CMV vaccine: phase II trial results

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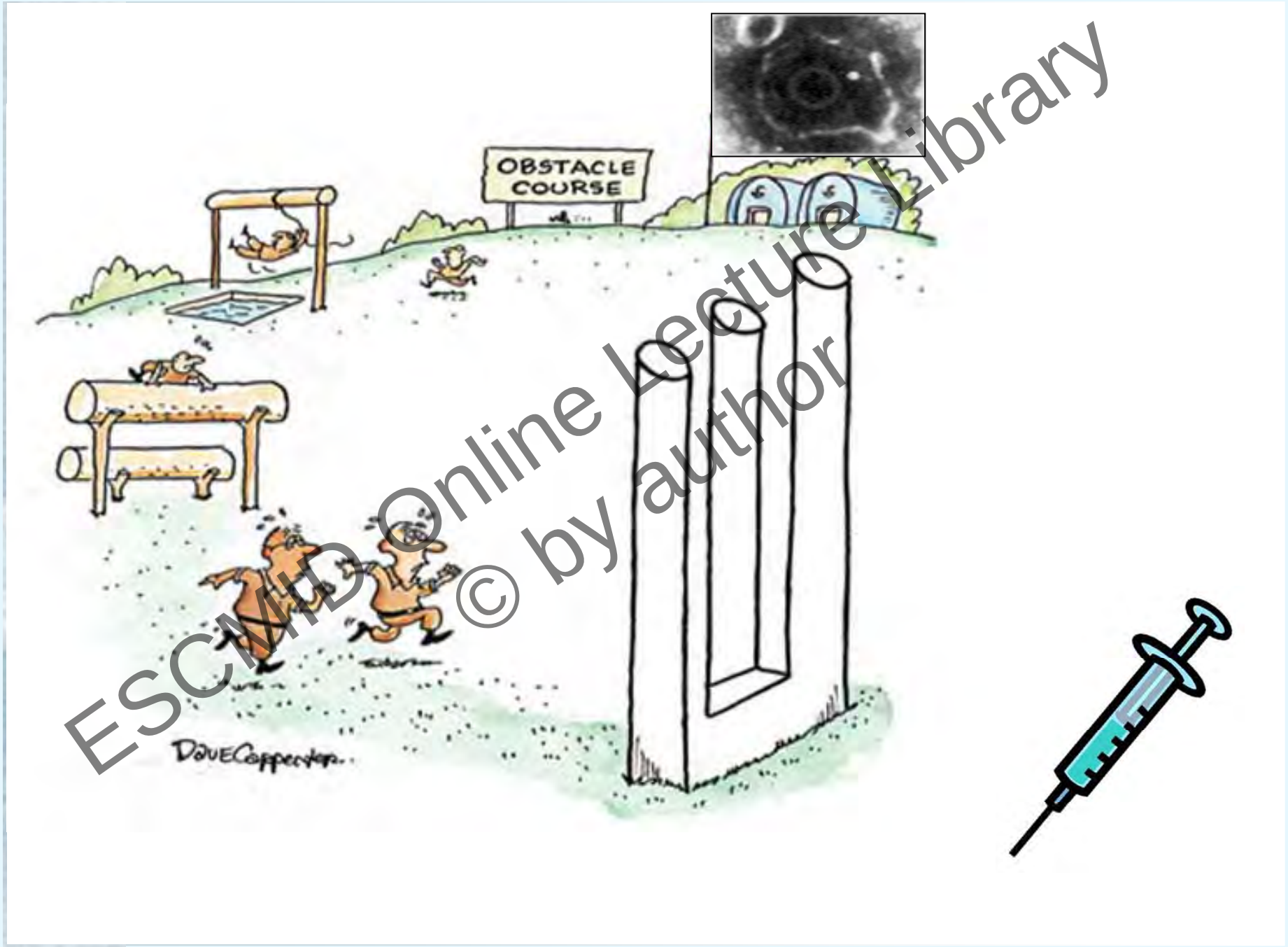


Published clinical vaccine trials in healthy adults
(March 2013)

Phase 1

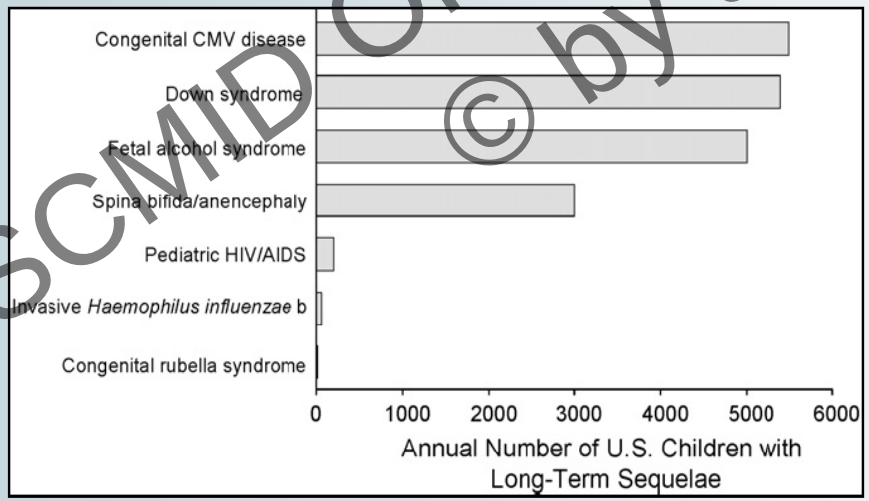
- Towne CMV live virus
- Canary pox vector/CMV pp65
- Canary pox vector/CMV gB
- CMV gB + MF59 adjuvant
- Live Towne/Toledo chimeric recombinant CMV
- Trivalent CMV DNA vaccine (gB, IE1, pp65)
- Bivalent CMV DNA vaccine (pp65, gB)
- Towne CMV live virus + rIL-12
- Pan HLA DR-binding epitope CMV pp65 fusion peptide
- Tetanus CMV pp65 fusion peptide

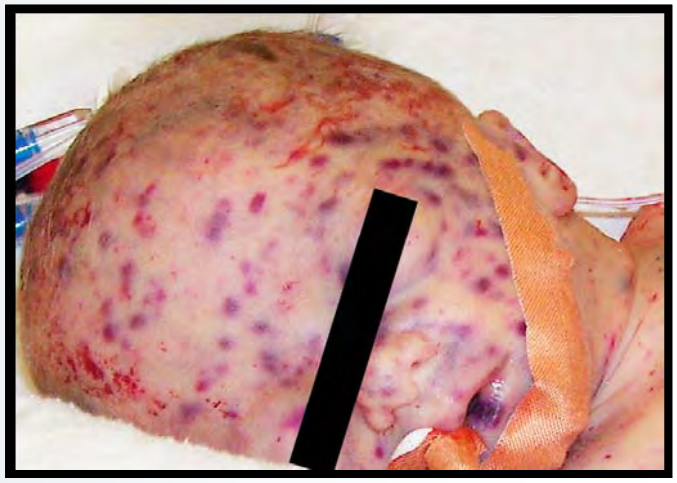
Phase 2

- CMV gB +MF59 adjuvant

Congenital CMV infection

- Most common congenital viral infection (birth prevalence, 0.6%)
- USA - 38 000 babies with congenital cytomegalovirus annually
  - 13% signs of infection at birth (neurologic)
  - 14% develop signs during the first 5 years of life (sensorineural hearing loss)



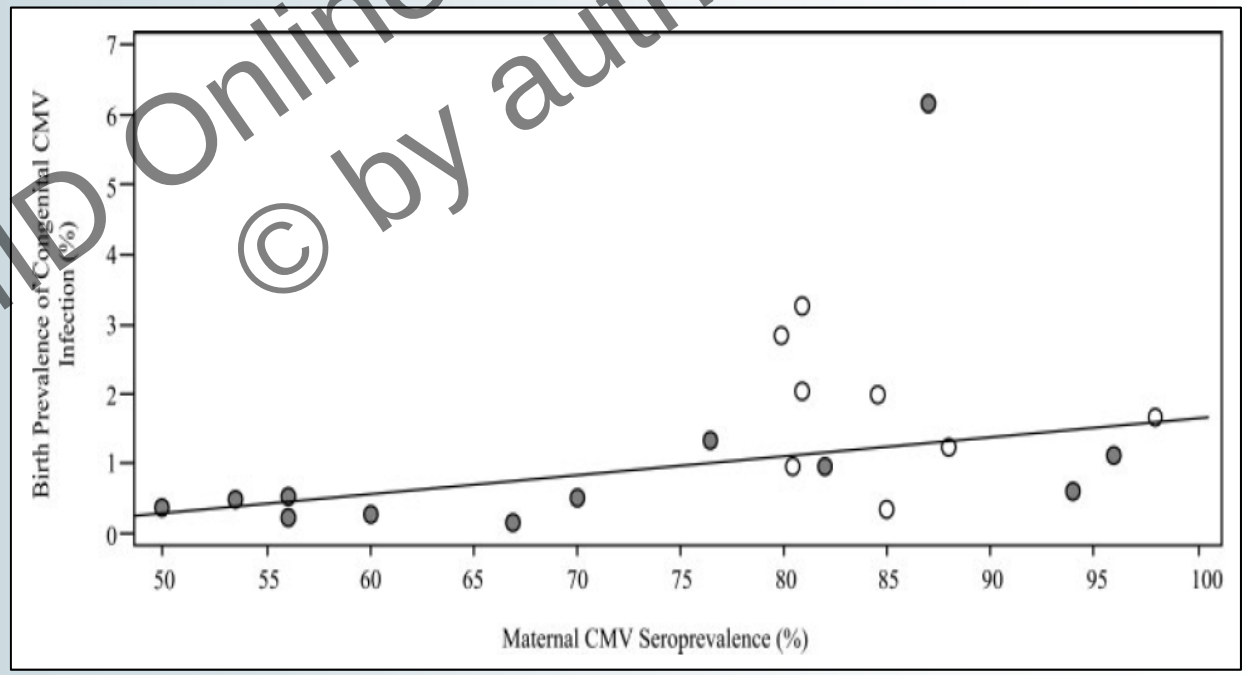


El-Amin Abdel-Latif & Sugo, NEJM 2010

Dahle et al. J Am Acad Audiol. 2000; Morton et al. N Engl J Med. 2006; Ross et al. J Pediatr. 2006; Stehel Pediatrics. 2008; Boppana et al. Pediatr Infect Dis J. 1992; Fowler J Pediatr. 1997; Boppana et al. N Engl J Med 2001; Yamamoto et al. Am J Obstet Gynecol 2010; Cannon & Davis BMC Public Health 2005;

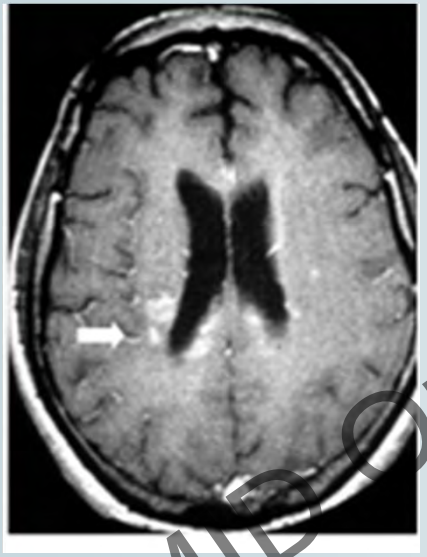
Modes of transmission in congenital CMV disease

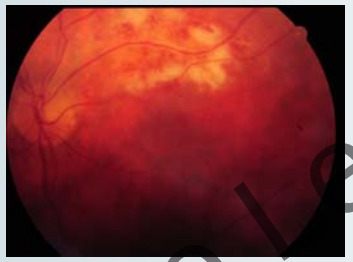
- CMV^- : Primary infection
- CMV^+: Reinfection with new strain/reactivation of latent CMV infection

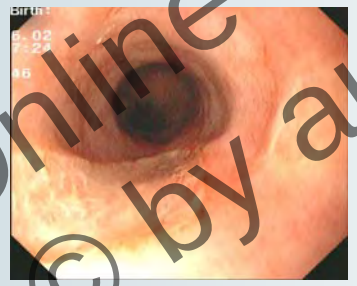


Arvin et al. Clin Infect Dis 2004; Azevedo & Amaku; Epidemiol Infect 2011; Boppana et al. NEJM 2001

CMV end-organ diseases in immunocompromised patients

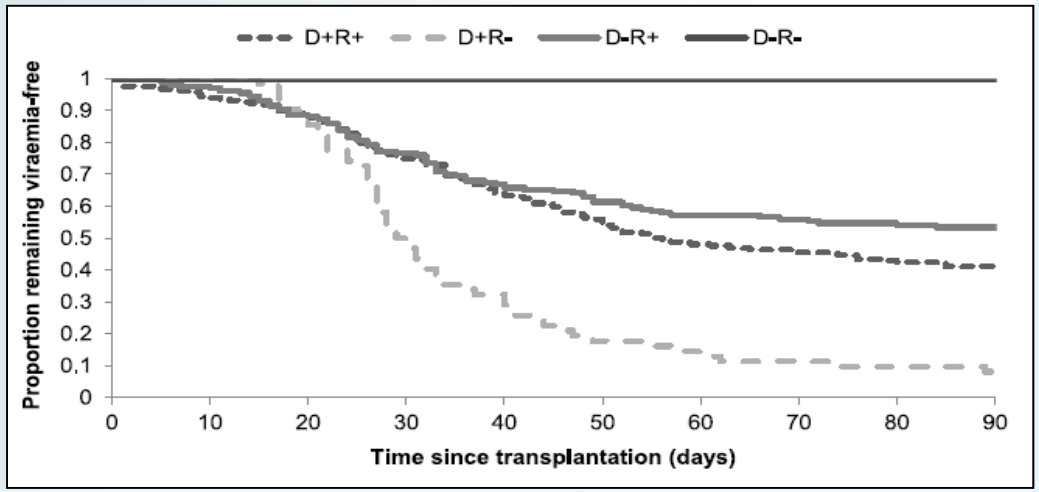






- Solid-organ transplant recipients
- Bone-marrow transplant recipients
- Advanced HIV-infection
- Inflammatory bowel disease (TNF-, Thiopurine, Corticosteroids)
- Critically ill patients

Sources: M Thumher, M Häfner, I Ruhswurm-Dejaco (Medical University of Vienna)



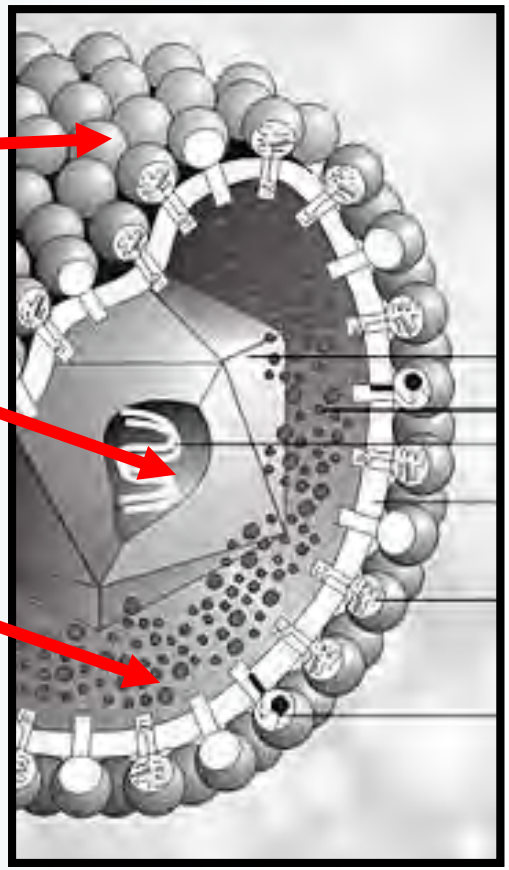
Atabani et al. Am J Transplantation 2012

Potential immunological targets for a CMV vaccine

- >20 immunogenic CMV proteins
  - Envelope (glycoproteins B, H, O, UL128C)
  - Non-structural (pp52 - DNA binding phosphoprotein)
  - Tegument (pp65, pUL32/pp150)

Inhibition of immunomodulation

- IL-10 (Logsdon et al. PlosOne2011)



Source: Dr. Reschke, Institute of Virology, Marburg, Germany

Phase 2 clinical trials of CMV vaccines (March 2013)

Vaccine	Type	Sponsor/ manufacturer	Study cohort	No. of subjects	Ref.
Towne	Live, attenuated	Pasteur-Merieux	Solid-organ transplant patients	61	Plotkin et al. Transplantation 1994
gB-MF59	Subunit (gB)	Sanofi-Pasteur (Chiron/Novartis)	Post-partum women	464	Pass et al. 2009
			Solid-organ transplant patients	140	Griffiths et al. Lancet. 2011
ALVAC-CMV	attenuated canary pox-based-pp65	National Heart, Lung, and Blood Institute (NHLBI)/Sanofi-Pasteur	Stem cell transplant donors	?	Not published
Transvax	Plasmid (gB & pp65)	Astellas (Vical)	Bone-marrow transplant	94	Kharfan-Dabaja et al. Lancet Infect Dis. 2012

Phase 2 clinical trial of gB-MF59 in postpartum women

Parameter	Description
Aim	Prevention of maternal CMV infection between pregnancies
Design	Double-blind, randomized, placebo-controlled
Endpoints	I°: Time to CMV infection II°: Rate of CMV infection, congenital CMV infection in offspring of the immunized women, decline in antibody levels over time
Population	Healthy, CMV-seronegative women (ages 14-40 years), postpartum
Groups	Group I: 20 µg gB + 13.25 mg MF59 (n=234) Group II: placebo (n=230)
Schedule	0, 1, 6 months
Follow-up	42 months
Enrollment	August 1999 – April 2006

Pass et al. N Engl J Med. 2009; Frey et al. J Infect Dis 1999; Pass et al. J Infect Dis 1999

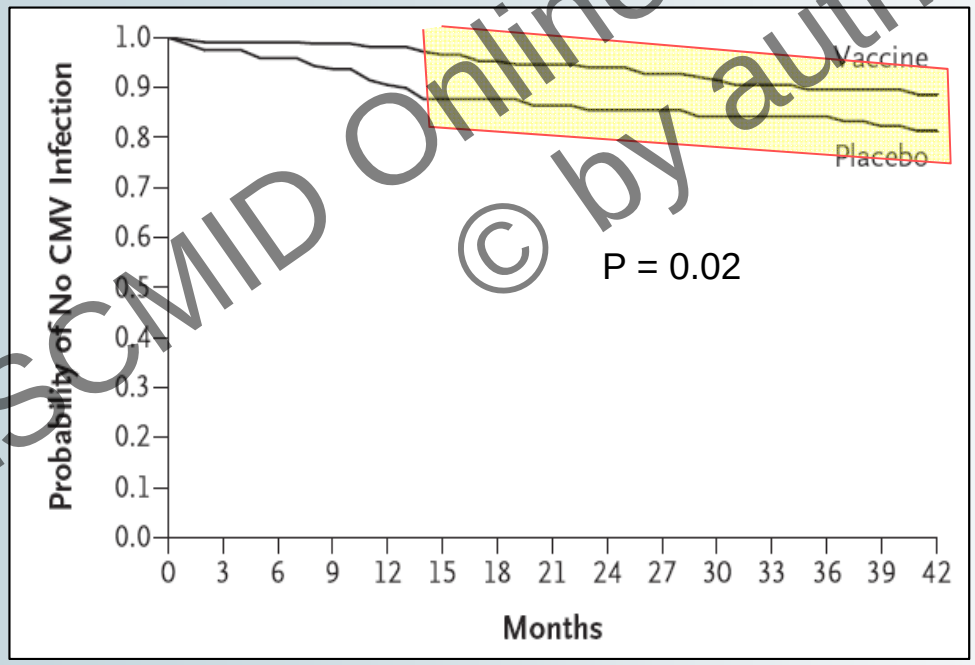
CS1 because most succeptible during this time! infection from child

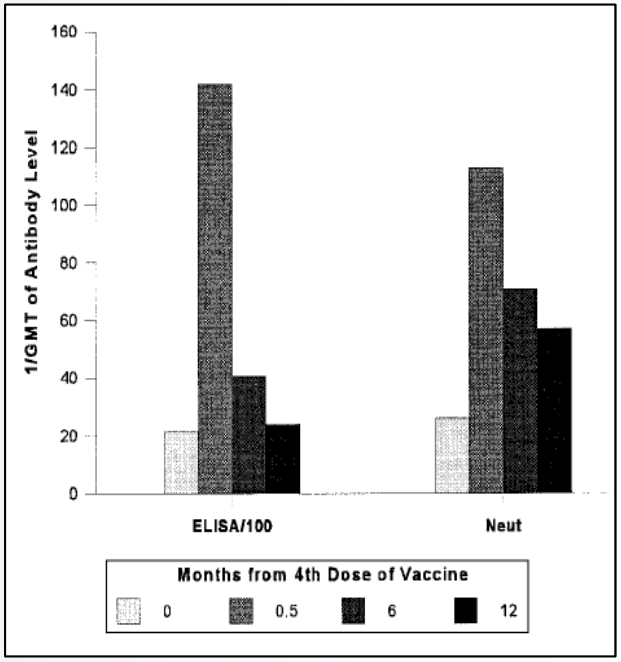
Dr. Christoph Steininger; 08.03.2013

Efficacy of gB-MF59 in postpartum women

- Vaccine efficacy – 50% (95% CI, 7 to 73)
- Rate of congenital CMV infection:

  Vaccine: 1/81 (1%) – Placebo: 3/97 (3%, P = 0.41)



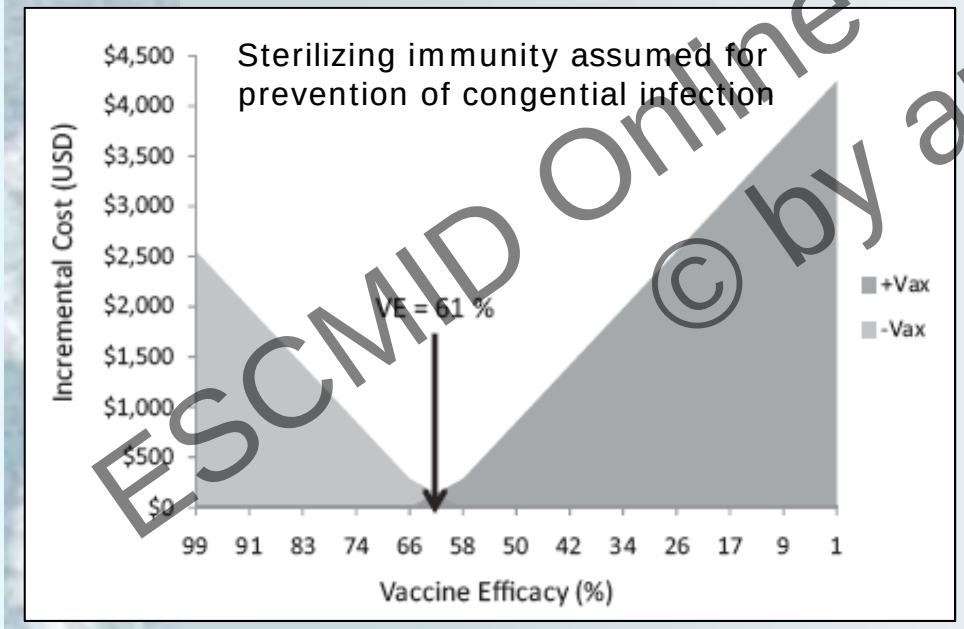


Pass et al. N Engl J Med. 2009; Pass et al. J Infect Dis 1999

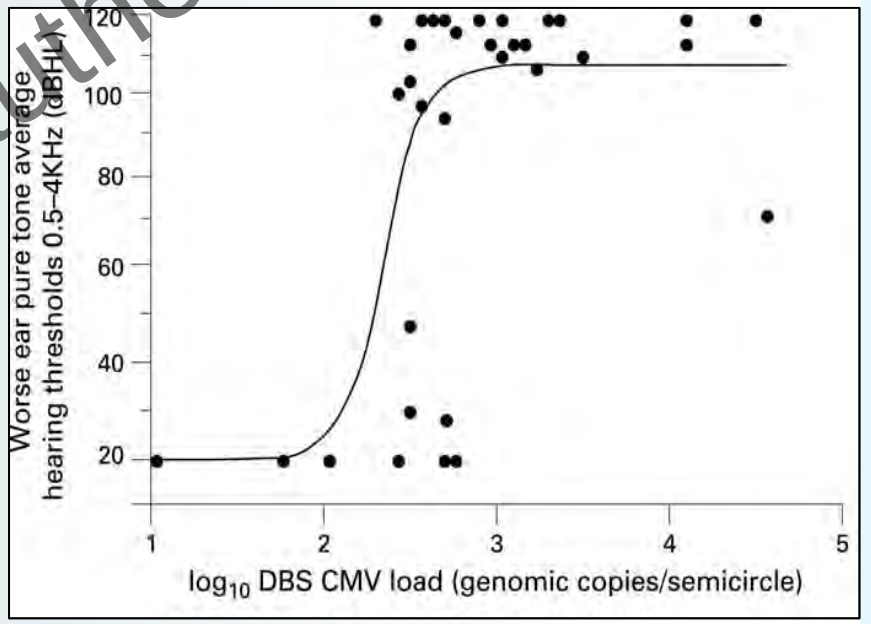
Desired vs. minimum effectiveness of a CMV vaccine

- Vast majority of vaccines introduced in the EU market have efficacies of at >80%

Threshold analysis of vaccine efficacy



Viral load vs. hearing threshold



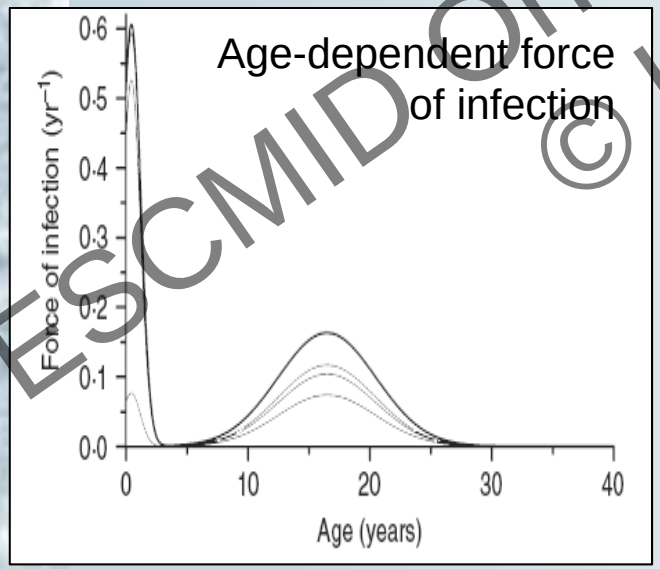
Dempsey et al. Vaccine 2012; Broder et al. MMWR 2006; Bilukha et al. MMWR 2005; Lu et al. BMC Infectious Diseases 2011; Shepard et al. Pediatrics 2005

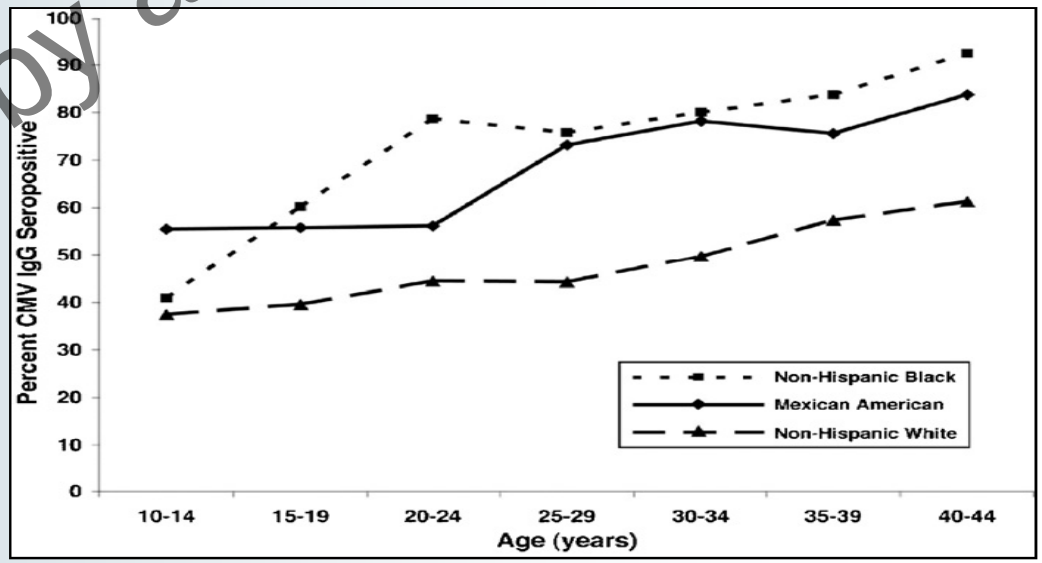
Changing pattern of CMV infection in industrialized nations

- Primary routes of transmission: perinatal and breast-feeding
- Formula feeding reduced infection rates in infants

→ 30%–50% of women of childbearing age in the United States and Europe are susceptible to CMV infection

→ <10% of women of childbearing age in developing countries are susceptible





Cannon; J Clin Virol 2009; Walter S et al. Arch Dis Child Fetal Neonatal Ed 2008; Dempsey et al. Vaccine 2012; Azevedo & Amaku; Epidemiol Infect 2011

Phase 2 clinical trial of gB-MF59 in solid-organ transplant patients

Parameter	Description
Aim	Moderation of end-organ disease by vaccine-induced immunity
Design	Double-blind, randomized, placebo-controlled
Endpoints	I°: Immunogenicity II°: Reduction in incidence/quantity of CMV-DNA detection in blood, immune protection, persistence of vaccine-induced neutralizing antibody, CD8 and CD4 responses
Population	Adults awaiting liver or kidney transplantation
Groups	Group I: 20 µg gB + 13.25 mg MF59 (n=67) Group II: placebo (n=73)
Follow-up period	Median, 95 days post transplantation
Enrollment	August 2006 –October 2008

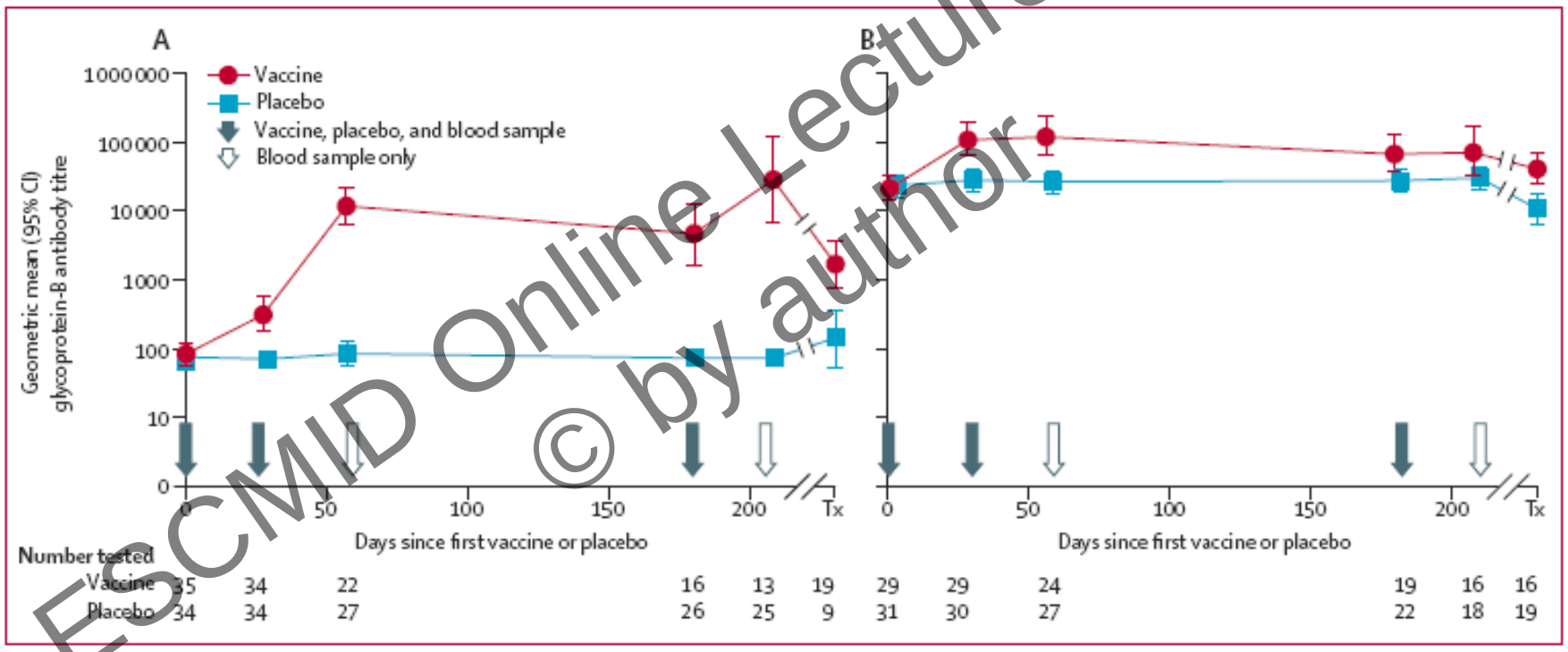
Griffiths et al. Lancet 2011

Study population of gB-MF59 trial in solid-organ transplant patients

	Vaccine group		Placebo group	
	CMV positive	CMV negative	CMV positive	CMV negative
No. of patients	32	35	38	35
No. of patients with TX	18	23	22	15
Number of doses of vaccine or placebo received before transplantation				
1	0 (0%)	1 (4%)	1 (5%)	0 (0%)
2	9 (50%)	16 (70%)	8 (36%)	6 (40%)
3	9 (50%)	6 (26%)	13 (59%)	9 (60%)
Cytomegalovirus status of donor				
Positive	7 (39%)	11 (48%)	15 (68%)	5 (33%)
Negative	11 (61%)	12 (52%)	7 (32%)	10 (67%)

Griffiths et al. Lancet 2011

Immunogenicity of gB-MF59 in solid-organ transplant patients

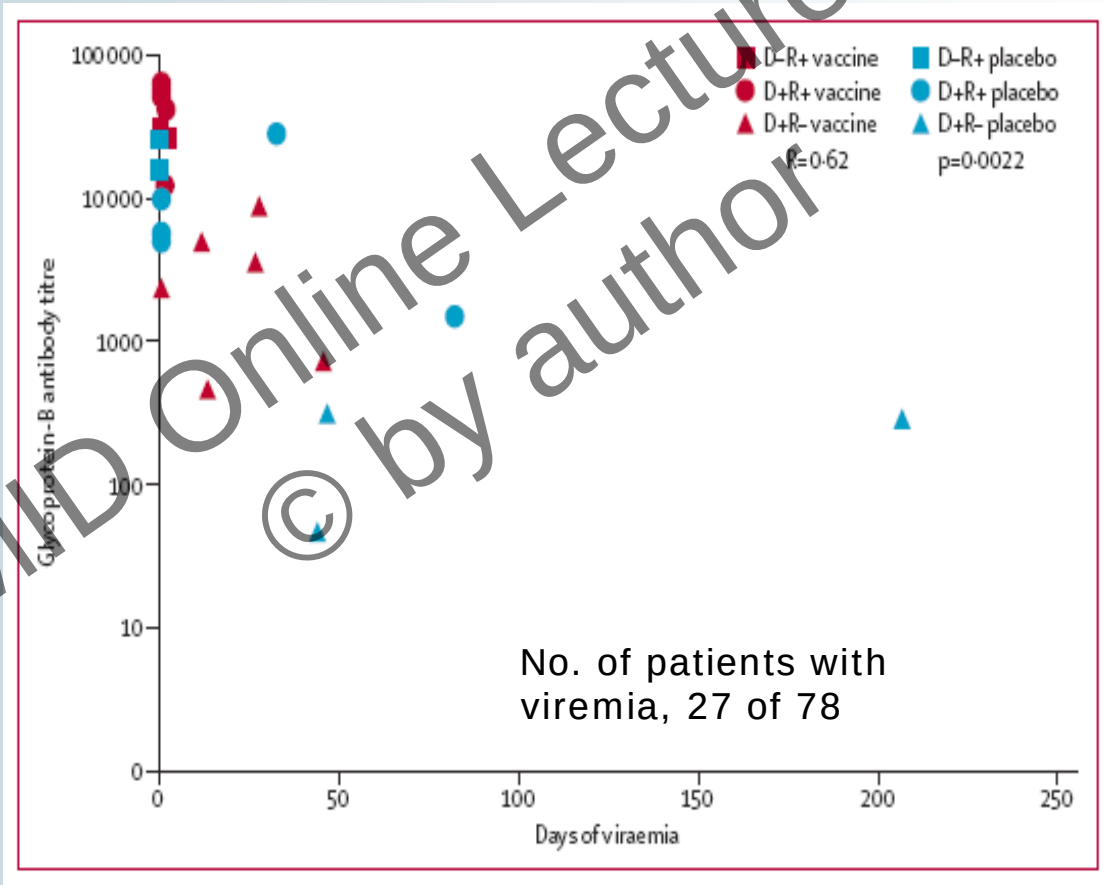


CMV-seronegative

CMV-seropositive

Griffiths et al. Lancet 2011

Efficacy of gB-MF59 in solid-organ transplant patients



Griffiths et al. Lancet 2011

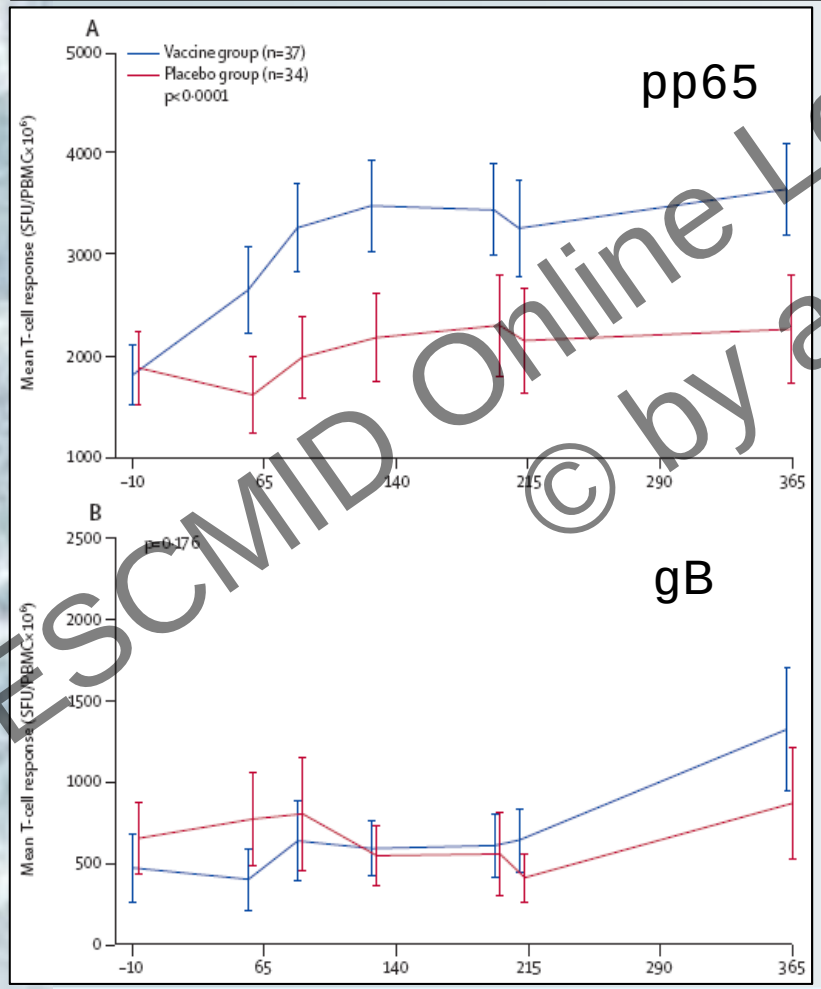
Phase 2 clinical trial of Transvax in bone-marrow transplant recipients

Parameter	Description
Aim	Safety and efficacy of a CMV therapeutic DNA vaccine
Design	Double-blind, randomized, placebo-controlled
Endpoints	I°: rates of cytomegalovirus viraemia resulting in initiation of CMV-specific antiviral therapy II°: ELISPOT responses to pp65 & gB, gB titers,
Population	CMV-seropositive bone-marrow transplant recipients
Groups	Group I: Transvax 5 mg/ml + CRL1005 i.m. (n=40) Group II: placebo (n=34)
Schedule	Day -5, 21-41, 84, 196 post transplantation
Follow-up period	365 days post transplantation
Enrollment	June 2006 – December 2011

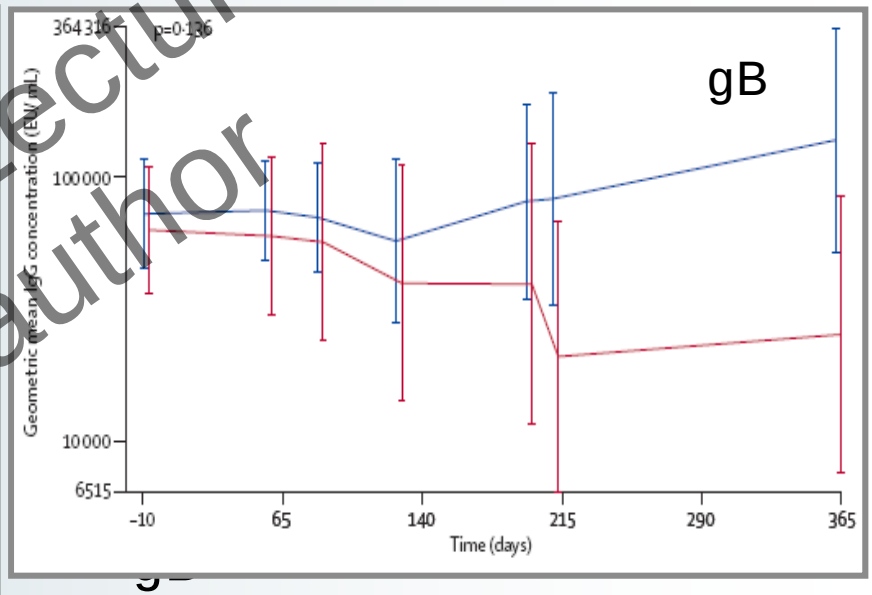
Kharfan-Dabaja et al. Lancet Infect Dis 2012

Immune response to Transvax

T-cell response



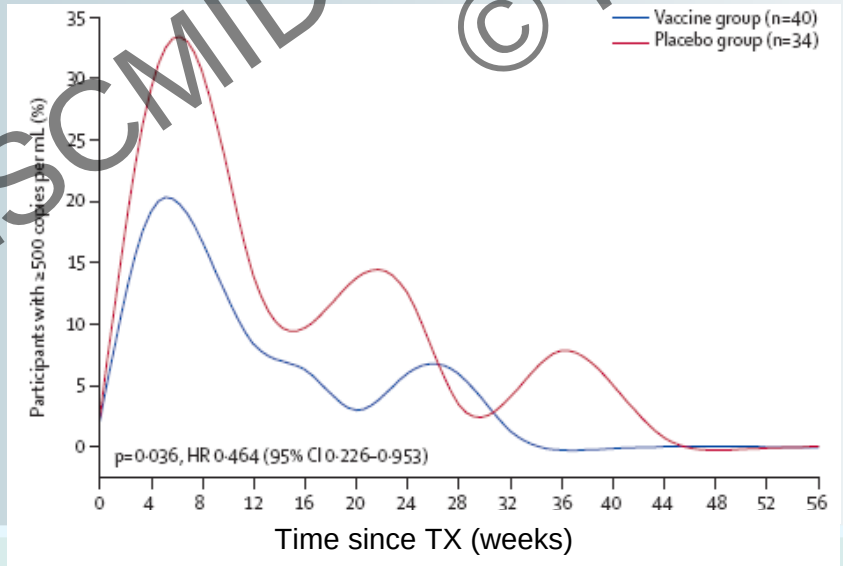
Ab response

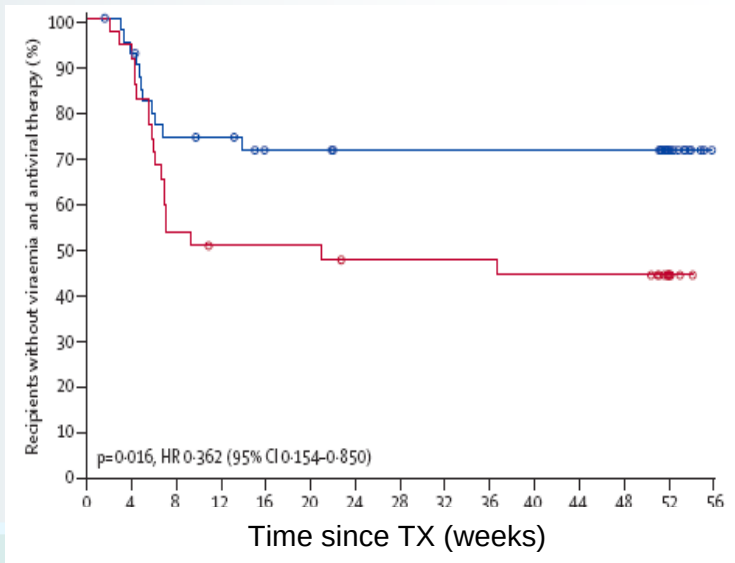


Kharfan-Dabaja et al.
Lancet Infect Dis 2012

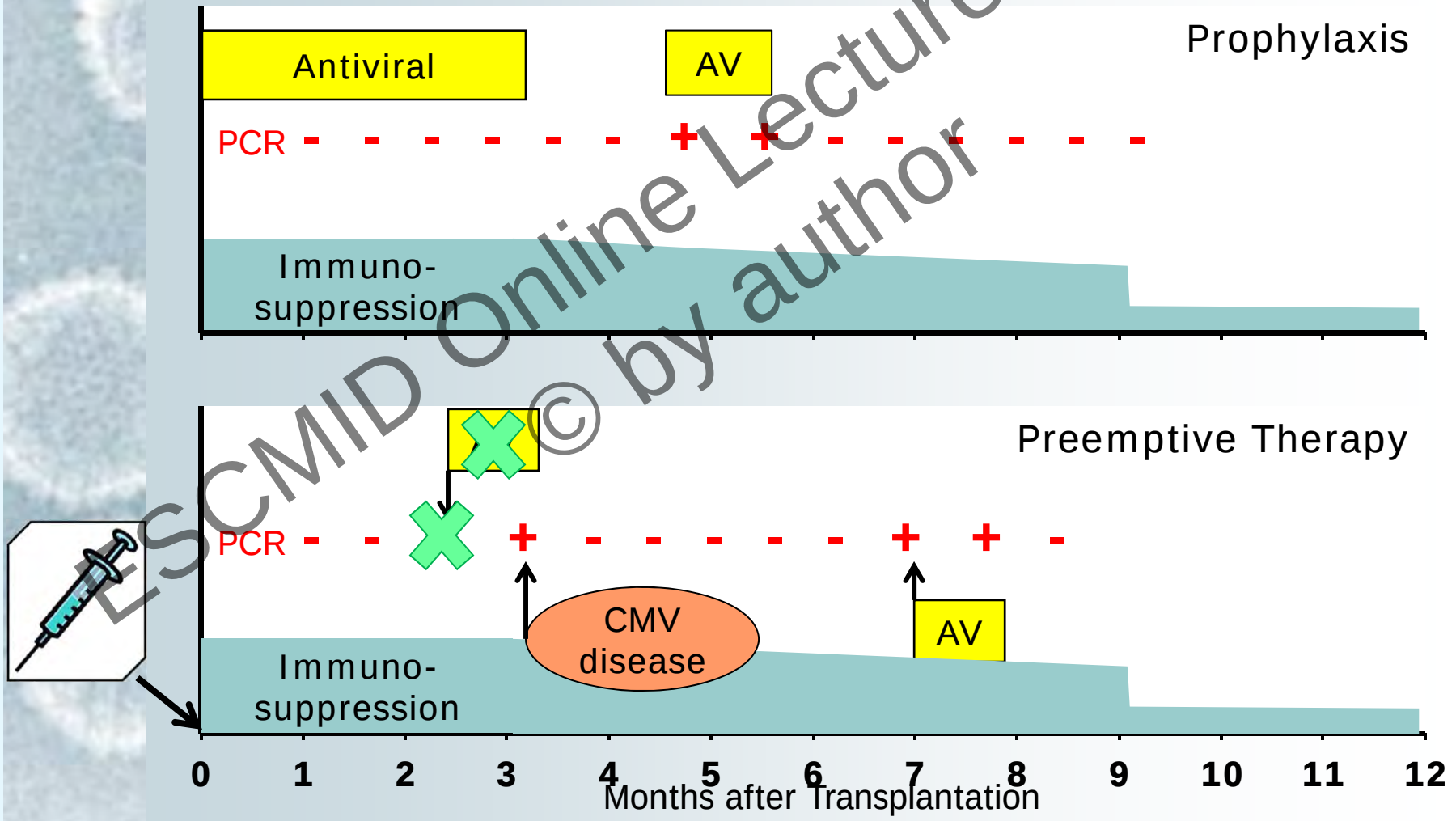
Protection from CMV infection and disease by the use of Transvax

	Vaccine (n=40)	Placebo (n=34)	p value
Median no. of CMV episodes	0	1	0·017
CMV viraemia (≥500 copies per mL)	33%	62%	0·008
Viraemia-free rate at 1 year, %	65%	36%	0·014
CMV-associated disease	8%	9%	1·000
Gastrointestinal	8%	6%	
CMV pneumonia	3%	3%	

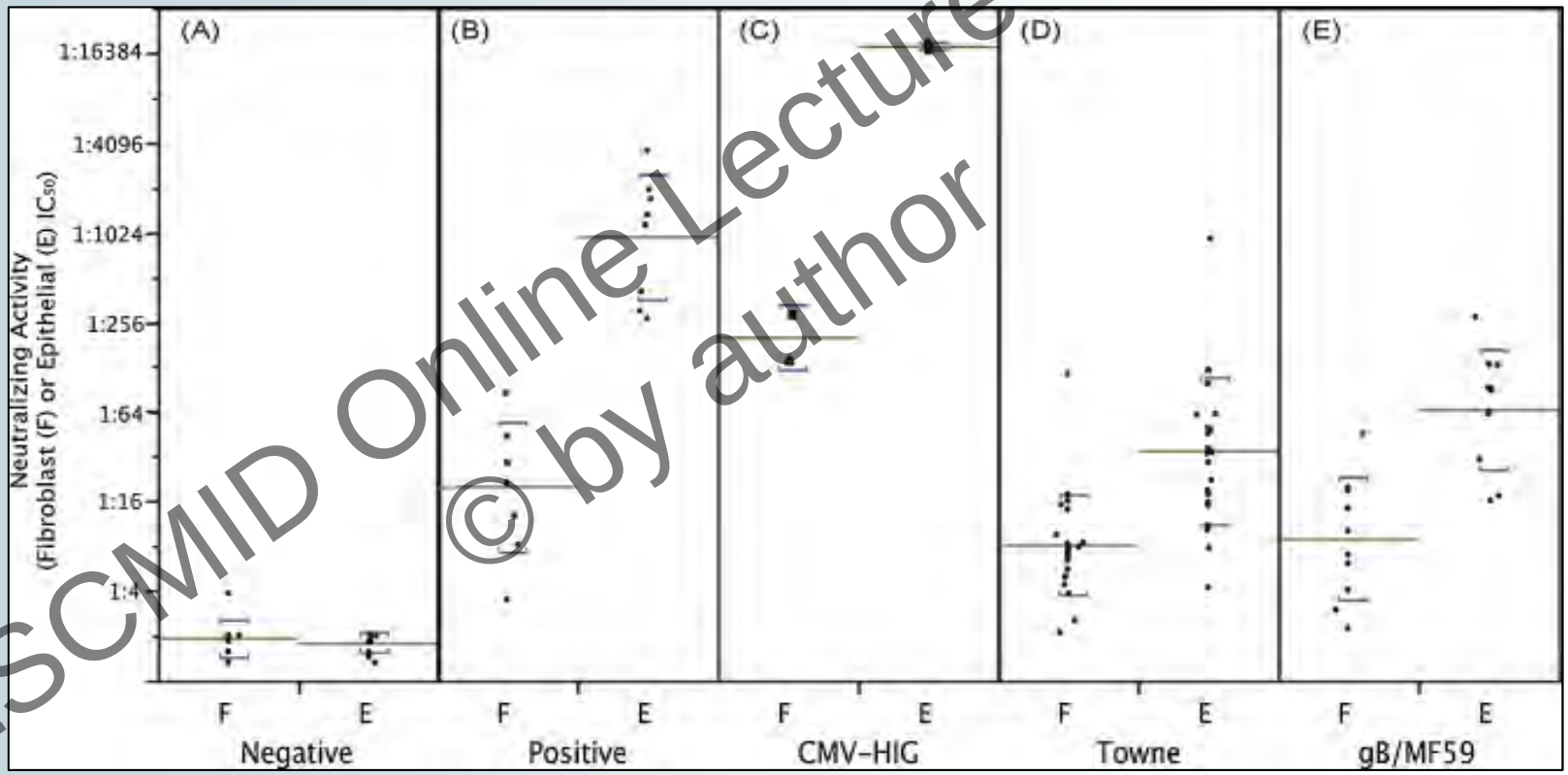




Prophylactic strategies in solid-organ transplant patients

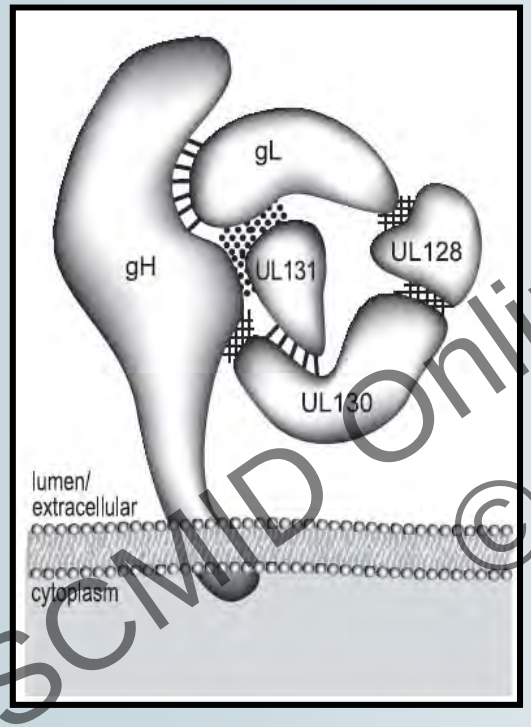


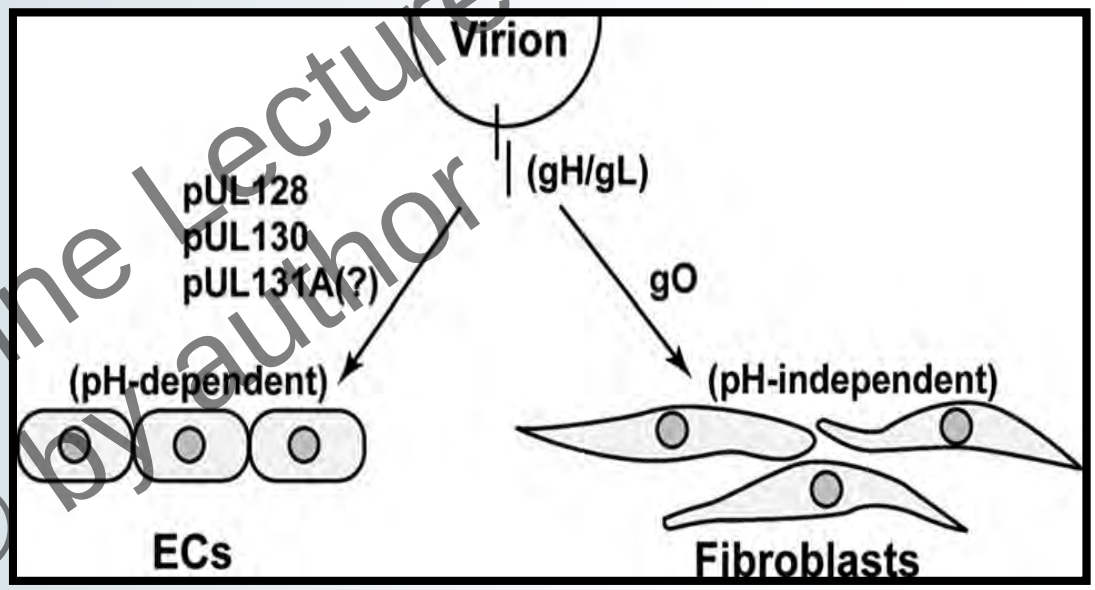
Next generation CMV vaccine candidates



Cui et al. Vaccine 2008

Pentameric virion complex (UL128C)
Glycoproteins gH/gL, UL128, UL130 & UL131A





Jarvis & Nelson , J. Virol. 2007; Wang & Shenk, PNAS 2005; Ryckman et al. J. Virol. 2008

Thanks for your attention!