciences, Tuscaloosa

Phase II CMV gB Vaccine: Methods

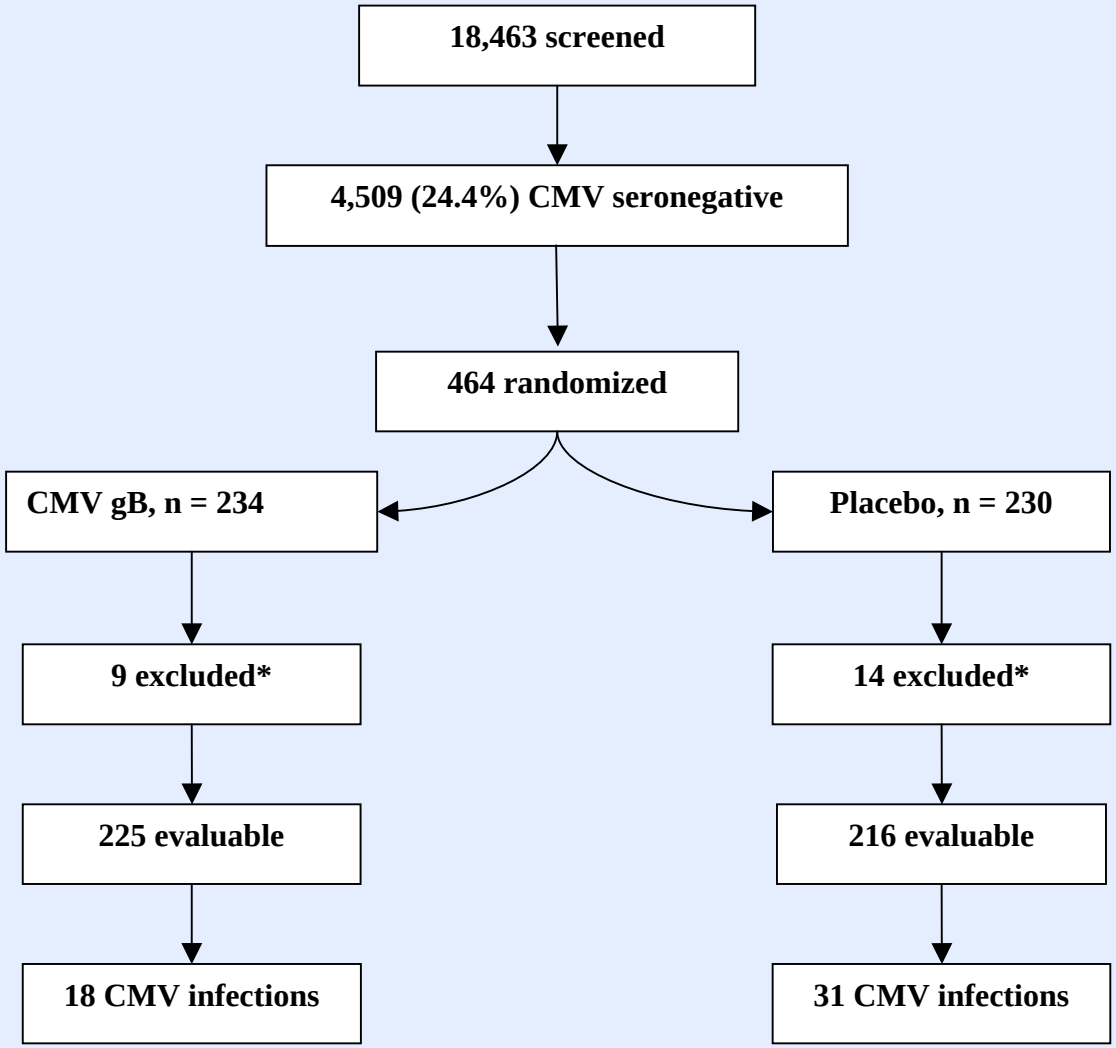
- Randomization – vaccine:placebo = 1:1
- Primary endpoint: time to CMV infection
- Sample size: 400
  - hypothesis of 50% efficacy
  - $\alpha \leq 0.05$ and power ≥ 0.80
- Primary statistical method: life table analysis (Kaplan-Meier) and log rank test
- Scheduled review of efficacy by DSMB with preset stopping rules

CMV gB Vaccine: Laboratory Methods

- Screening & visit 1: Axsym® System CMV IgG (Abbott Laboratories)
- CMV infection screening: gB absorbed CMV IgG* quarterly through 17 visits (3.5 years)
- CMV infection confirmation:
  - Virus culture (saliva, urine or vaginal swab)
  - Real time PCR (blood, serum, saliva, urine or vaginal swab)
  - Western Blot (*recom*Blot CMV, Mikrogen, Neuried, Germany)

***Zhang & Pass, Detection of cytomegalovirus infection during clinical trials of glycoprotein B vaccine. Vaccine 23:507-10, 2004.**

CMV gB phase II: Study population and endpoint accrual



From Pass et al, NEJM 2009; 360:1191-9

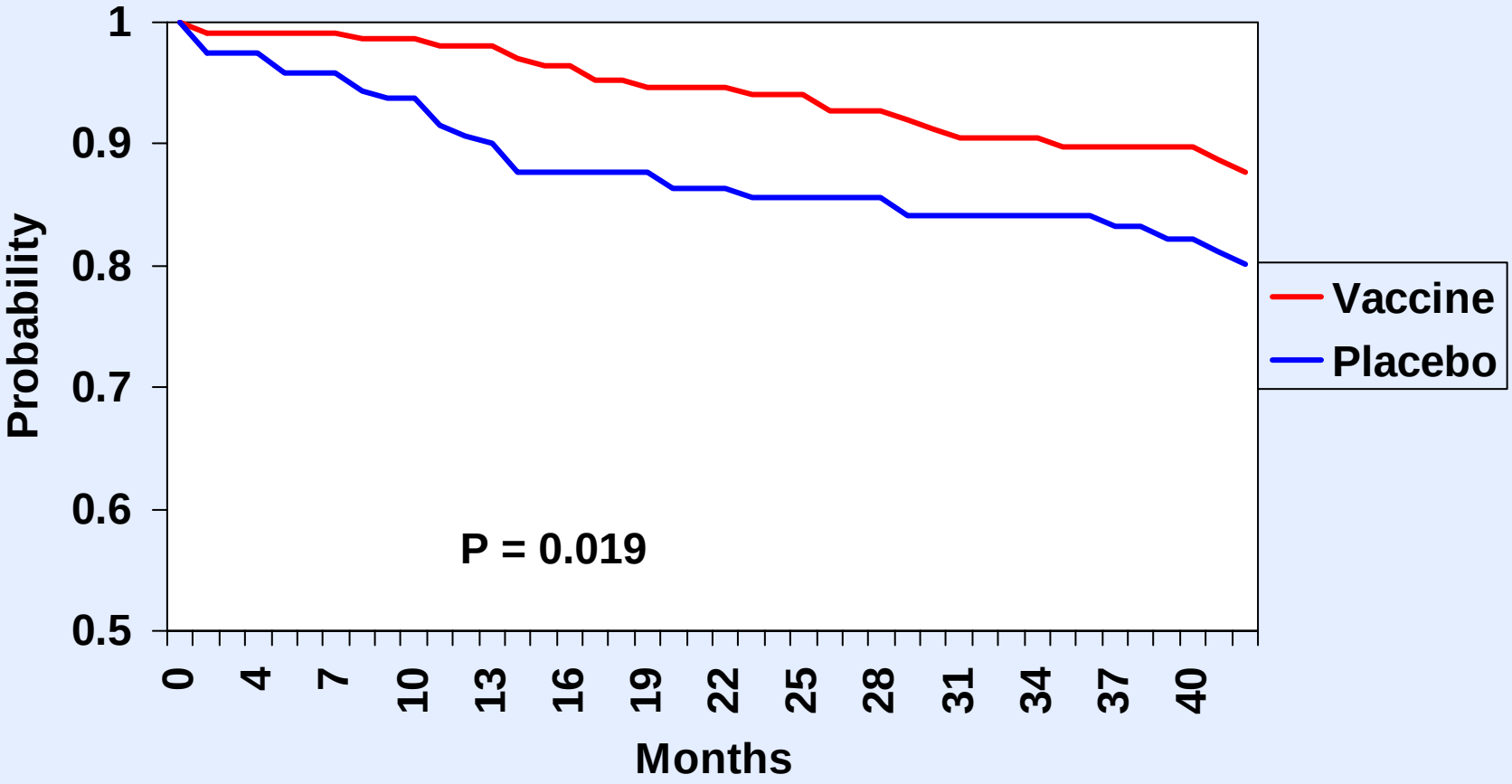
Phase II CMV gB Vaccine, Results: Efficacy at Interim Analysis

Pass et al, N Engl J Med 360:1191, 2009.

- After scheduled interim efficacy analysis
  - Difference in time to CMV infection had crossed a preset boundary
  - CMV gB vaccine was superior to placebo
- DSMB recommended
  - Analyze data when all subjects complete follow-up 6 months post 3rd vaccine
  - Unblind study
- Clinical trial completed January 2010

CMV gB Vaccine Increases the Probability of Remaining CMV Negative up to 42 Months

(ITT Population)



CMV gB vaccine, phase II: preliminary vaccine efficacy data

- Infection rates per 100-person years (over 42 months)
  - Vaccine, 3.3
  - Placebo, 6.6
  - Efficacy = 50%
- Cox proportional hazards, only regimen (CMVgB vs placebo) statistically significant
- Multivariate analysis: regimen, age, race, height
  - Only regimen significant, P = 0.024
  - Hazard ratio 0.51

CMV gB/MF59 reactogenicity

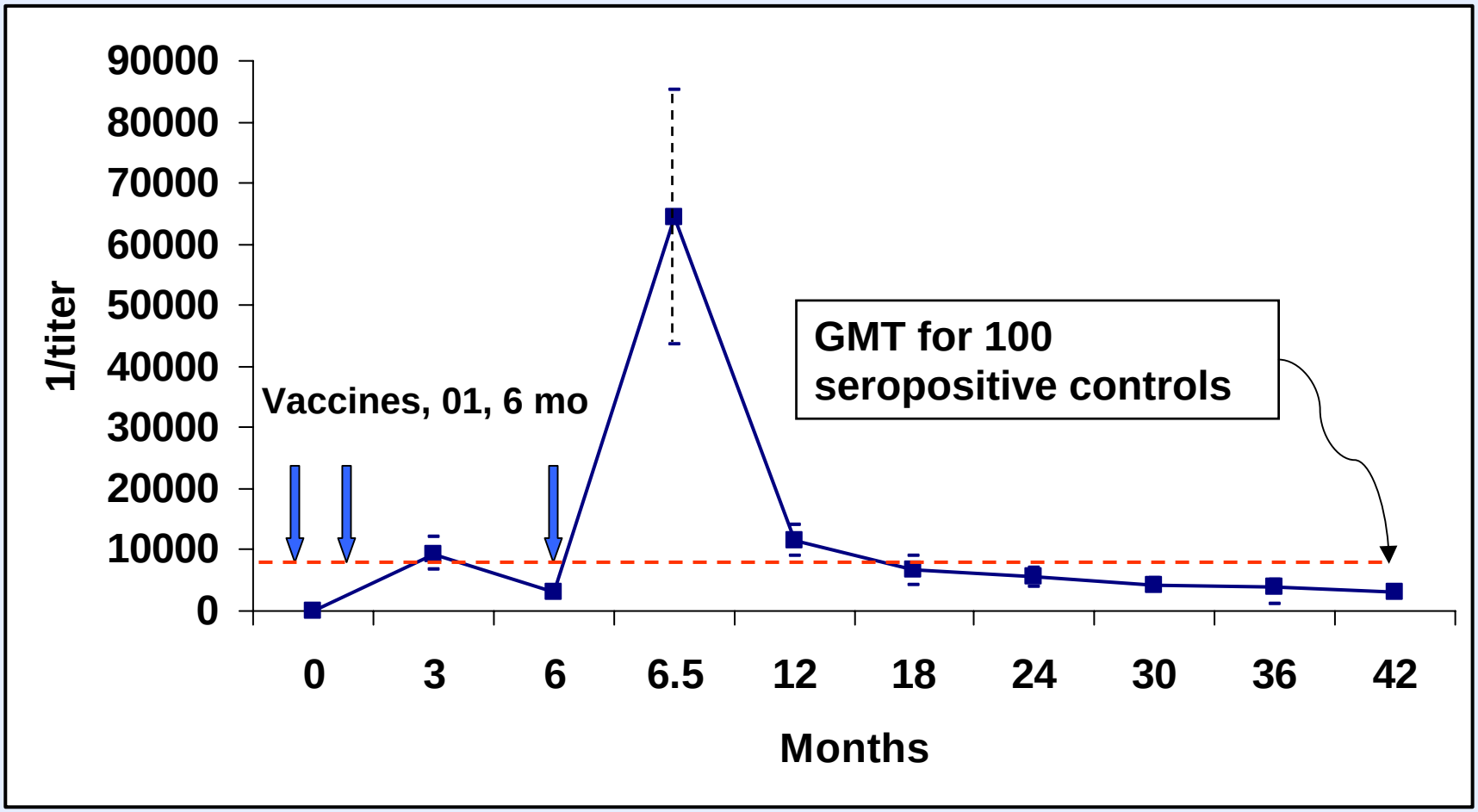
- Local reactions in vaccine recipients across 3 immunizations
  - Pain, 48-59%
  - Warmth, 13-17%
  - Erythema, 7-14%
  - Induration, 5-18%
- Systemic reactions
  - Headache, fever, nausea, fatigue, rash, no difference compared with placebo recipients
  - Arthralgias, chills, myalgias occurred in 6-16%
- Majority of local and systemic reactions were mild and cleared in one day

CMV gB Vaccine phase II: Unsolicited Adverse Events

Event	CMV gB	Placebo	P value
AE, any severity	81%	78%	0.35
AE, ≥ moderate	71%	71%	0.88
AE, possibly related	9.1%	5.3%	0.12
SAE	14%	8%	0.07
SAE, possibly related	0.43%	0.44%	0.99
SAE in baby	7.4%	8.2%	0.85

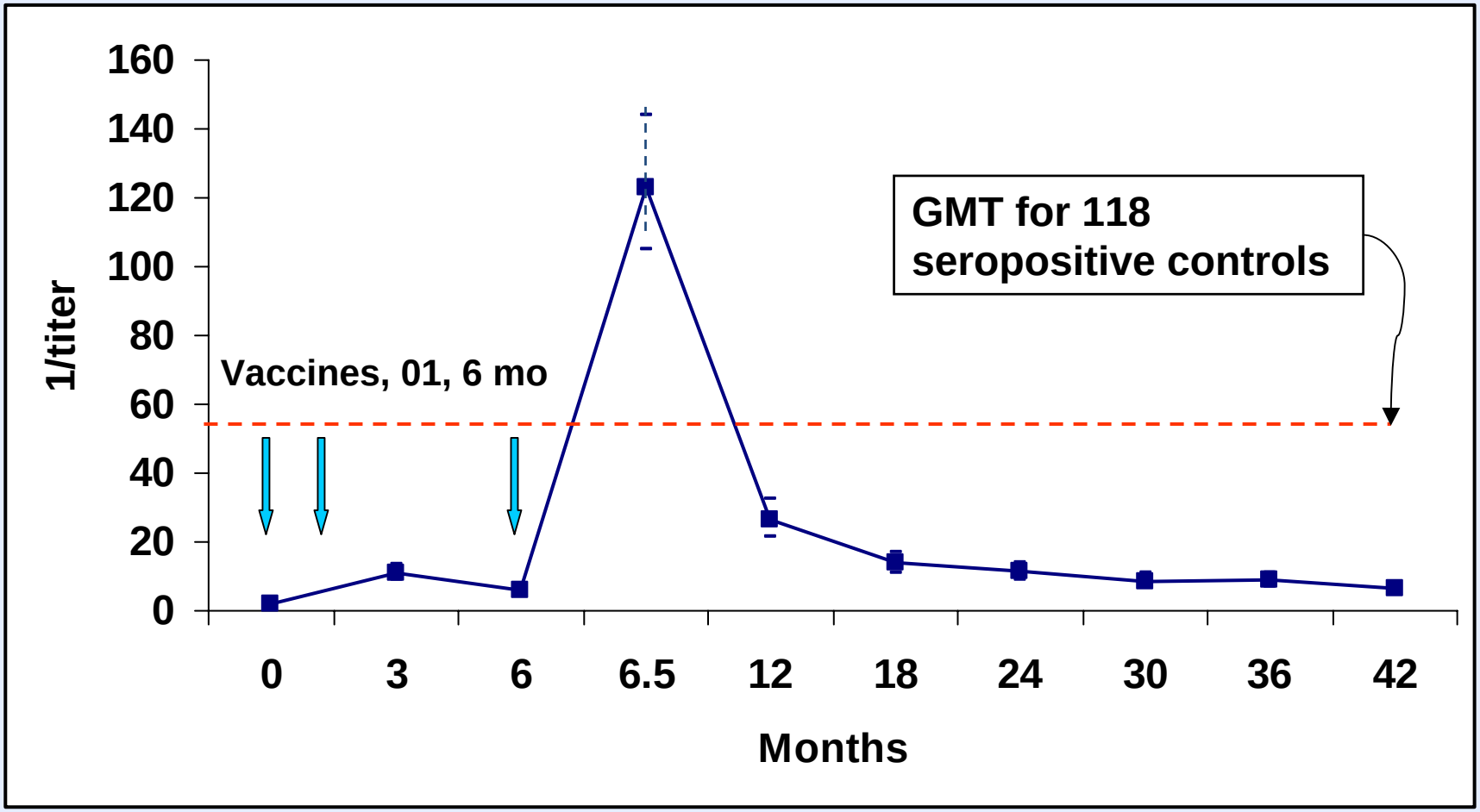
IgG antibody to gB among 117 recipients of 3 injections of CMV gB vaccine: GMT and 95% C.I.

N from 77-117



Neutralizing antibody to gB: 136 recipients of 3 injections of CMV gB vaccine, GMT and 95% C.I

N from 92 to 136



Antibody response in uninfected recipients of 3 injections of CMV gB vaccine

- CMV gB vaccine with MF59 is consistently immunogenic in young, healthy women
- 100% serum IgG antibody to gB
- 99.3% neutralizing antibody to Towne CMV
- Three years post 3 vaccine series:
  - 100% had serum IgG to gB
  - 60% had neutralizing antibody

CMV gB phase II: Virological Data

32 infected placebo and 19 infected vaccine recipients

- All but 2 infected subjects shed virus or had pos PCR of blood, urine, saliva or vaginal swab
- ~ 50% of subjects have CMV DNA in blood by real time PCR at time infection detected
- 3 month interval of testing for infection may miss early viremia
- No clear difference between infected vaccine and placebo recipients in viral shedding

Conclusion: Vaccine prevention of maternal CMV infection is possible

- CMV gB vaccine has ~50% efficacy over a 3.5 year period
- Why did it work?
- Could efficacy be greater for congenital infection than for maternal infection?
- How can we build on this success?