Update and Prospects for CMV Vaccine

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Disclosures: Partial interest in a patent related to CMV gB vaccine, expert witness re occupational exposure to CMV. Consultant to Merck and Astellas in recent past.

Will not discuss off-label use of drugs or biologics.

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Vaccine Prevention of Congenital CMV Infection: Scope

- Medical & economic impact of congenital CMV disease
- Sources of maternal CMV infection
- Rationale for vaccine prevention
- Progress in CMV vaccine development

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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

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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**

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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

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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

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Rationale for CMV vaccine development

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

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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)

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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
- Highly variable viral genome
- Clear evidence that persons with naturally acquired infection can be reinfected

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CMV vaccine clinical trials up to 2013

Highlighted have studied populations relevant to congenital CMV

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	Entering phase 3 trial in stem cell transplant
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

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Towne CMV, live attenuated vaccine created 1970s

- Prevents disease in D+/R- renal transplant patients (Plotkin et al, Ann Int Med 114:525, 1991)
- Stimulates humoral and cellular immunity to CMV
- Good safety record in multiple human trials
- Virus not recovered from vaccinees
- No efficacy in young mothers (Adler et al, J Infect Dis 171:26, 1995)

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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

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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
- Vaccine antigen acquired by Aventis Pasteur (now Sanofi Pasteur), 2000
- NIAID supported phase II efficacy trial at UAB, opened 1999; results published 2009
- NIAID supported efficacy trial in transplant patients at UCL, London; results published 2011
- NIAID supported efficacy trial in adolescent females, U of Cincinnati, in progress

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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

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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

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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)

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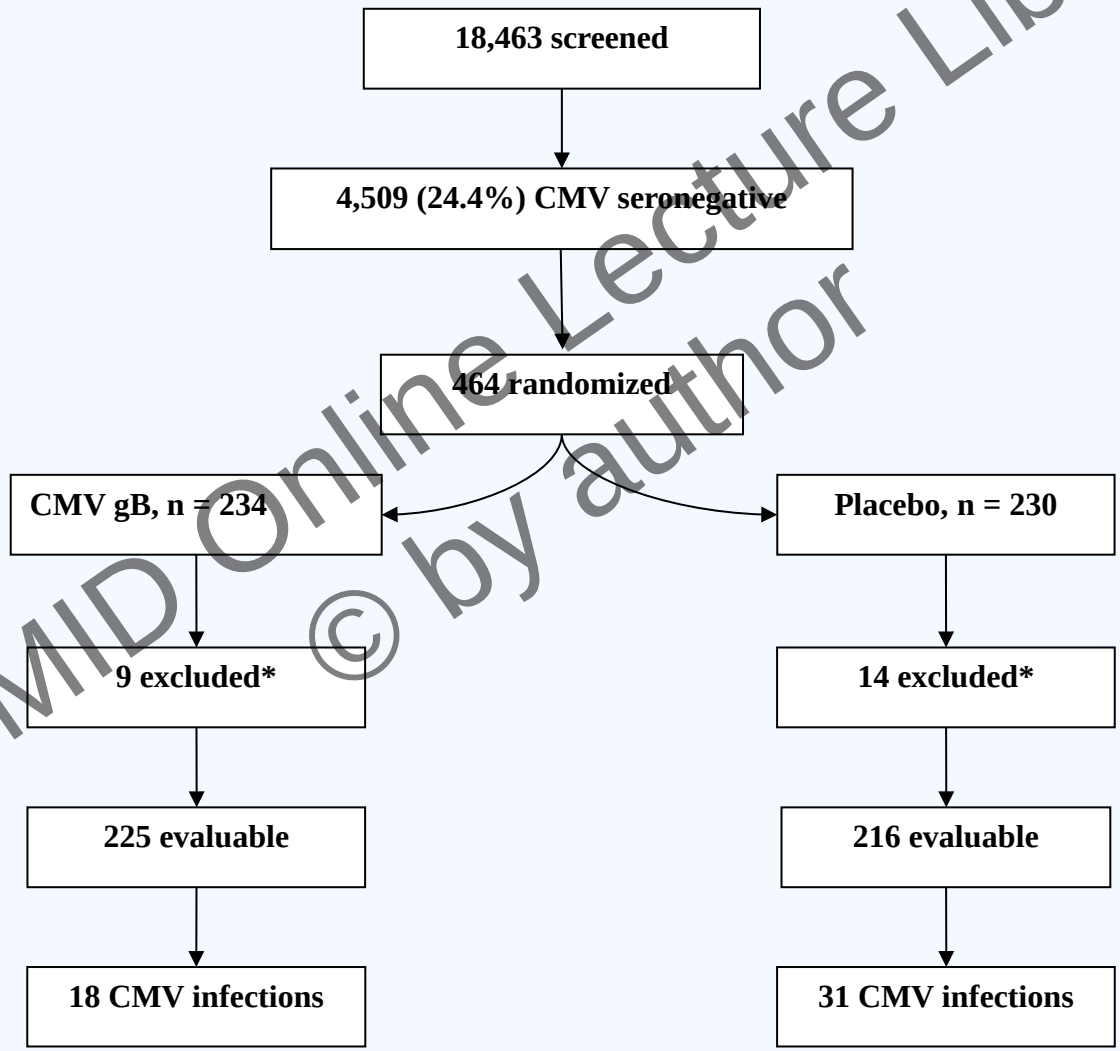
***Zhang & Pass, Detection of cytomegalovirus infection during clinical trials of glycoprotein B vaccine. Vaccine 23:507-10, 2004.**

CMV gB phase II: Study population and endpoint accrual



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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

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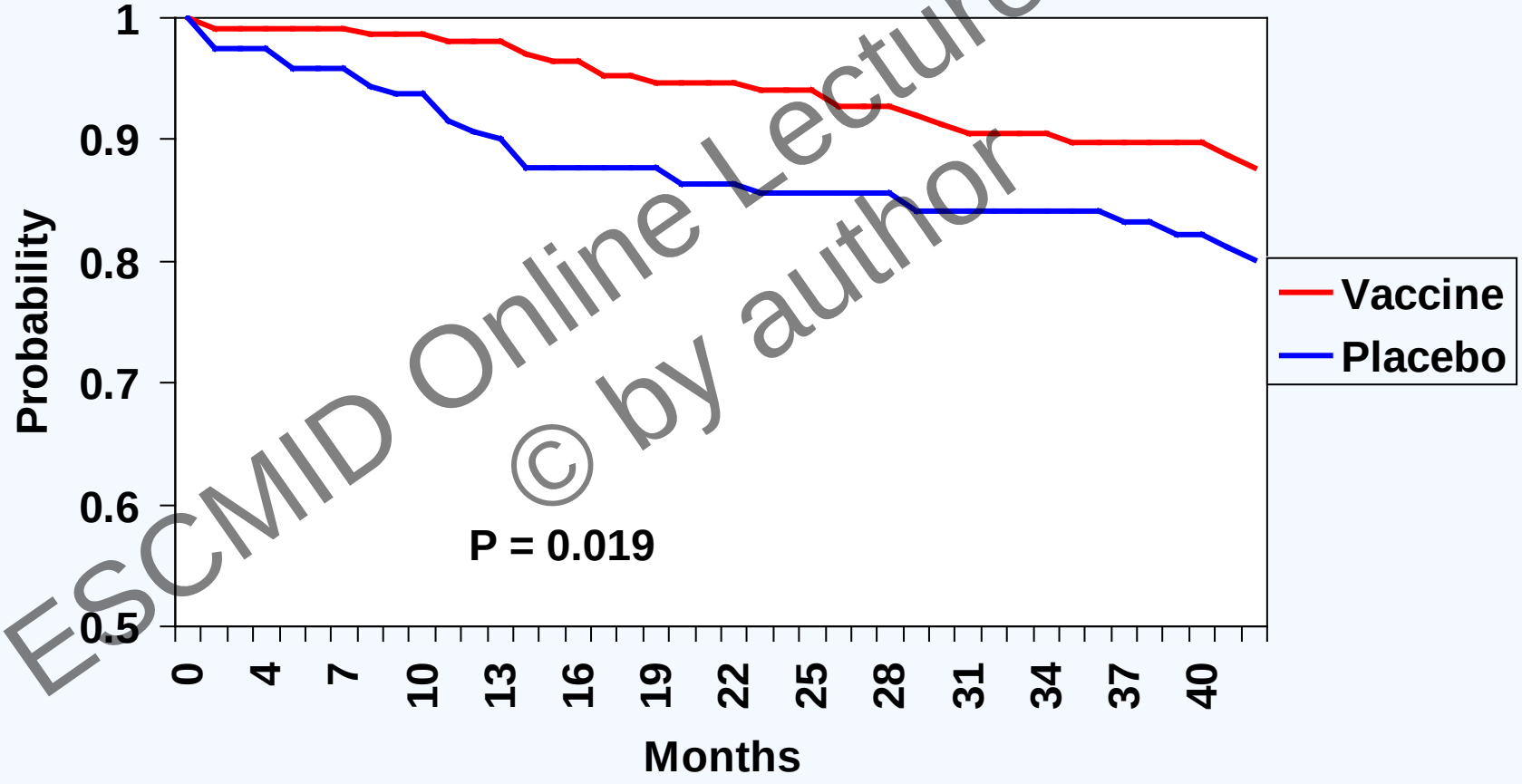
CMV gB Vaccine Increases the Probability of Remaining CMV Negative up to 42 Months

(ITT Population)



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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% (95% CI: 7,73)
- 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

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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

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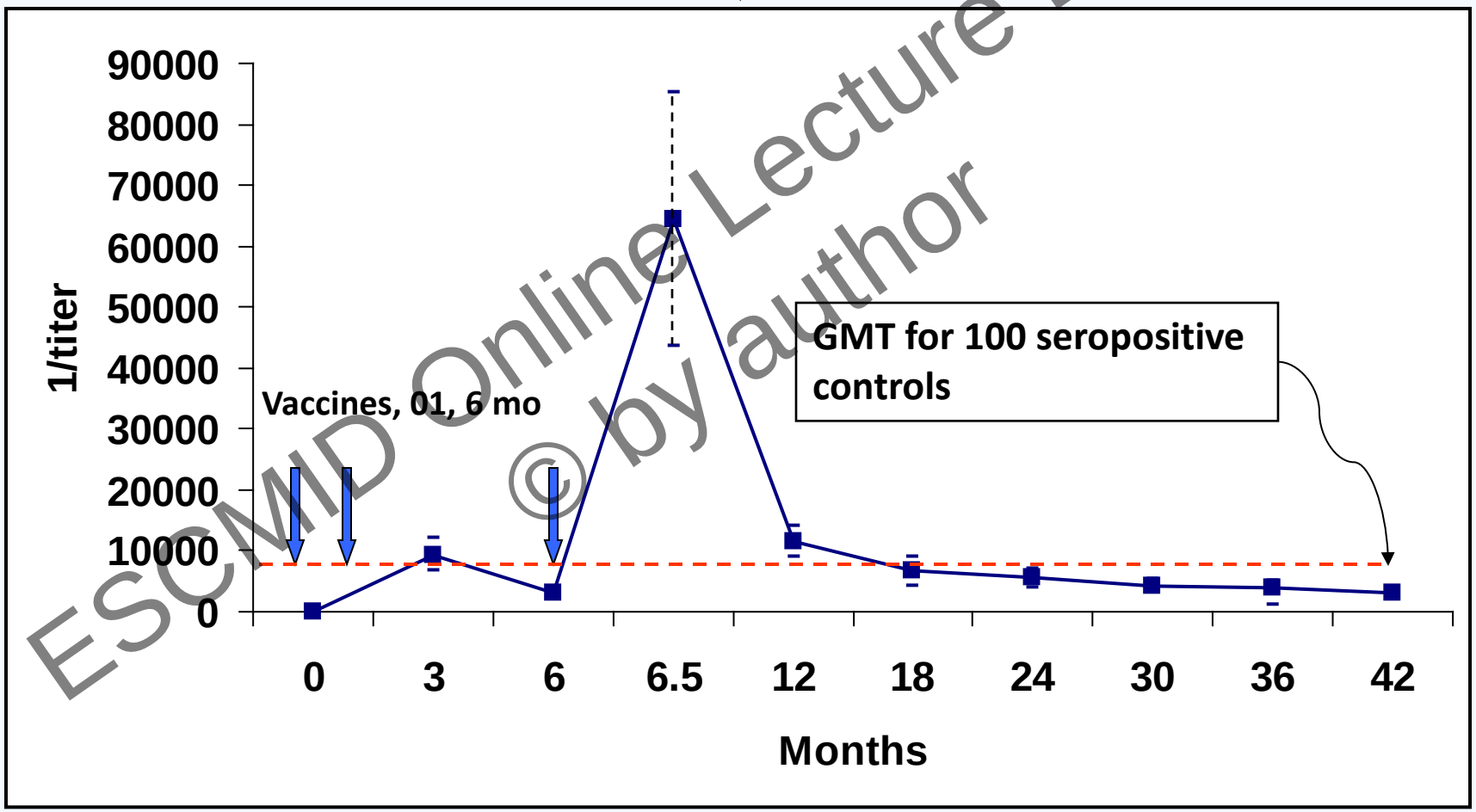
IgG antibody to gB among 117 recipients of 3 injections of CMV gB vaccine: GMT and 95% C.I.

N from 77-117



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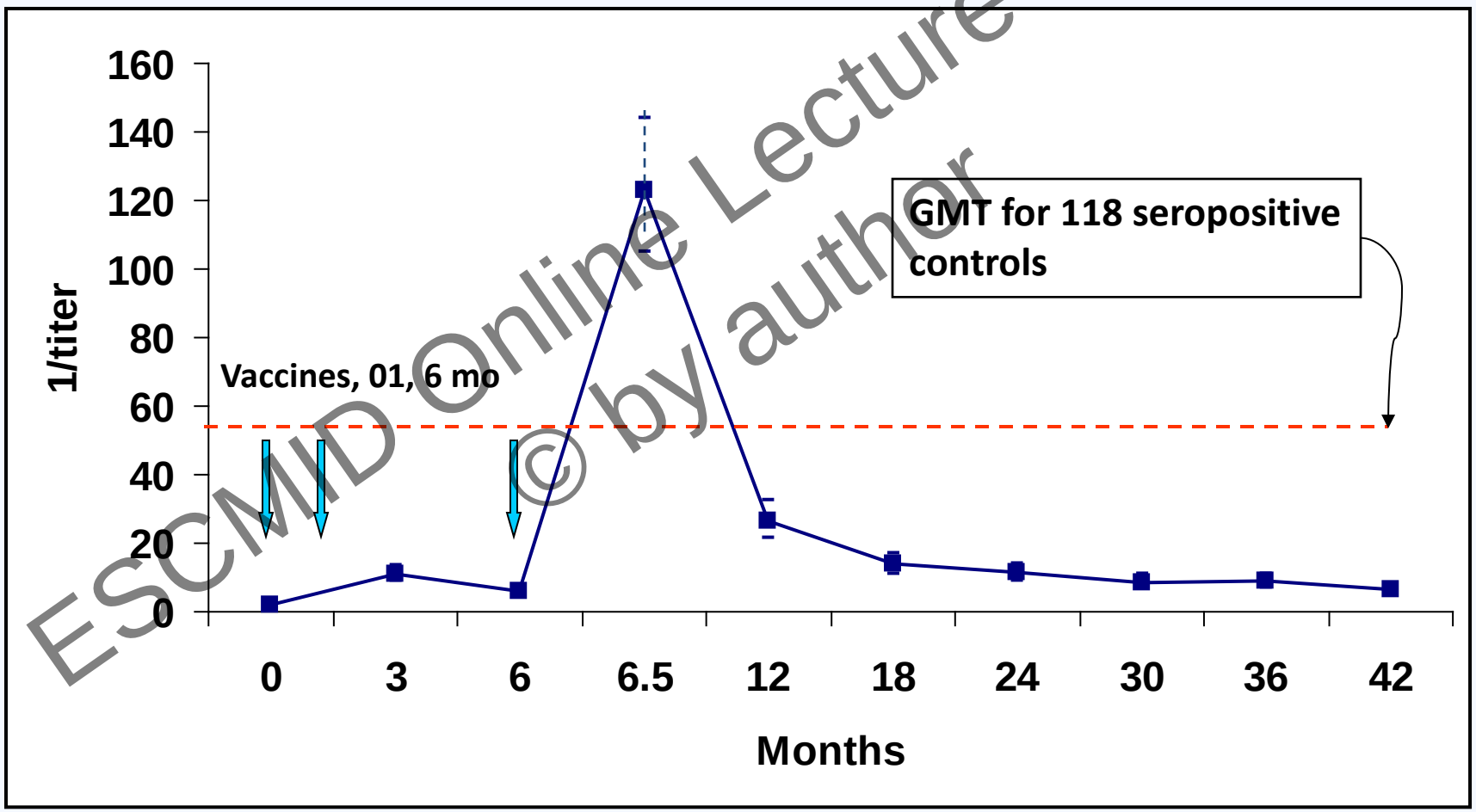
Neutralizing antibody to gB: 136 recipients of 3 injections of CMV gB vaccine, GMT and 95% C.I.

N from 92 to 136



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

- 100% serum IgG antibody to gB
- 99.3% neutralizing antibody to Towne CMV (in fibroblasts)
- Three years post 3 vaccine series:
  - 100% had serum IgG to gB
  - 60% had neutralizing antibody

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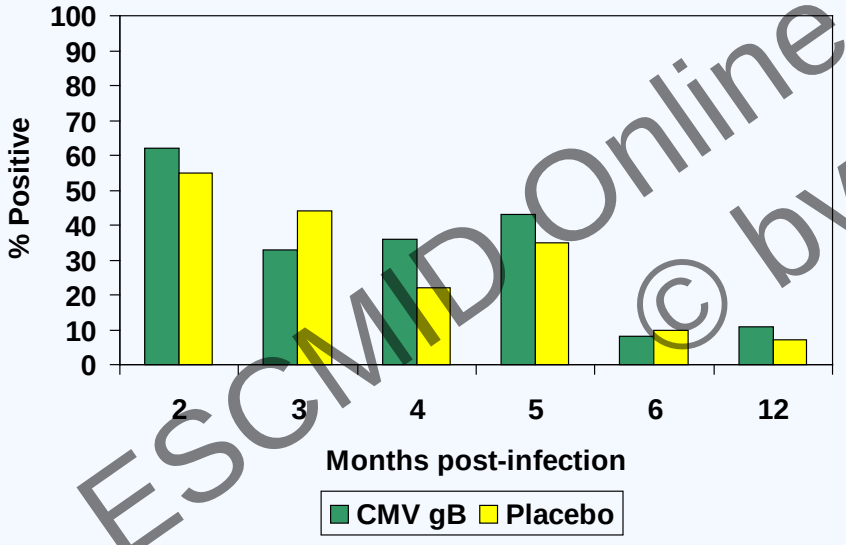
CMV infection in gB vaccine and placebo recipients: No statistically significant differences in rate of viremia or quantity of CMV DNA in whole blood

Qualitative PCR results for whole blood up to 12 months after the estimated time of infection.



- Initial sample for virology collected within 2-4 weeks of detection of infection
- Infection onset estimated at midpoint of 3 month screening interval
- Initial viral load in whole blood, $\log_{10}$ ge/ml
  - 3.4 (2.5-5.1), CMV gB
  - 3.1 (1.8-5.1), placebo

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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

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CMV gB/MF 59 vaccine: assessing the results of phase 2 trial in young women

- Positives
  - 1st demonstration of vaccine prevention of infection in humans
  - Well tolerated, no significant safety signals
  - Immunogenic
  - Good model for testing vaccine to prevent maternal & congenital CMV infection
- Disappointments
  - Limited efficacy, ~50%
  - Efficacy decreased with time post-vaccine
  - Vaccine immunity did not result in better control of infection
  - Rapid decline in neutralizing antibody levels (fibroblasts) and low or nonexistent neutralizing antibody in epithelial cell systems

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Vaccine Prevention of Congenital CMV Infection: What next

- Sanofi Pasteur is working to improve gB vaccine
- Multiple other CMV vaccines are in development and will be evaluated further in humans
- Multiple novel CMV vaccines are in preclinical development

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