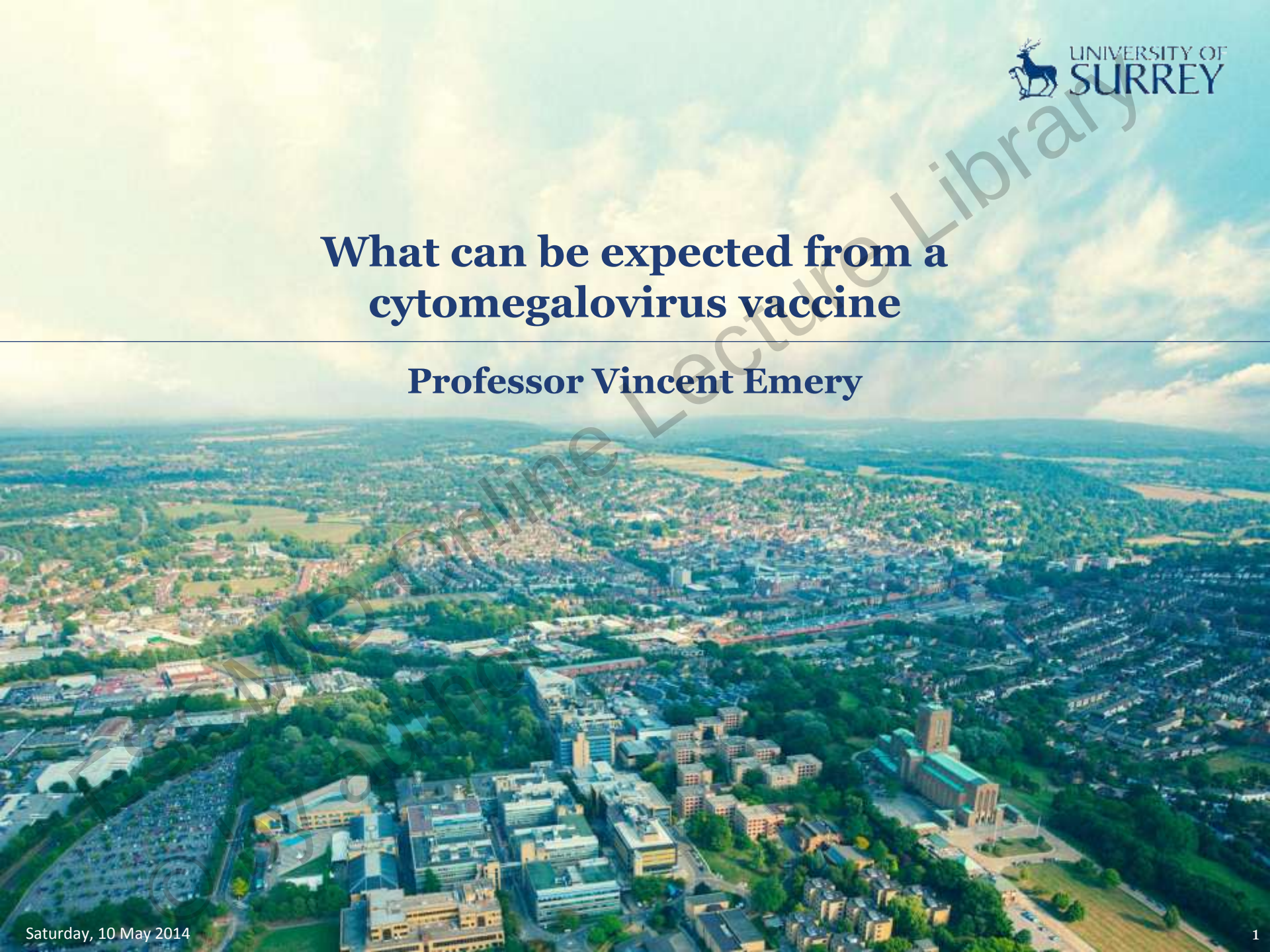
What can be expected from a cytomegalovirus vaccine

Professor Vincent Emery



Overview

- Summarise existing CMV vaccines under development
- Review trials of CMV vaccines in transplantation
    - gB vaccine – solid organ
    - DNA vaccine – stem cell transplant
- Can we do better ?
    - Efficacy and impact
    - Combinatorial approaches
    - New opportunities

General considerations – CMV vaccination

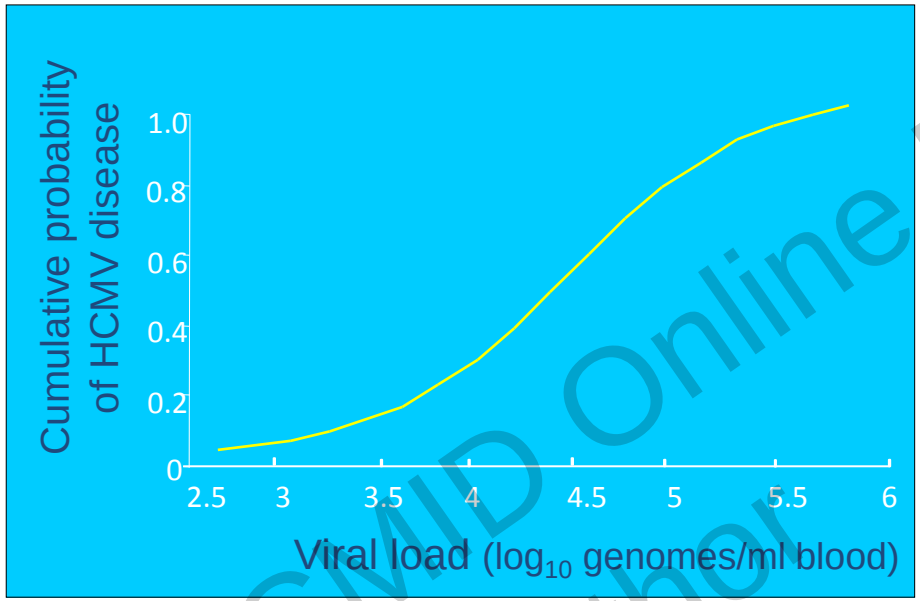
- Correlates of protection
  - T-cells (CD4 and CD8)
  - Antibodies (neutralising and ADCC)
- Patients with ESRD and ESLD often have reduced responses to vaccination
  - Antibody titres
  - T-cell responses?
- Optimal vaccination strategy is prior to end-organ failure
- Post transplant immunosuppression will impact on immunity
  - How much?
- What target efficacy do we need?
- Length of protection required?
- Study endpoints?

T-cell immunity predicts spontaneous clearance?

- Prospective study of 37 SOT patients with asymptomatic DNAemia (1140 copies/ml)
- 78.4% of patients spontnaeously cleared DNAemia
- Quantiferon IFNγ assay used to enumerate CMI
- IFNγ cut-off >0.1 or >0.2IU/ml associated with spontaneous clearance (p~0.005)
- 0.2 IU/ml had a sensitivity and specificity of 83% and 75% and a RR of 7.90 for progression
- Absolute levels of IFNγ inversely correlated with CMV load

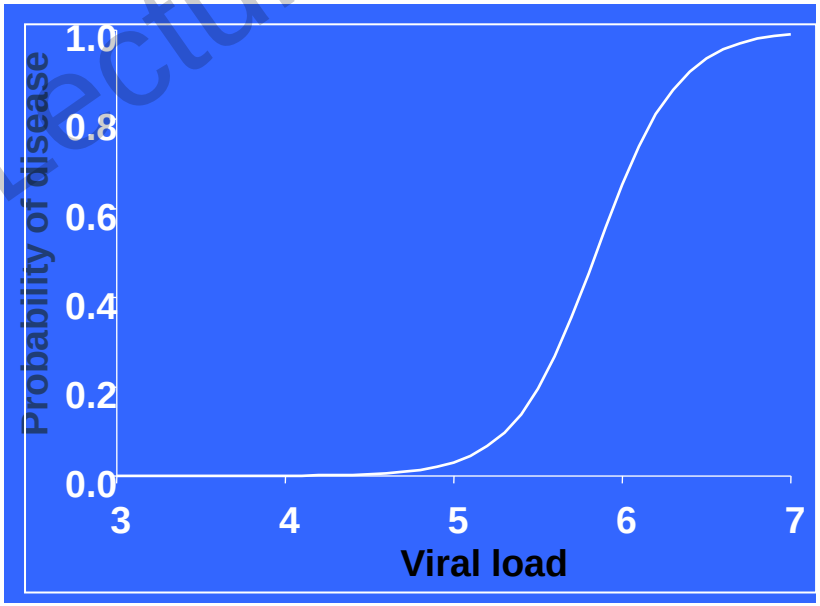
Lisboa et al (2012) Transplantation 93;195-200

CMV load and disease probability



Gor D, Bone Marr Transpl **21**, 597 - 606, 1998

HSCT



Cope AV et al, 1997, J Infect Dis,176,1484-90

SOT

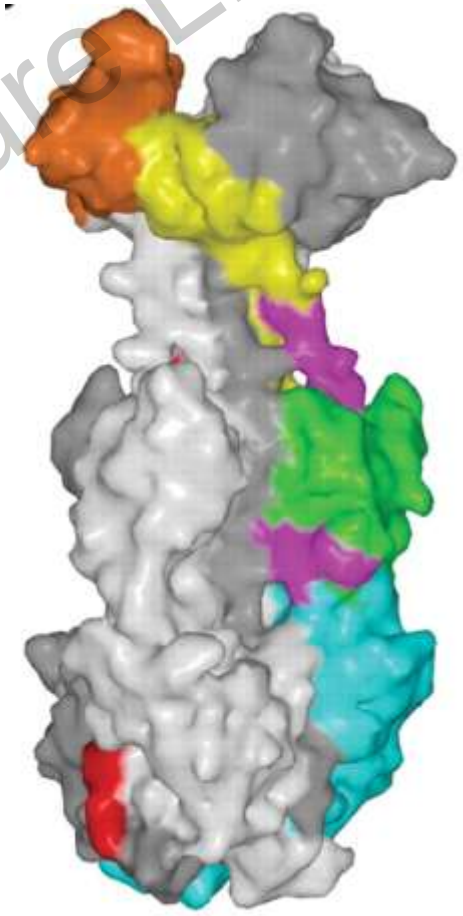
Approaches to produce a CMV vaccine

- Live attenuated viruses
  - Lab adapted strains (AD169 and Towne)
  - Chimaeric viruses
- Recombinant proteins
  - gB, gH/gL, gM/gN,
  - pentameric gH/gL,UL128,130,131 complex[1]
  - Likely to produce predominantly B-cell responses
- Peptide vaccines (CMV-PADRE)[2]
- DNA vaccines
  - Target major B and T-cell antigens such as gB and pp65
- Virus vectors
  - Canarypox producing gB and pp65
  - Alphaviruses producing gB and pp65/IE1

1.Fotus et al (2012) J Virol (April – epub) 2. La Rosa et al (2012) J Infect Dis 205:1294-304

gB vaccine trial @ UCL

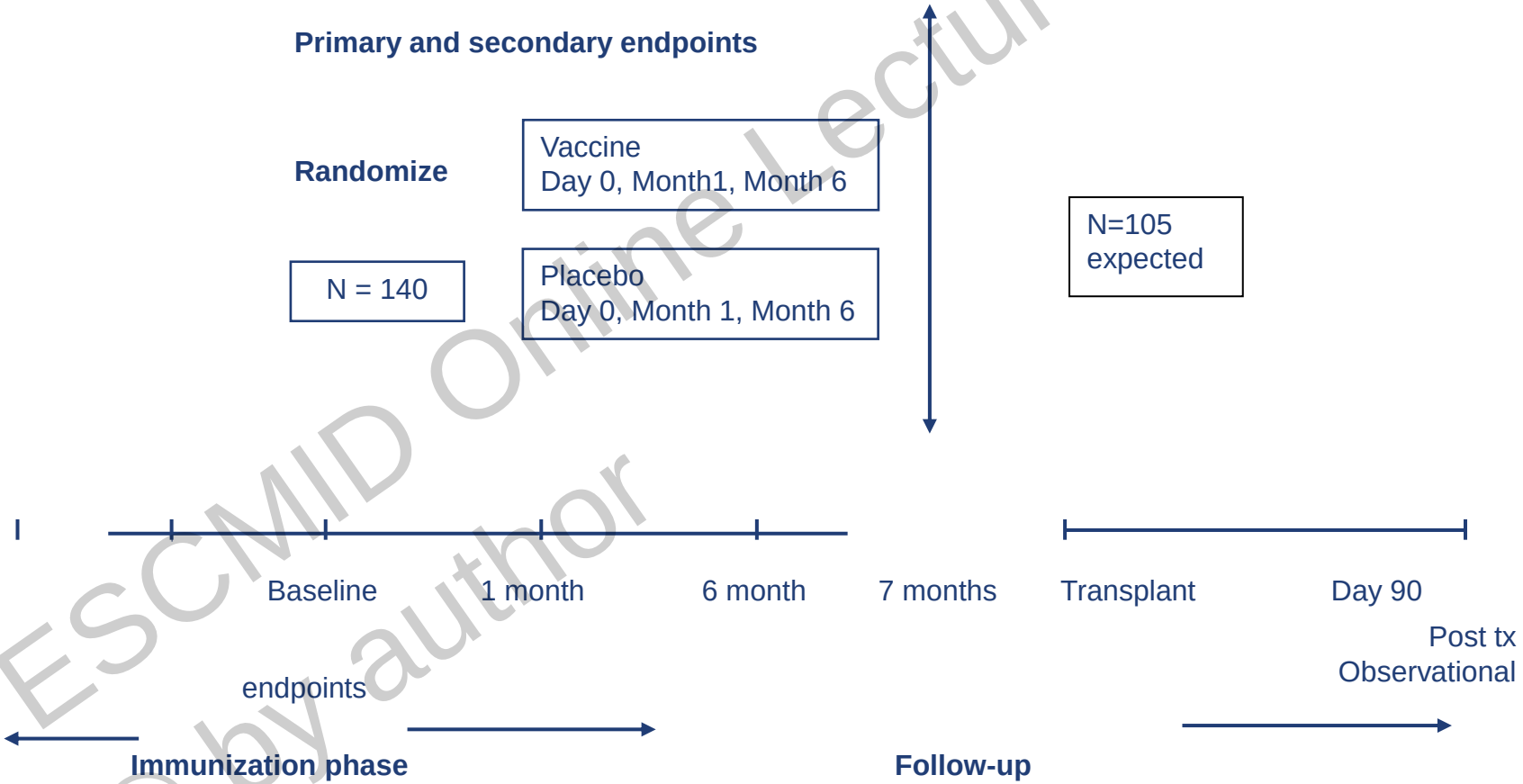
- 140 patients on the waiting list for a renal or liver transplant
- Recombinant modified gB vaccine produced in CHO cells and administered with the MF59 adjuvant
- Patients randomised 1:1 to vaccine or placebo
- Immunologic (antibodies) follow-up after each vaccine dose
- Virologic and immunologic (T-cells and antibodies) follow-up post transplant (n= 72)



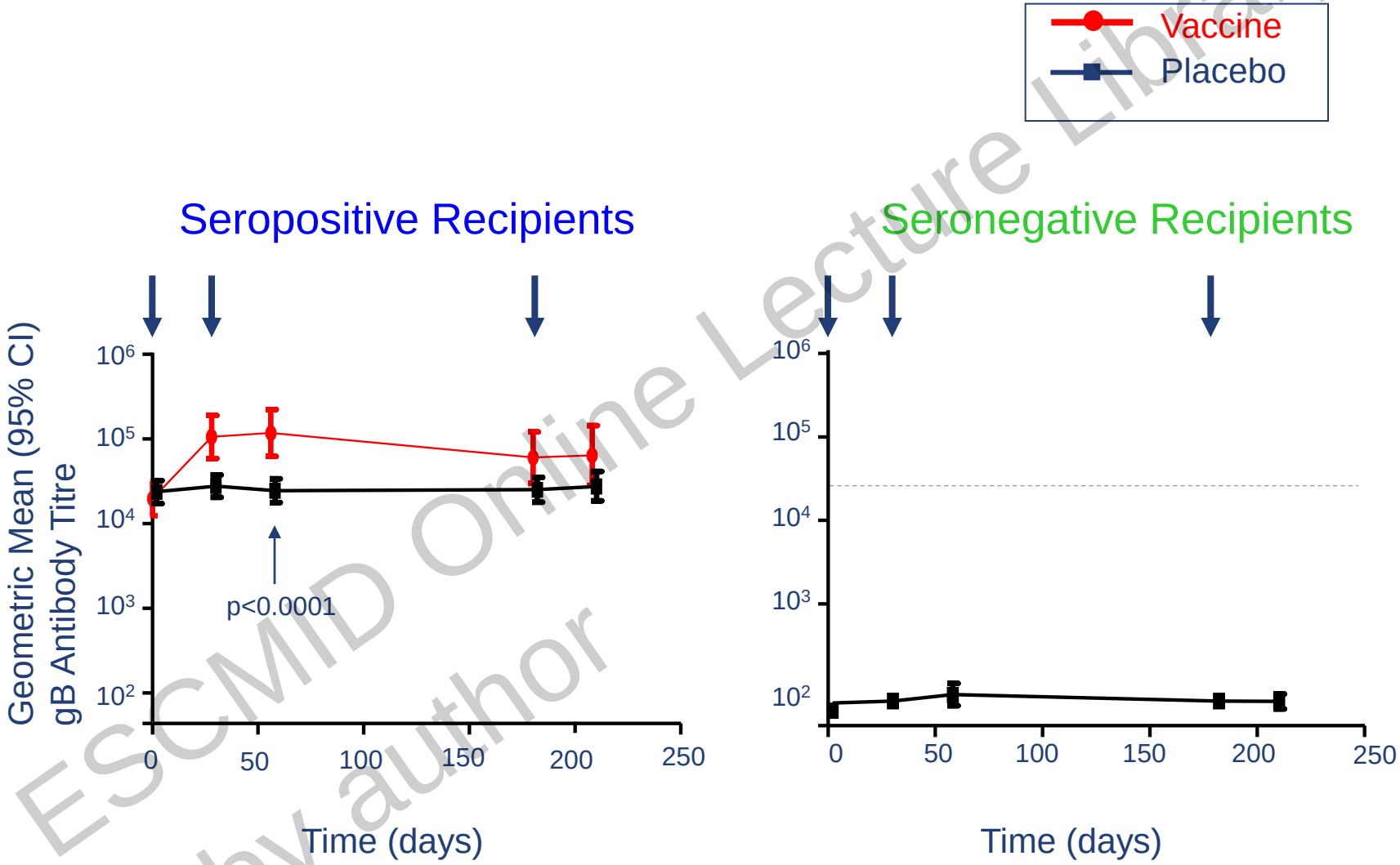
Griffiths PD et al (2011) Lancet 377(9773):1256-63.

Study Design

(70 seronegative: 42 renal, 28 liver / 70 seropositive: 42 renal, 28 liver)



Immunogenicity



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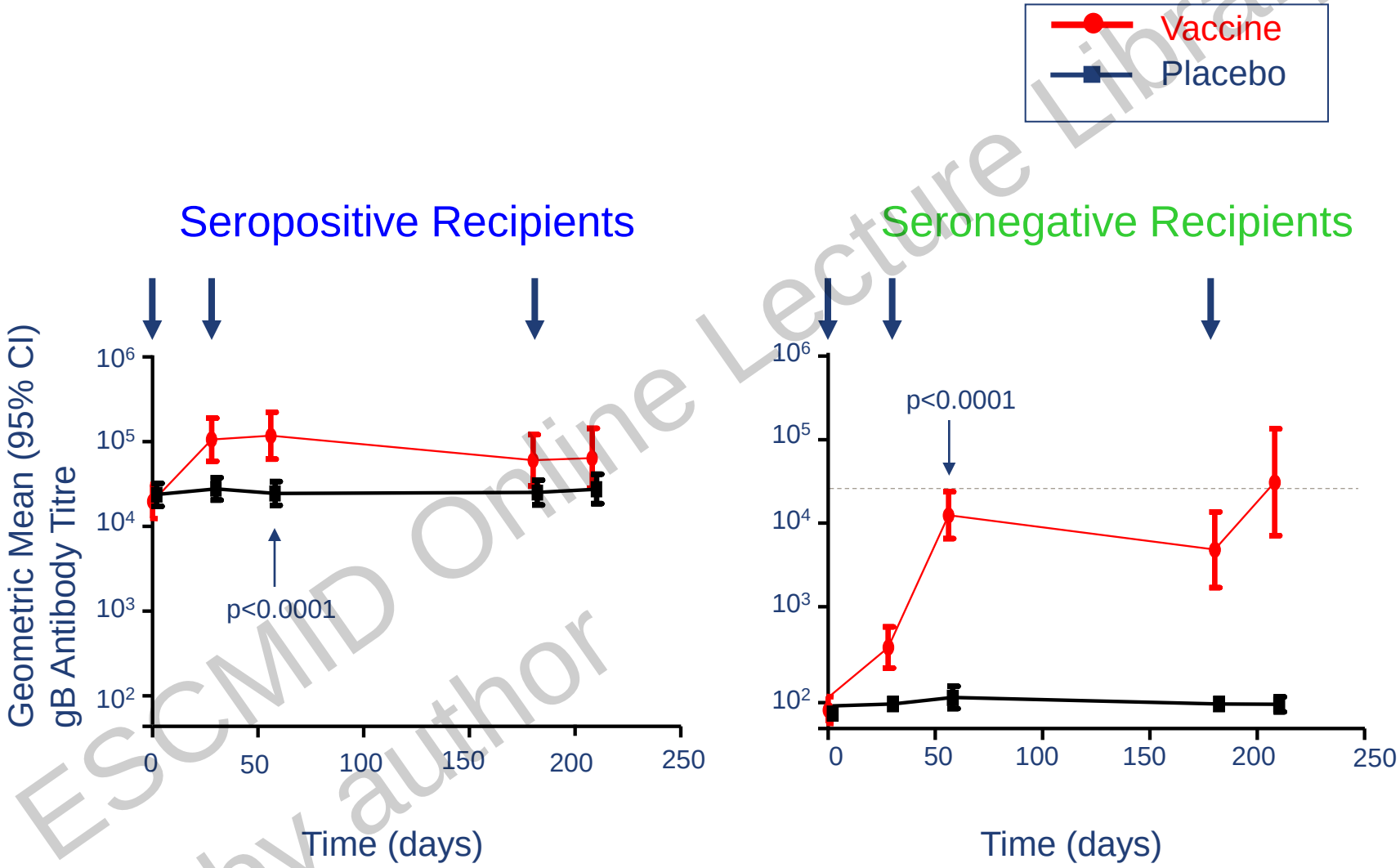

Efficacy

Sub-group		Number with Viremia
D- R- (n=21)	Placebo 10	0
	Vaccine 11	0
D-R+ (n=18)	Placebo 7	2
	Vaccine 11	3
D+ R+ (n=17)	Placebo 10	4
	Vaccine 7	4
D+ R- (n=16)	Placebo 5	5
	Vaccine 11	6

No effect on incidence of viremia

100% transmission

55% transmission

Incidence of viremia reduced: transmission blocked?

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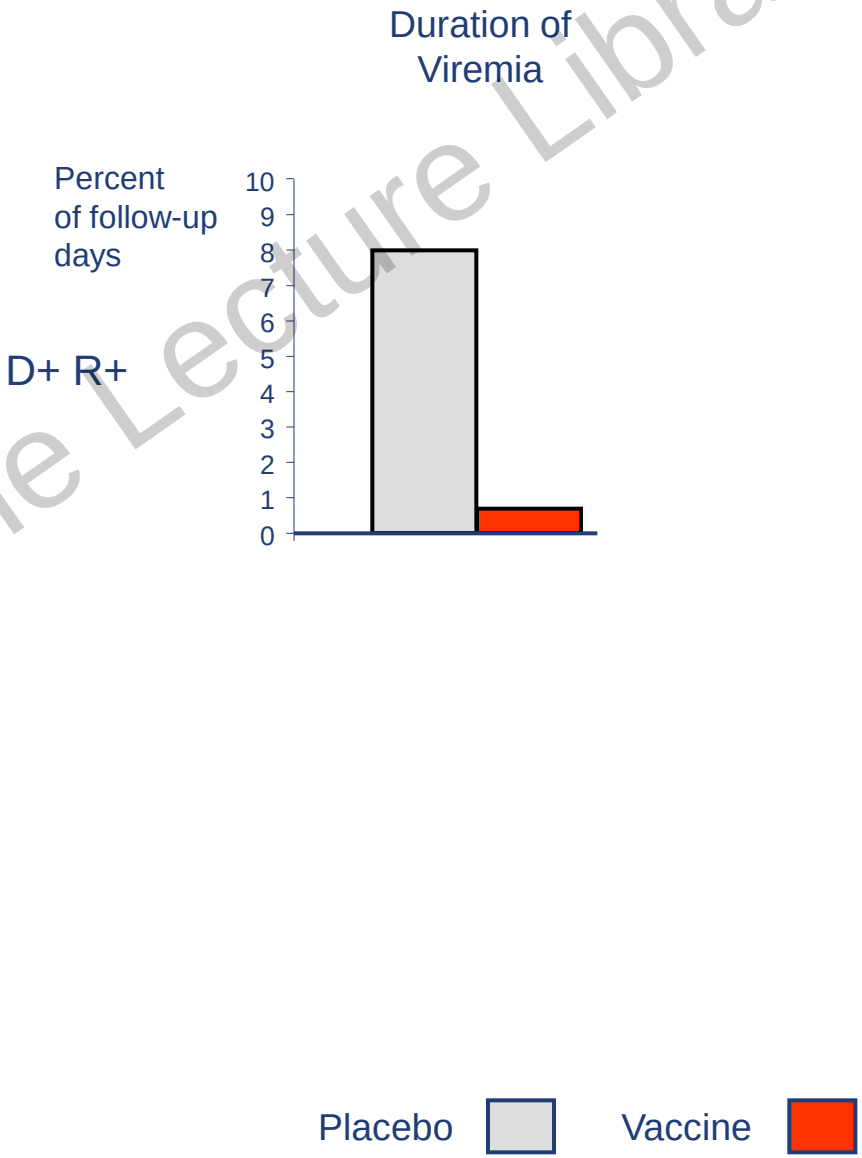

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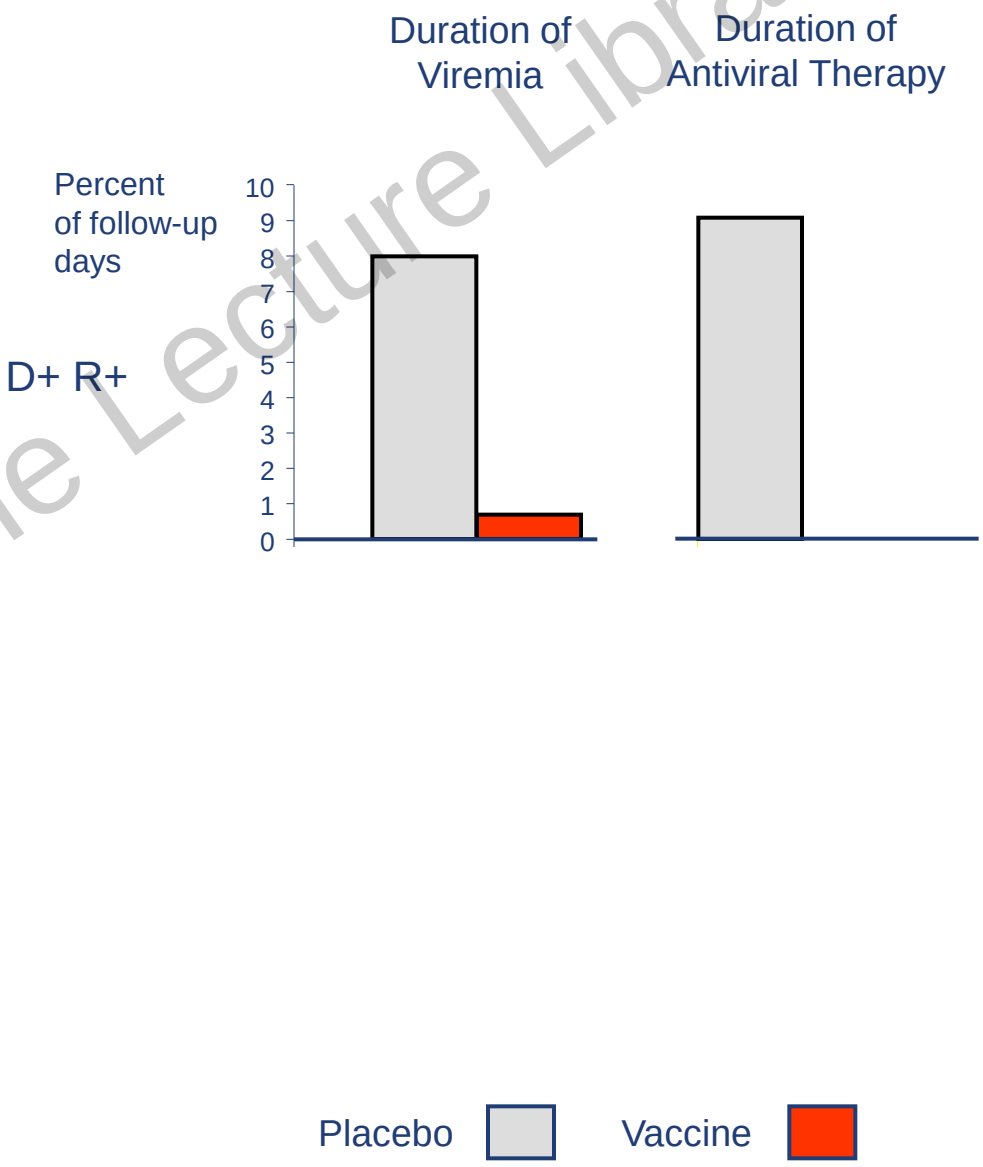

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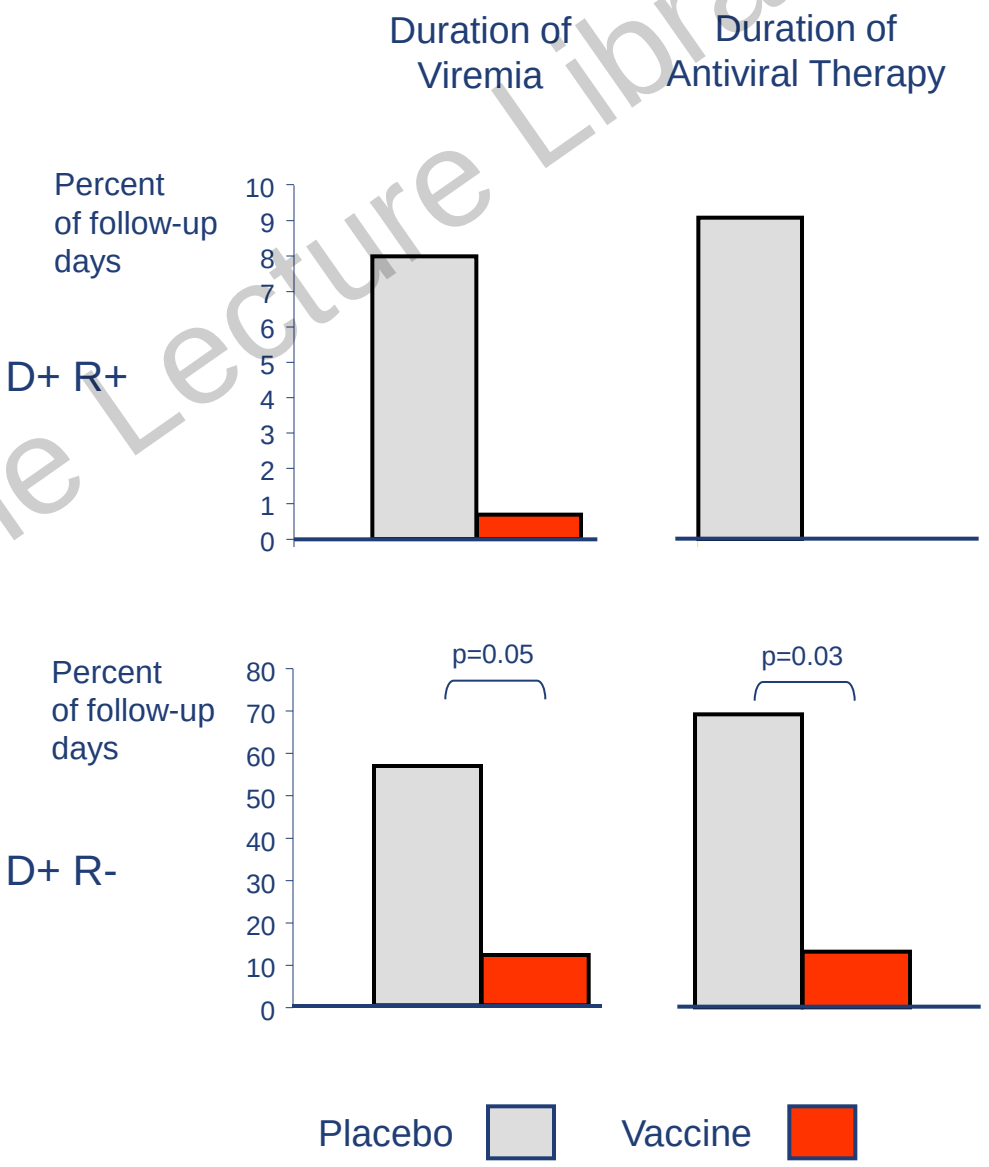
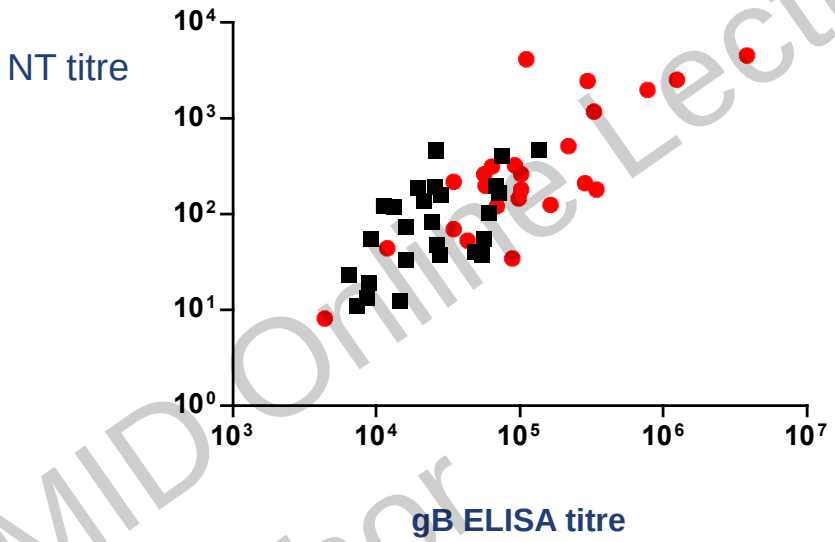


Neutralising antibody: seropositives



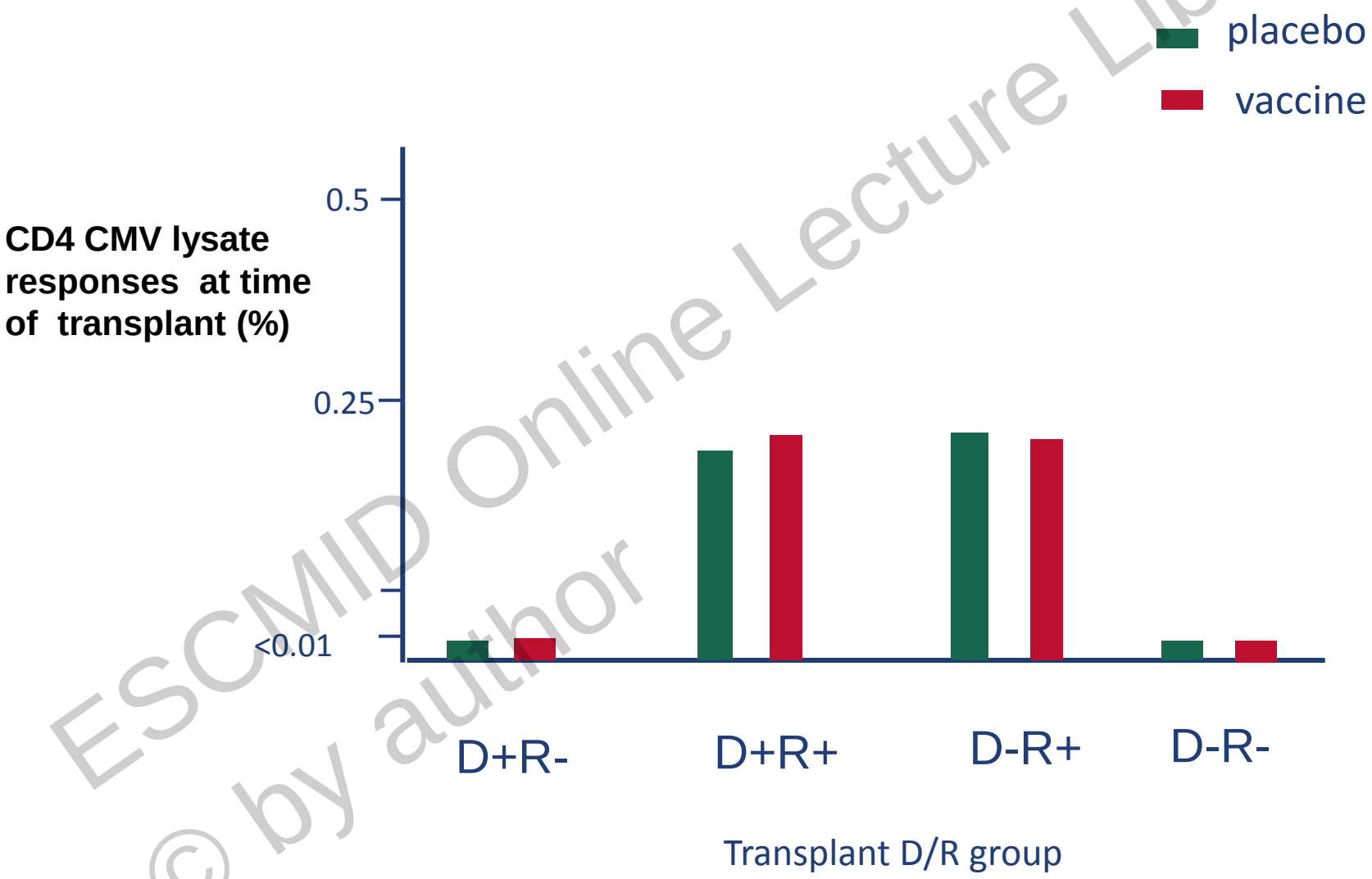
Vaccine

Placebo

All seropositives in study

Correlation between total gB response and NT response

Correlates of protection - CD4 T-cells



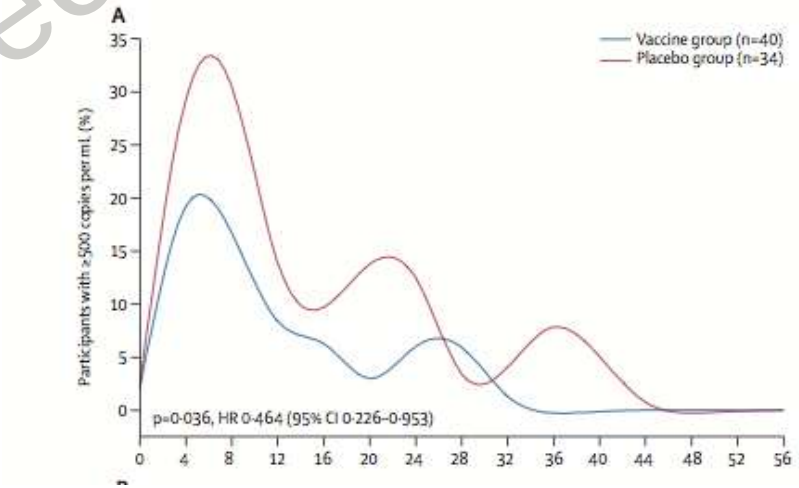
Phase 2 study of a therapeutic CMV DNA vaccine in HSCT recipients

- Randomised, double blind placebo controlled study of DNA vaccine containing gB and pp65 with poloxamer CRL1005 and benzalkonium chloride
- Vaccination prior to conditioning and at months 1,3 and 6 after transplantation
- 108 patients randomised (94 HSCT recipients and 14 paired donors)
- Efficacy population based on 74 unpaired HSCT patients

Karfan-Dabaja et al (2012) Lancet Infect Dis12:290-99

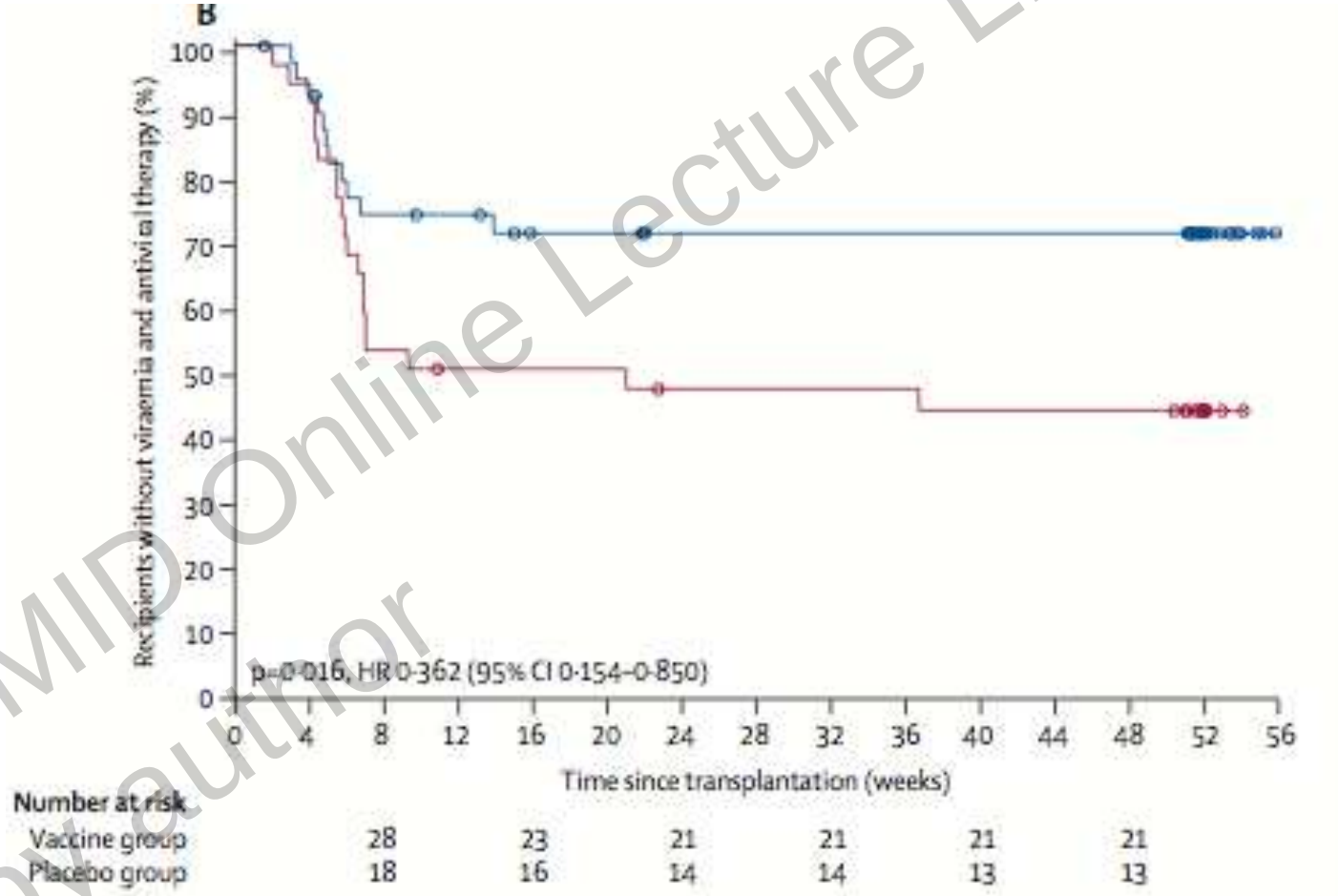
DNA Vaccine trial in HSCT recipients: results

- Initiation of pre-emptive therapy reduced in the vaccine arm
  - 61.8% to 47.5% (p=0.145)
- CMV viremia (>500 copies/mL) significantly reduced in vaccine arm
  - 61.8% to 32.5% (p=0.008)
- episodes of replication significantly reduced in vaccine arm (p=0.017)
- Mean duration of viremia significantly reduced in vaccine arm (7.7% days to 4.9% days; p=0.042)



Karfan-Dabaja et al (2012) Lancet Infect Dis12:290-99

Time to Viremia/antiviral therapy



Expectations and Impact

Are these results what we might have expected?

- Can we sense how good the natural immune control of CMV is in the immuncompromised?
- How much impact would we need to influence CMV viremia?
- How much impact would we need to influence CMV disease and how would we assess this endoint?

Basic reproductive number (Ro) for CMV

- In liver transplant recipients:
  - D+R- Ro = 15
  - D+R+ Ro = 2.4
- In stem cell transplant recipients
  - D-R+ Ro = 4.3
  - D+R+ Ro = 1.9
- Overall efficacy of the seropositive immune system 56-84%
- Target efficacy to reduce Ro <1
  - D+R- LTx is ~93%
  - D+R+ LTX is ~ 58%
  - D-R+ SCT is ~76%
  - D+R+ SCT is ~ 48%
- But - based on patients from the 1990s

Emery et al (2002) J Infect Dis 185, 1723; unpublished data

Basic reproductive number (Ro) for CMV:2014

- Analysis of 374 liver and 368 renal transplant recipients at the Royal Free hospital, London
- In liver transplant recipients:
  - D+R- : average Ro = 1.82
  - R+ : average Ro = 1.40
- In renal transplant recipients:
  - D+R-: average Ro = 1.78
  - R+ : average Ro = 1.37
- Target efficacy needed to reduce Ro < 1 in primary infection about 45%

Atabani et al (2012) Am J Transplant 12(9):2457-64

Potential impact of a vaccine

- If the Ro estimates are accurate then a vaccine with ~ 50% efficacy would have a high impact on the incidence/duration of viremia
- If a vaccine achieved greater efficacy then it is likely that primary infection could be prevented
    - Role of antibodies/ADCC
- In recurrent or re-infection a 50% efficacy would be sufficient but this will depend on the type of immunity generated
    - Bigger role for T-cell immunity in this context
- What about CMV disease
    - Low incidence with pre-emptive therapy so not a useful endpoint

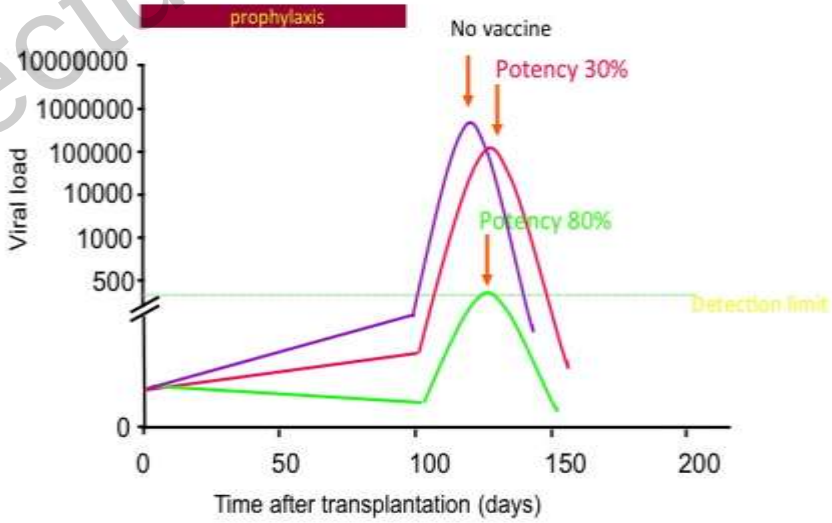
HCMV Immune responses after prophylaxis

- CD8 T-cell responses to HCMV in patients receiving standard HCMV prophylaxis with valganciclovir analysed by the QuantiFERON IFNγ assay at months 1,2,3
- 108 patients studied
  - D+R+ n=39
  - D+R- n= 35
  - D-R+ n= 34
- At 3 months 35% of patients had a CD8 response
- Late HCMV disease occurred in 5.3% of patients with a CD8 response vs 23% in those with no CD8 response
- In D+R- patients with CD8 responses late disease occurred in 10% vs 40% in those without a response
- CD8 responses at 3 months may help identify a risk population for late HCMV disease

Kumar D et al (2009) Am J Transplant 9:1214-22

An alternative approach

- Given the incidence of post prophylaxis CMV infection and syndrome/disease in D+R- solid organ transplantation - could this provide a new opportunity for a vaccine trial?
- Vaccination pre/post transplant to boost B or T-cell immunity
    - Endpoints of occurrence of viremia and CMV syndrome/disease
    - Faciliates multicentre trials in high risk patients
    - Addresses an important clinical need
    - Prime-boost strategies could be evaluated

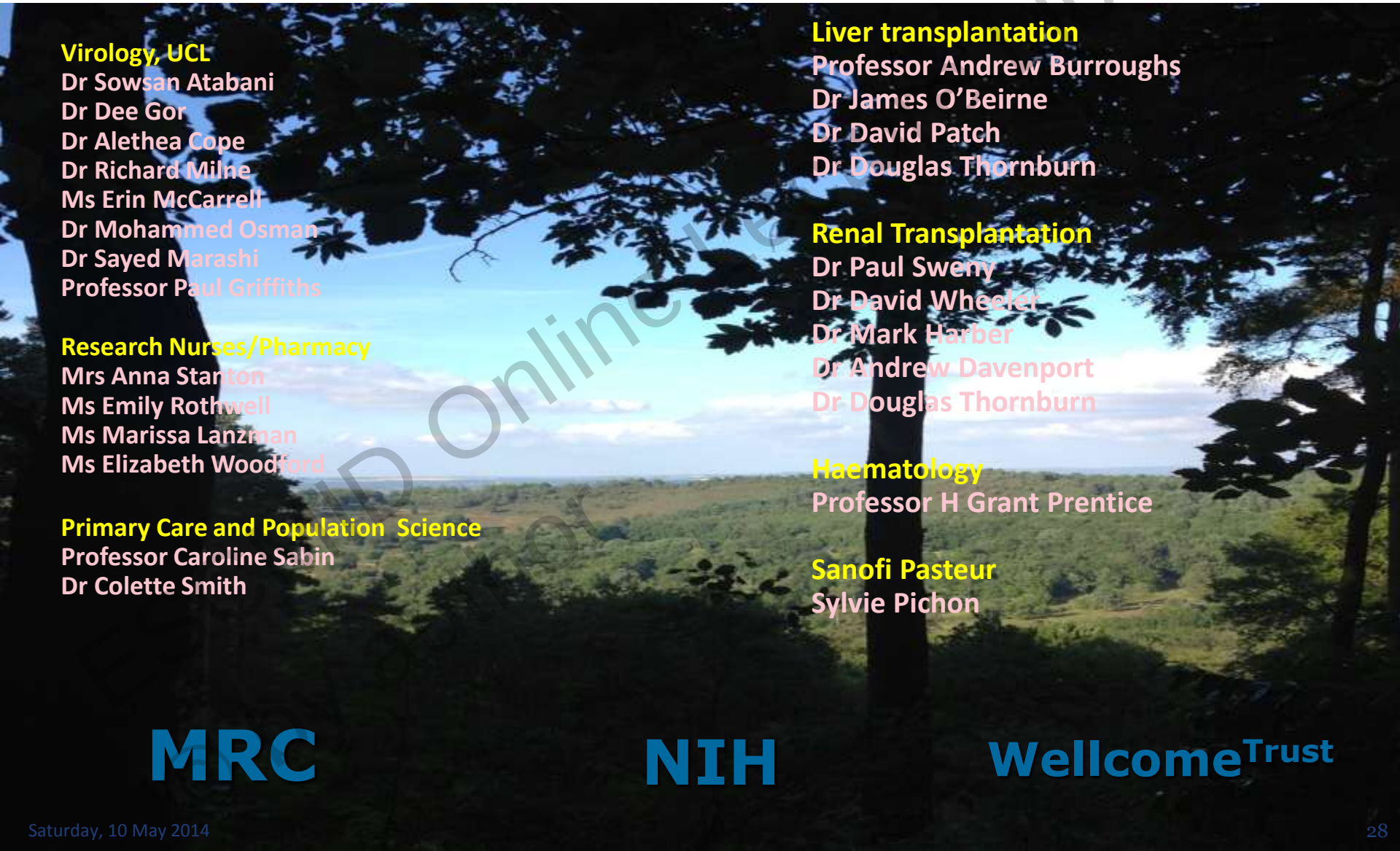


Conclusions

- Use of virologic markers as a readout of vaccination success now established
- Vaccination of patients on the waiting list for solid organ transplantation with a recombinant gB impacts on post transplant replication and need for antiviral therapy
- Vaccination of HSCT patients post transplant with a DNA vaccine containing gB and pp65 impacts on CMV replication
- What is the ideal composition for a vaccine?
  - Other neutralising entities (eg. gH pentameric complex)
  - Other T-cell targets
- Future trials of the alphavirus replicon vaccine in transplant recipients are awaited
- Prime-boost strategies may be attractive
- Ability of a vaccine to reduce or eliminate post-prophylaxis CMV disease is an attractive option

Acknowledgements

This talk is dedicated to the memory of Professor Andrew Burroughs (1954-2014)



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