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Dissecting immunity to RSV using human challenge trials

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Respiratory syncytial virus

- Leading cause of respiratory infection in infants
  - 33.1 million ALRIs per annum
  - 3.2 million hospital admissions
  - Up to 118-199,000 deaths (99% in developing world)
- Major contributor to mortality in elderly & immunosuppressed
  - Up to 10% of elderly adults annually
  - ~10% of pneumonias with up to 5% fatality rate
  - Severity of hospitalised cases similar to influenza
- No effective vaccine

Shi *et al.* Lancet 2017
Falsey *et al.* NEJM 2005

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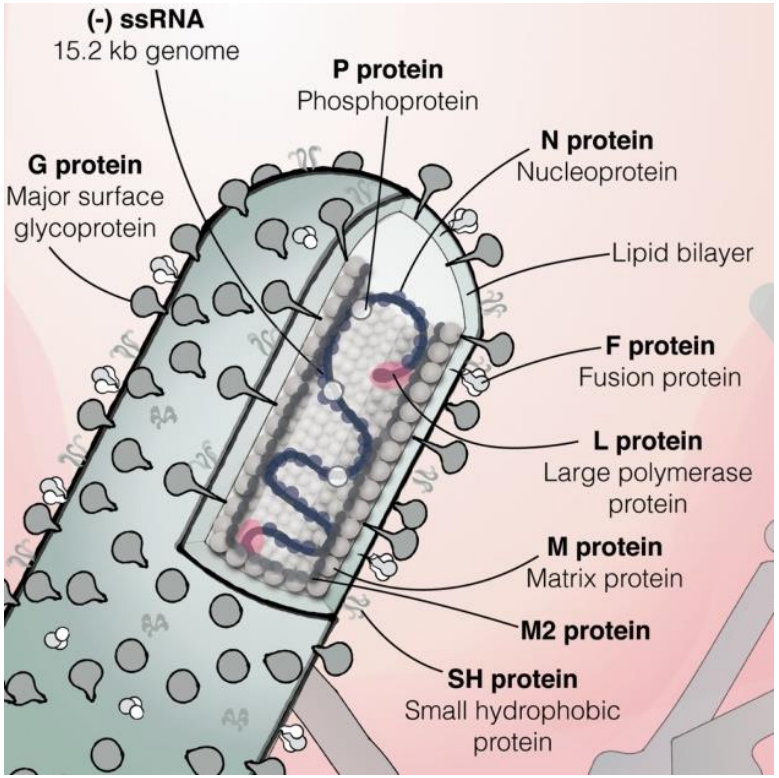
Hurdles to effective RSV vaccines

- Natural infection induces partial protection only
- Correlates & mechanisms of protection poorly understood
- Different high risk populations with different needs
- Safety issues
- Recent advances in understanding B cell epitopes



Lambert *et al.* Front Immunol 2014

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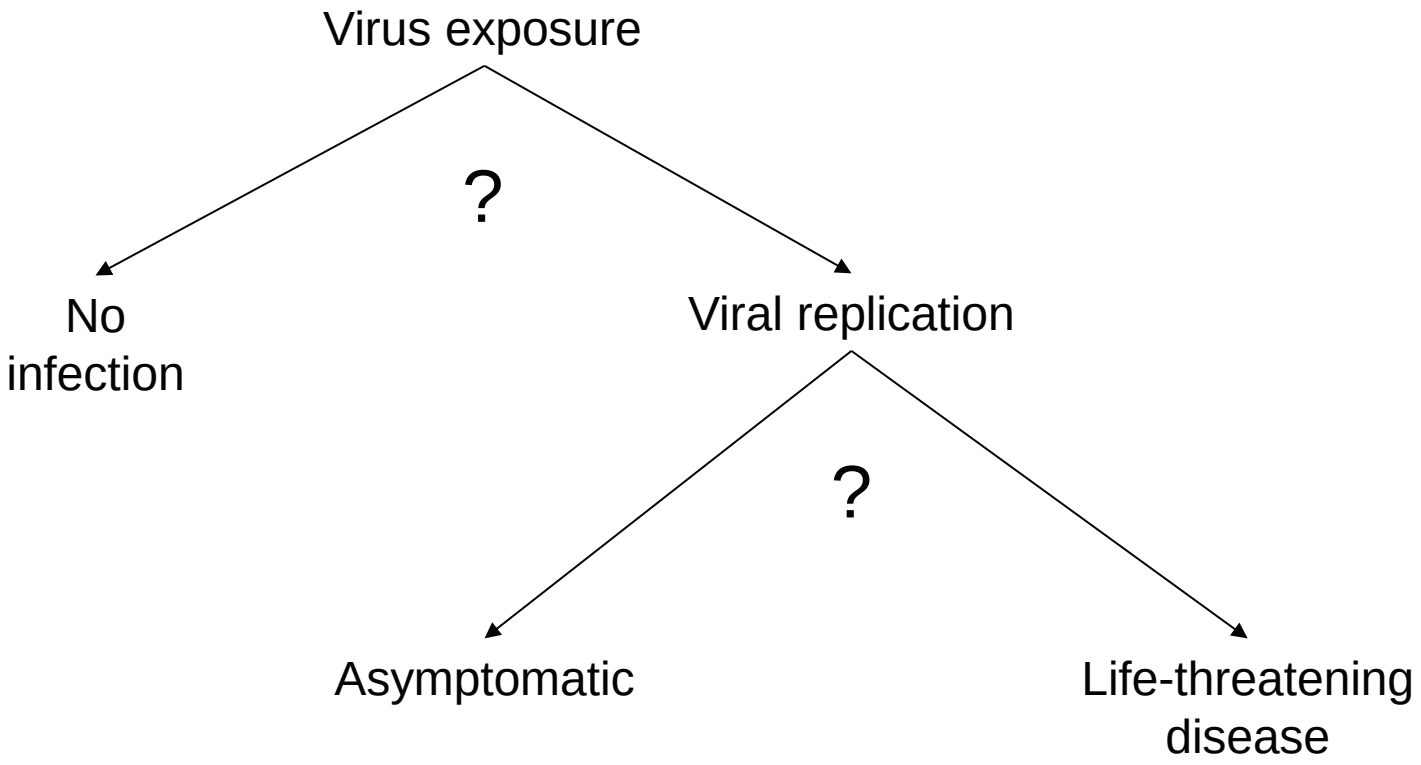
What determines outcome of infection?



Pre-existing antimicrobial effectors

Early pre-symptomatic responses

Adaptive immune response

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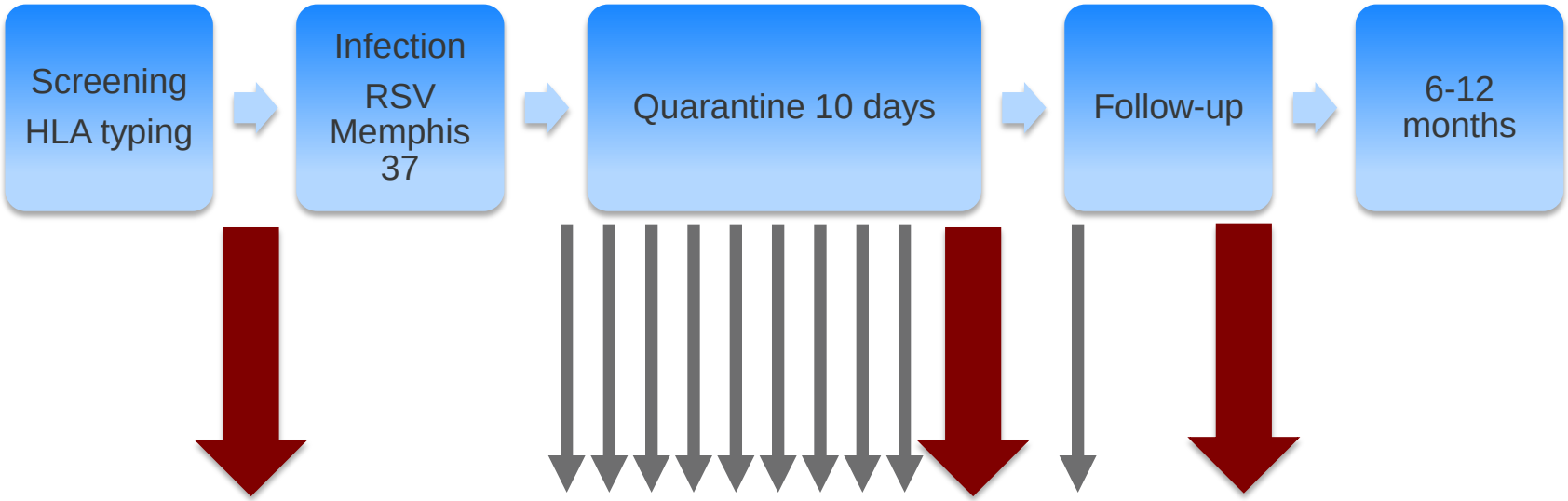
Experimental schedule



Blood

Nasal lavage, curettage & nasosorption

Broncho-alveolar lavage

Bronchosorption

Bronchial brushings

Bronchial biopsies

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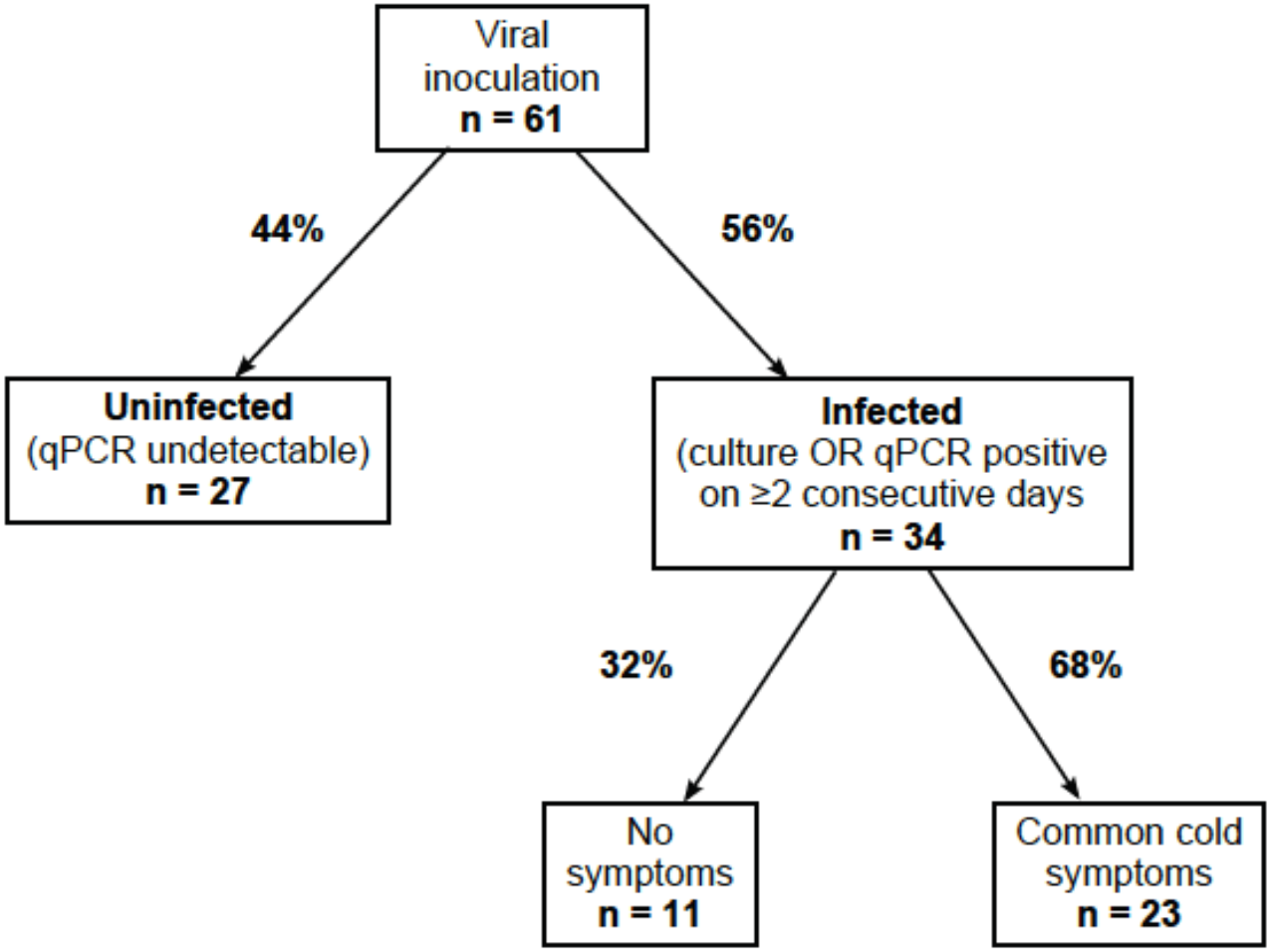
Heterogeneity of outcome



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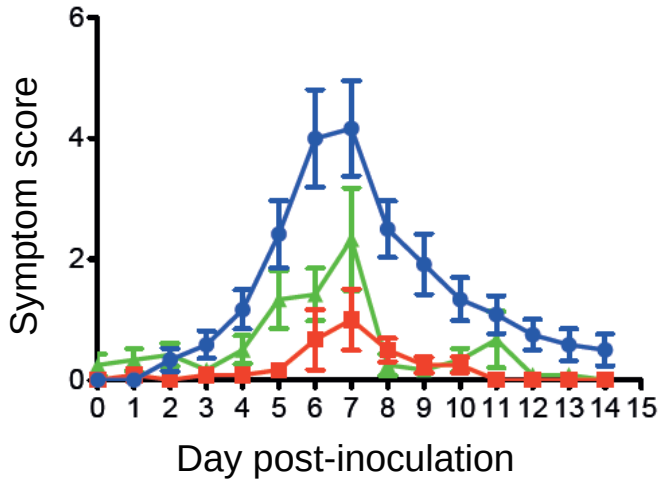
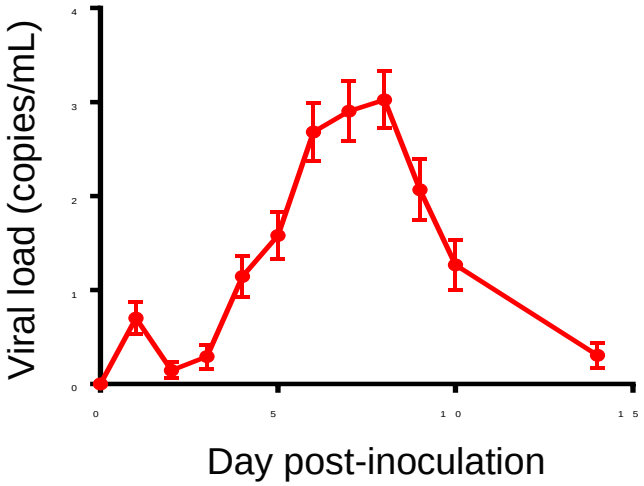
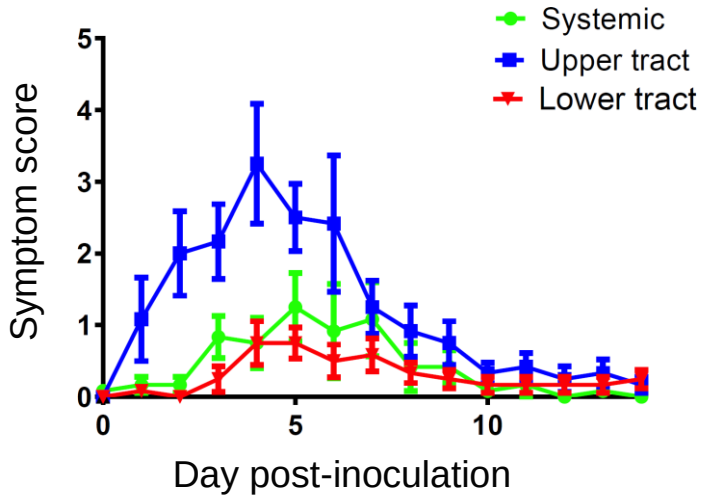
Symptoms & viral load

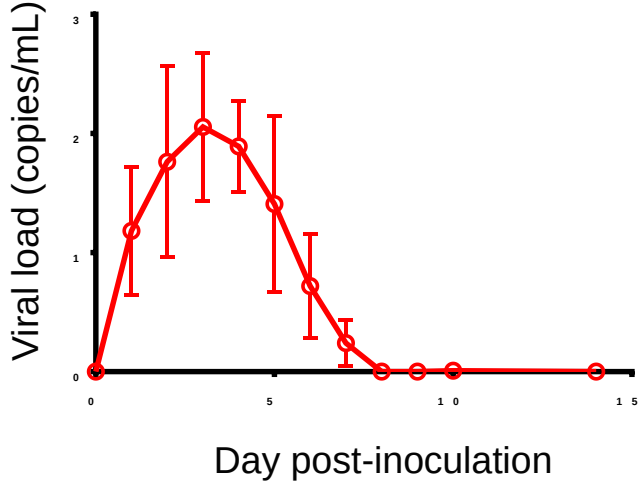
RSV





Influenza





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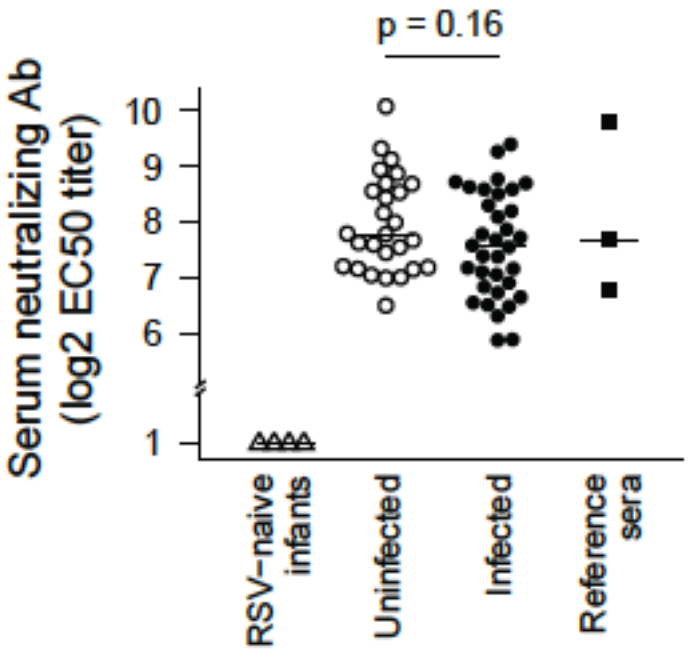
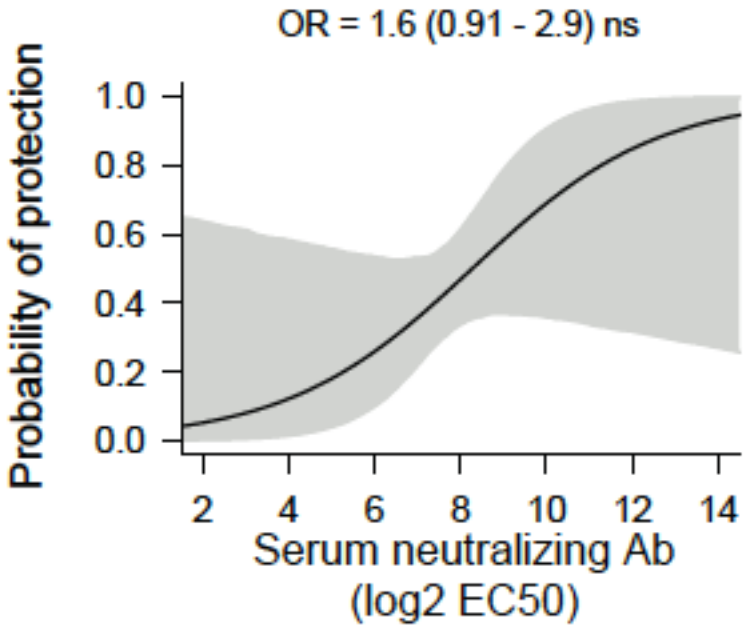
Serum neutralising Ab poorly predicts infection risk





Habibi *et al.* AJRCCM 2015

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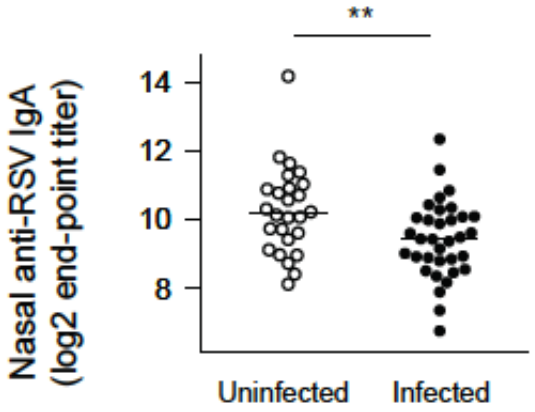
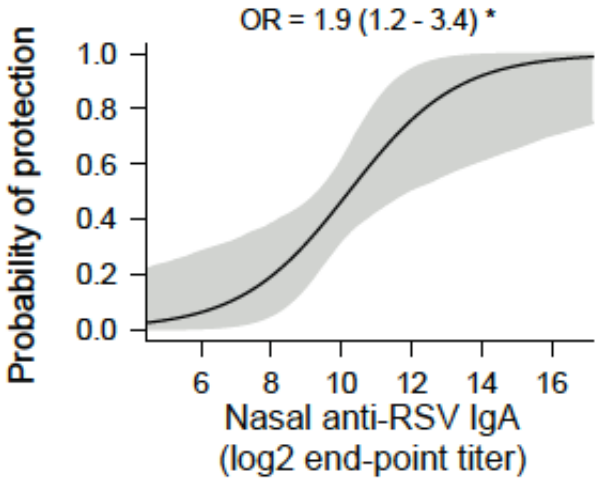
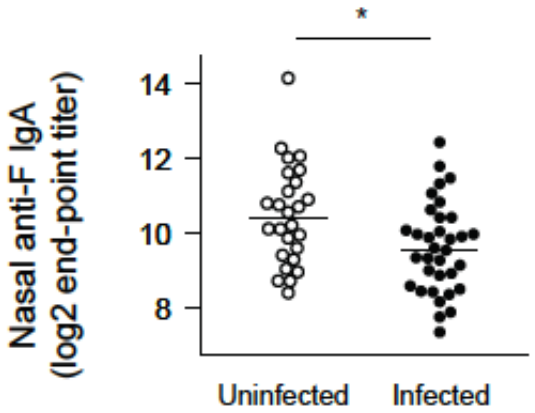
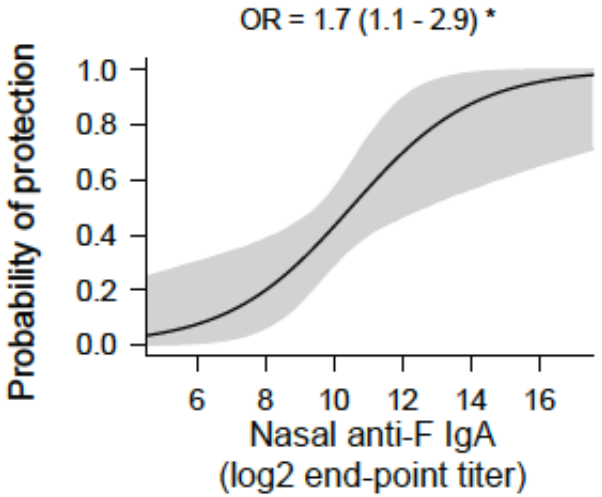
RSV-specific nasal IgA as a correlate of protection









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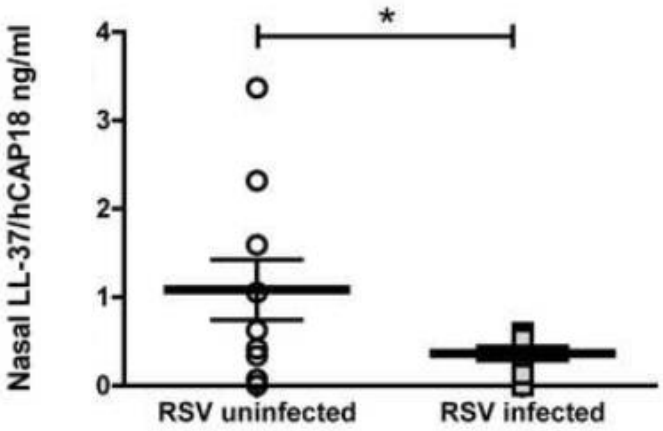
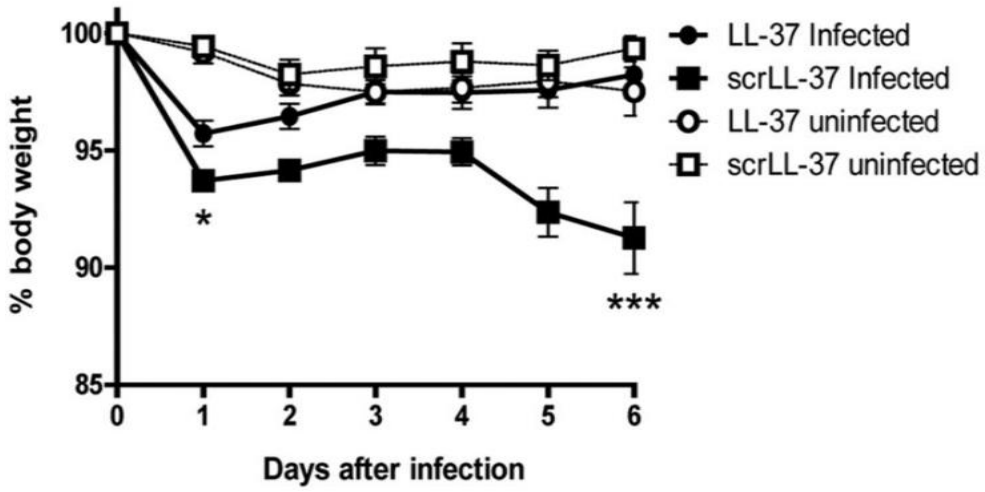
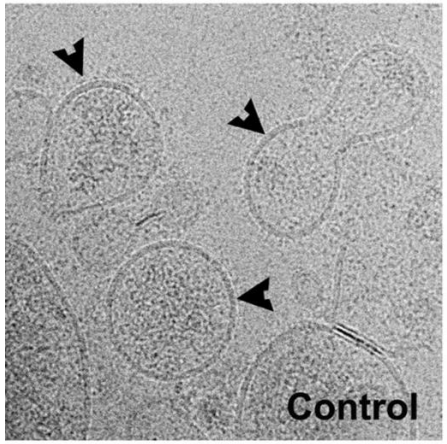
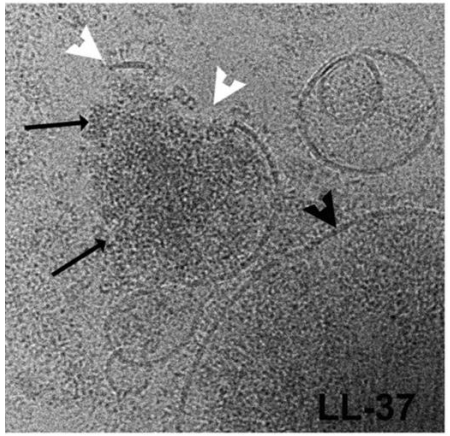
Additive/synergistic effect of cathelicidin?









Currie *et al.* J Immunol 2016

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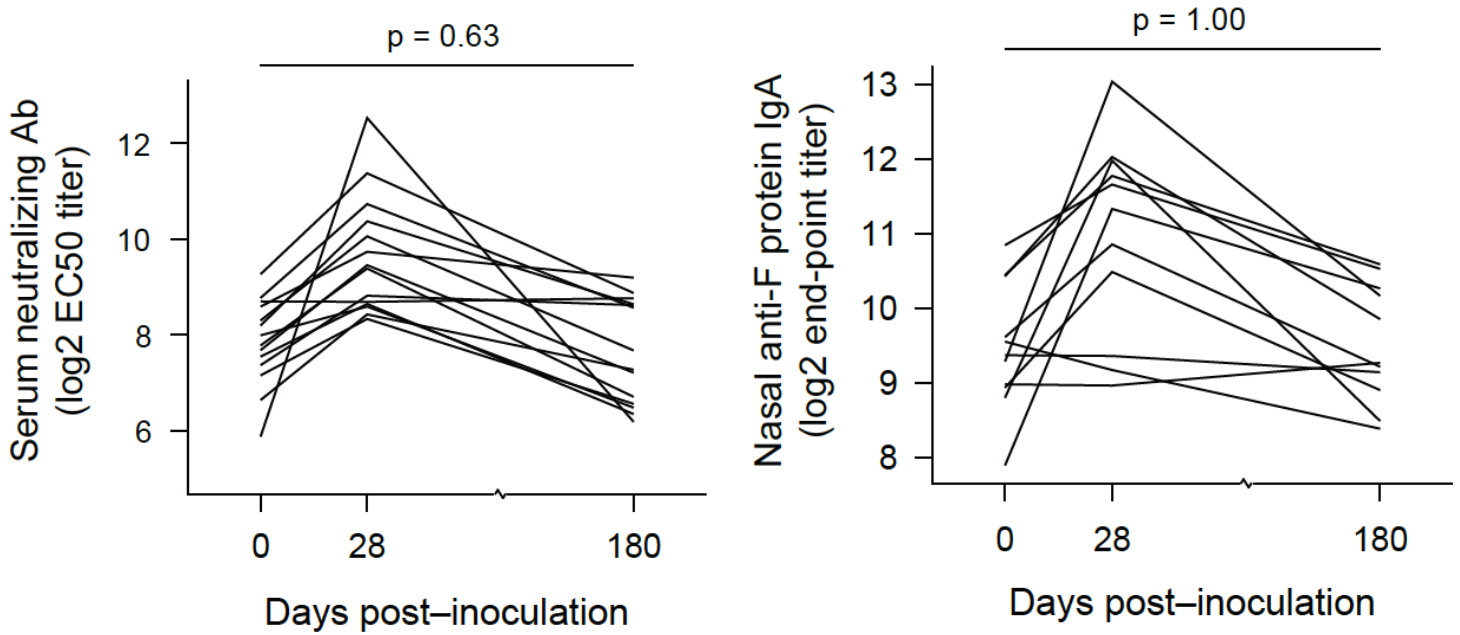
Anti-RSV antibodies are short-lived



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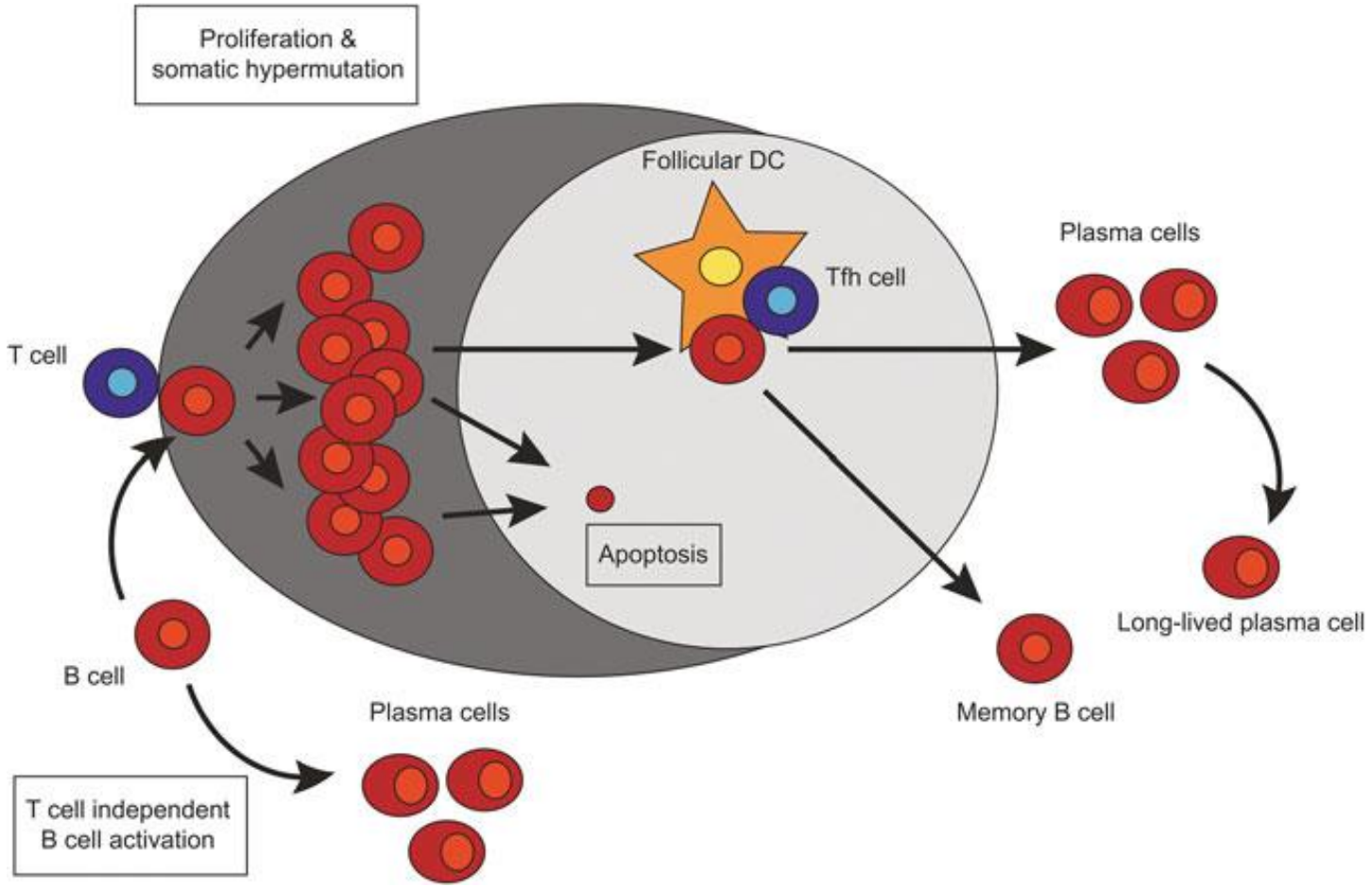
Generation of humoral immunity



Chiu *et al.* Curr Top Microbiol Immunol 2015

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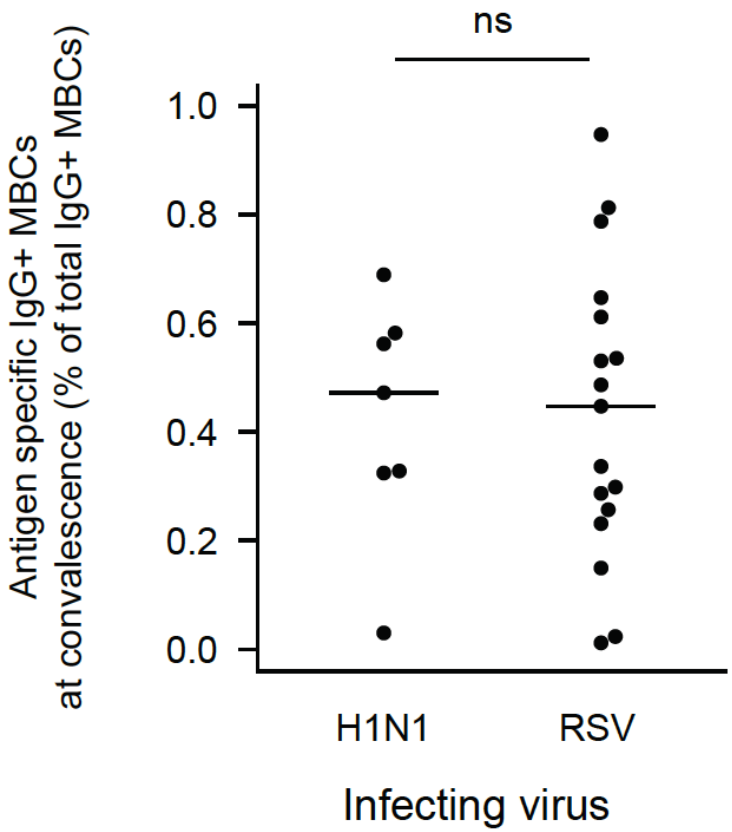
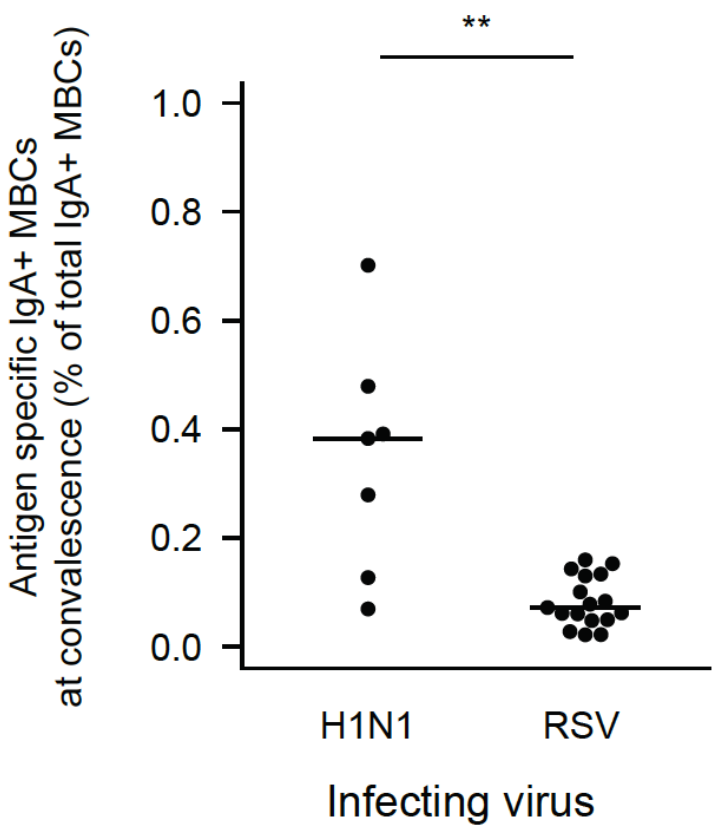
Poor induction of IgA+ memory B cells





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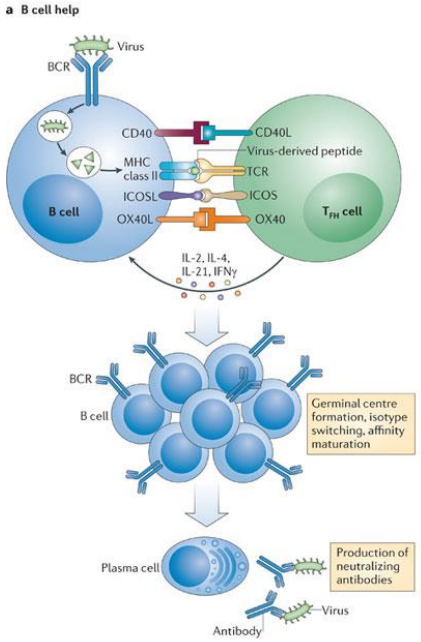
Cell mediated immunity

- Sterilising immunity is difficult to achieve
- Enlisting cell-mediated immunity
  - CD8+ & CD4+ T cells clear infected cells
  - CD4+ T follicular helper cells enhance B cell immunity
  - CD4+ T cells help long-lived CD8+ T cell memory
- Limited data in human RSV infection
  - Children with deficient CMI
  - Reduced RSV-specific T cells in older adults
  - Most data from PBMCs



Swain *et al.* Nat Rev Immunol 2012

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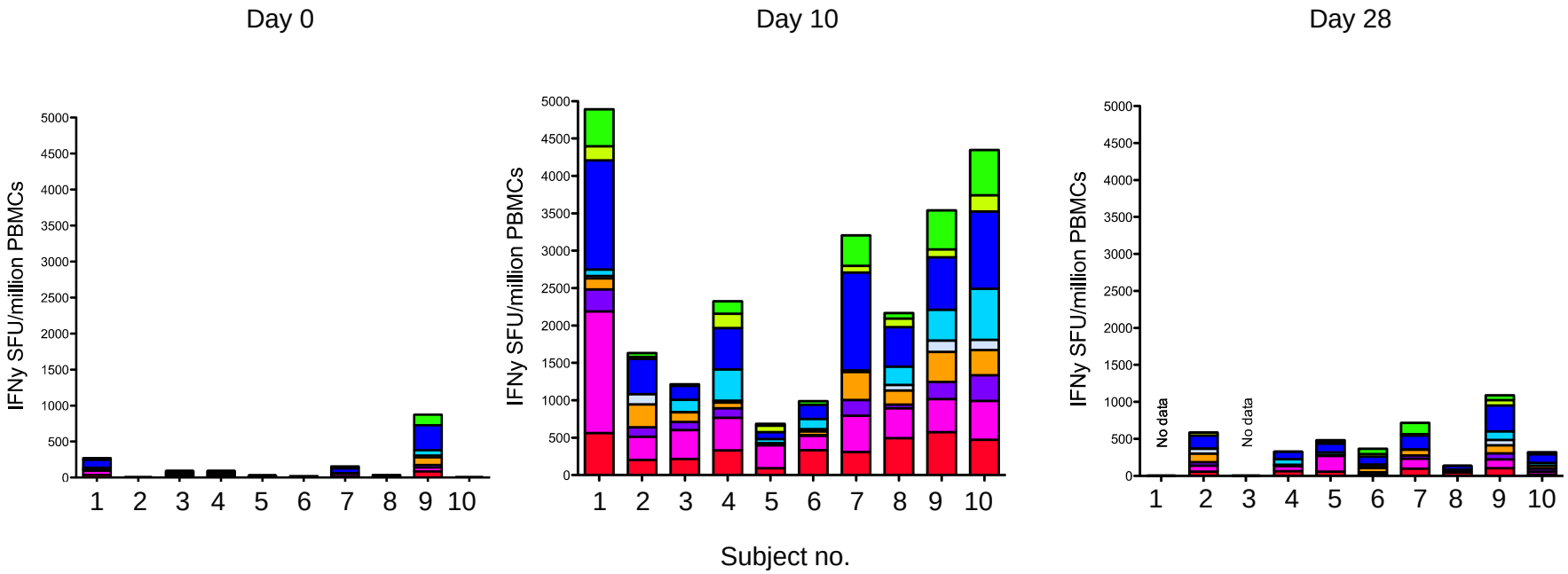
Expanded T cell populations allow in-depth analysis



NS N P M SH G F M2 L

Aleks Guvenel, unpublished

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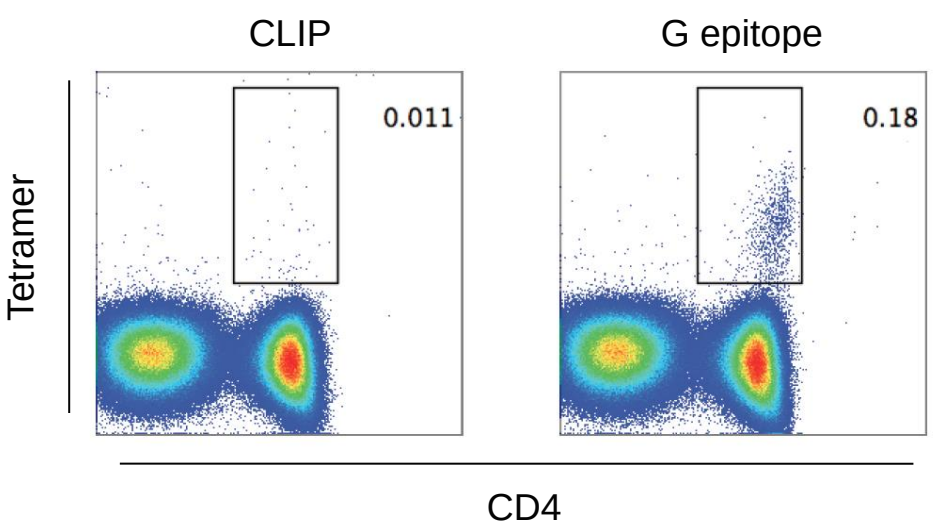
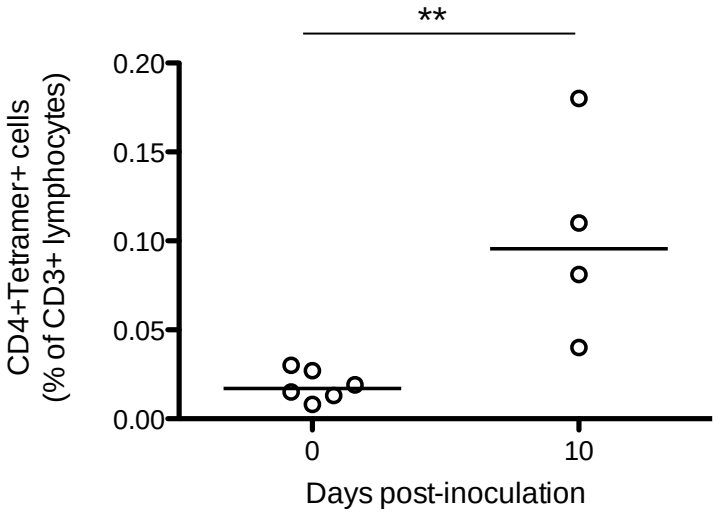
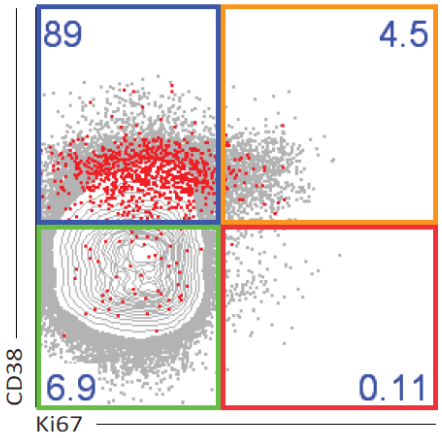
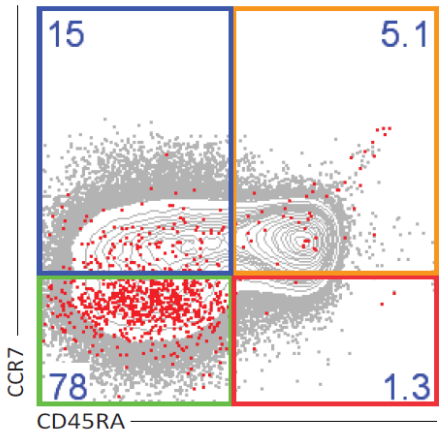
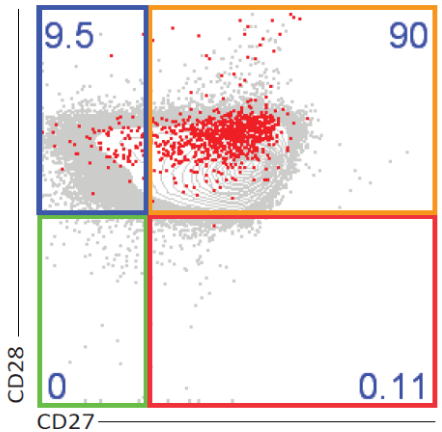
Novel tetramers identify RSV-specific CD4+ T cells

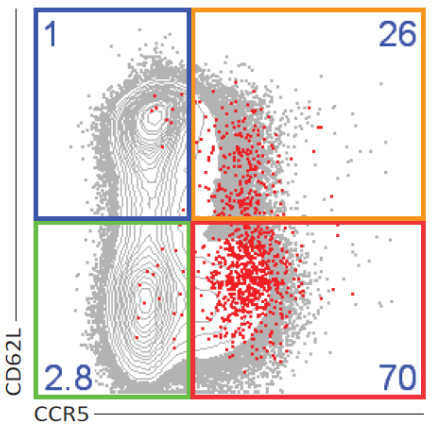












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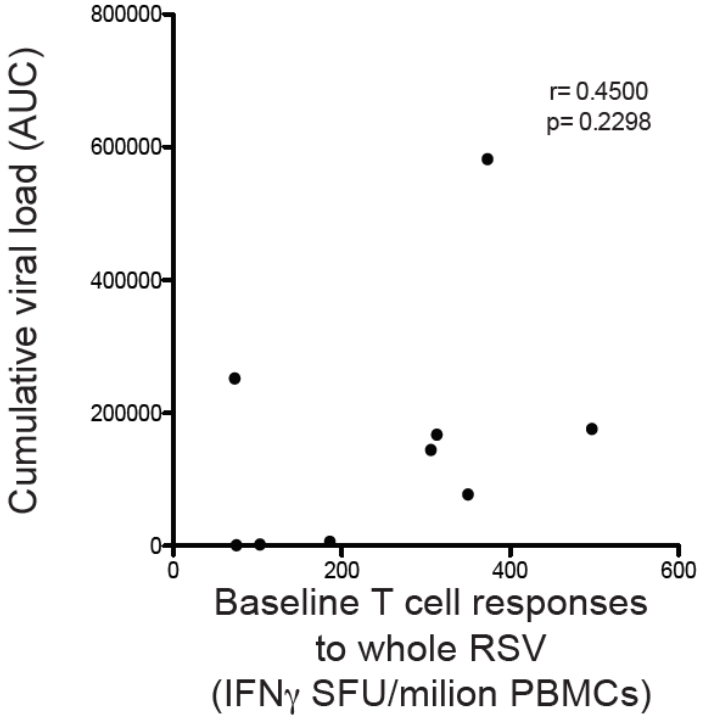
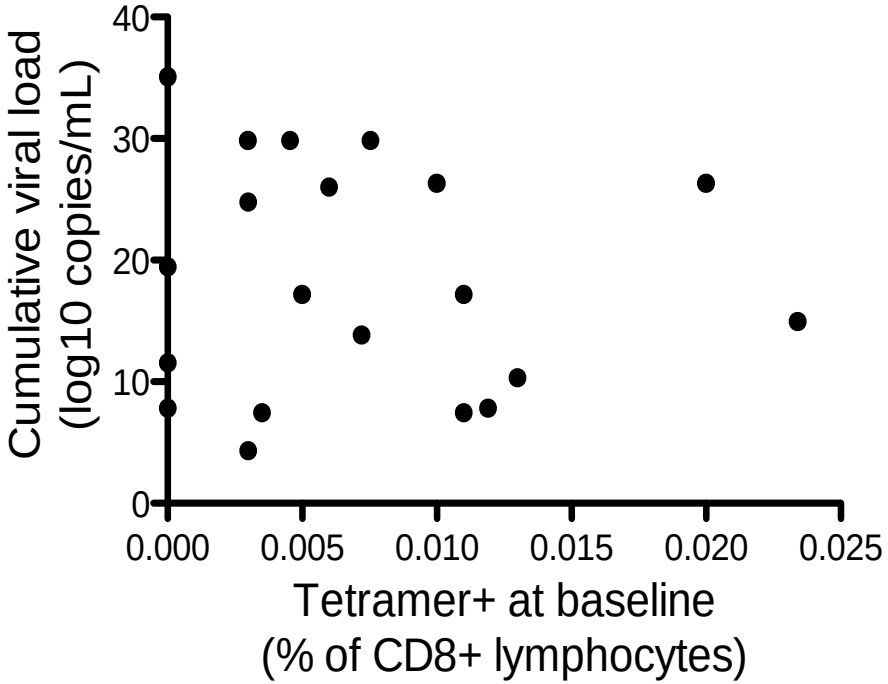
Tm cells in blood correlate poorly with protection





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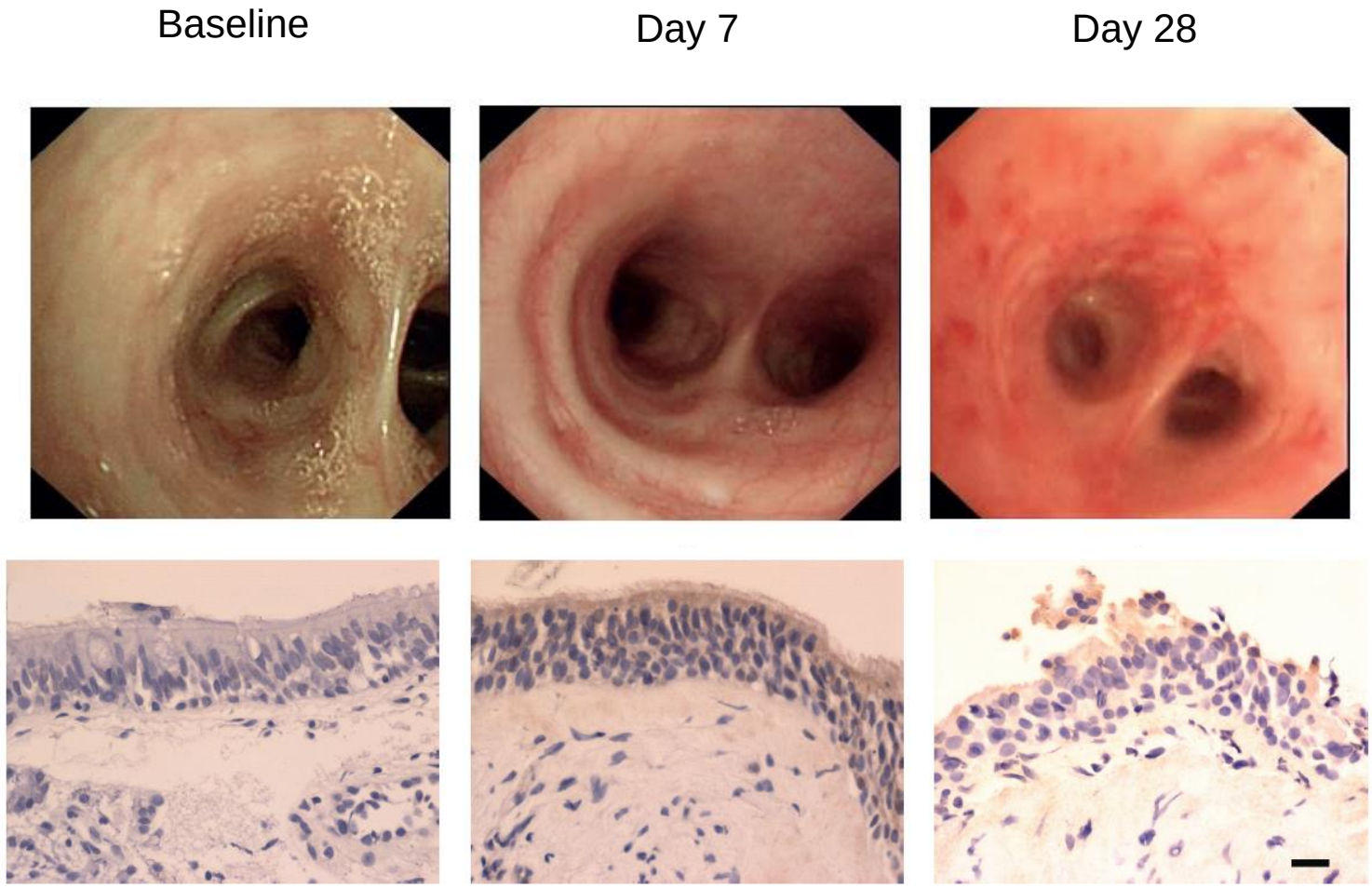
RSV challenge induces lower airway inflammation



Jozwik *et al.* Nat Commun 2015

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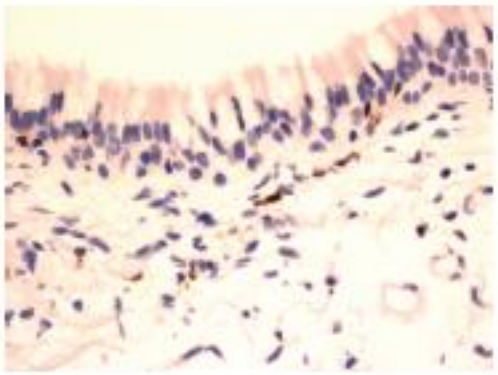
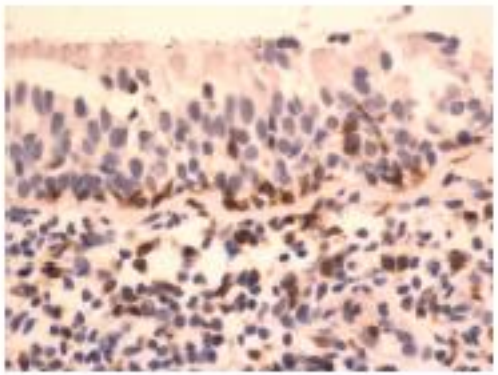
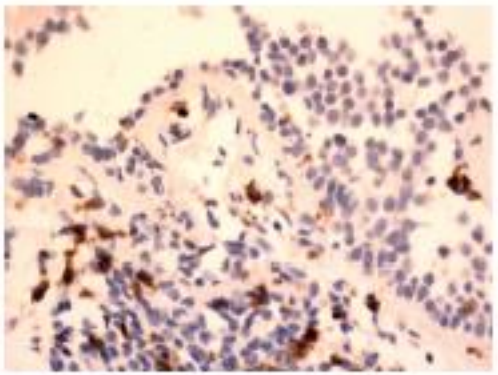
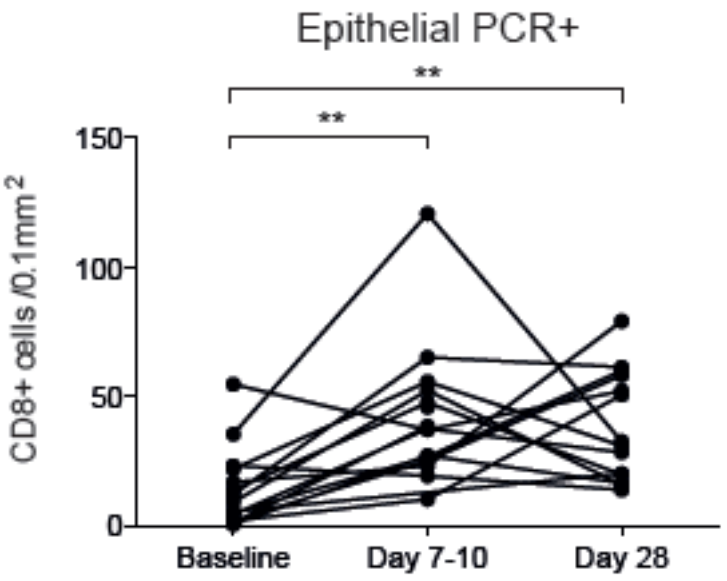
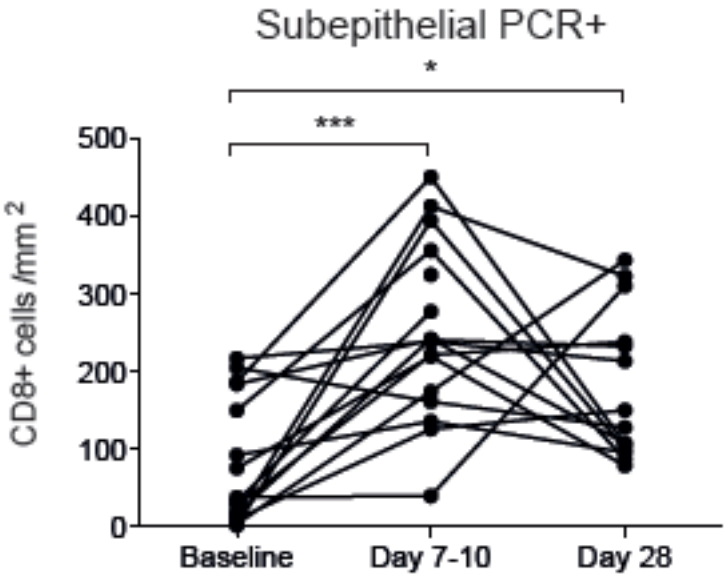
T cells infiltrate respiratory mucosa











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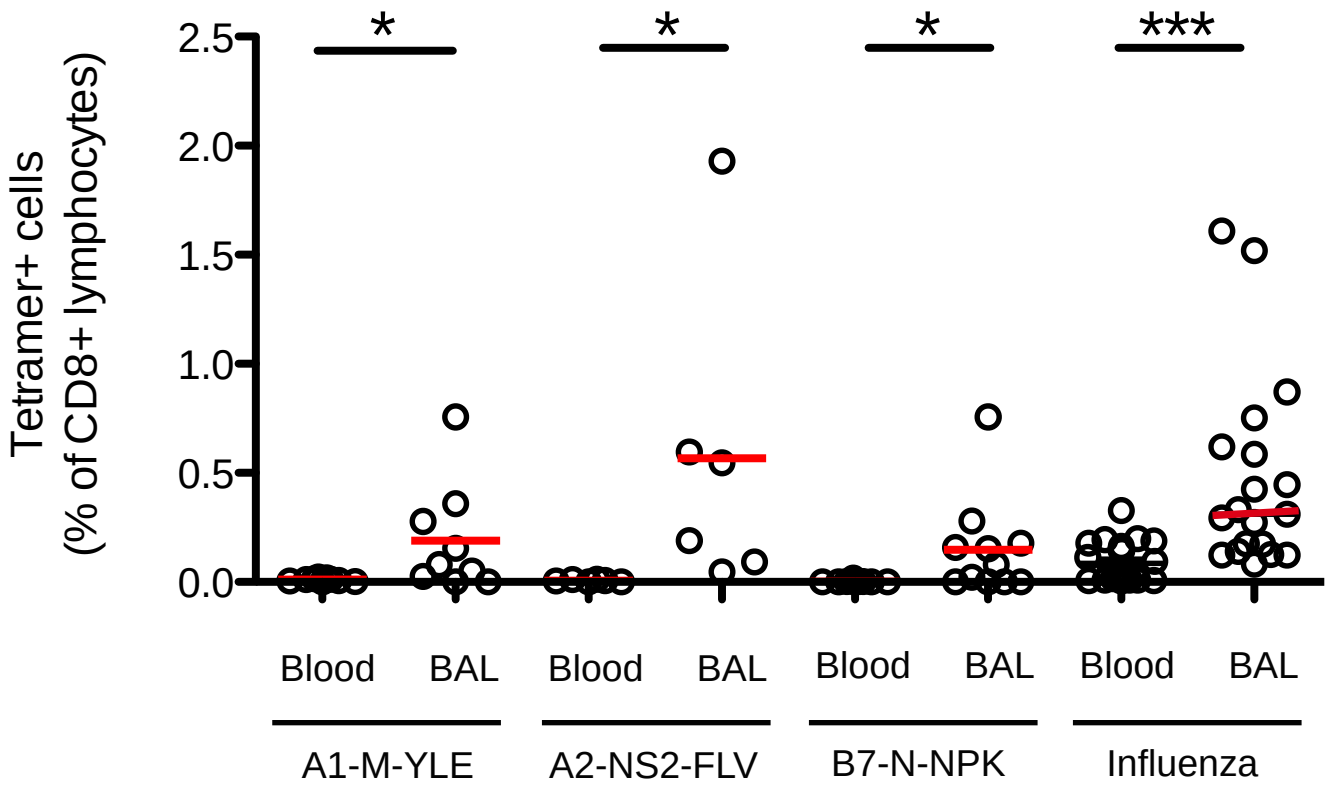
RSV-specific CD8+ Trm cells are enriched in BAL at rest



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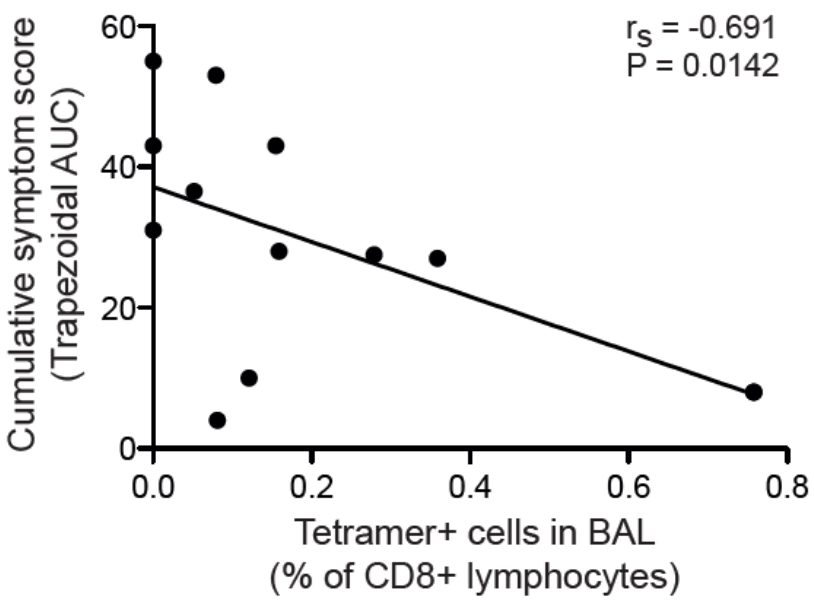
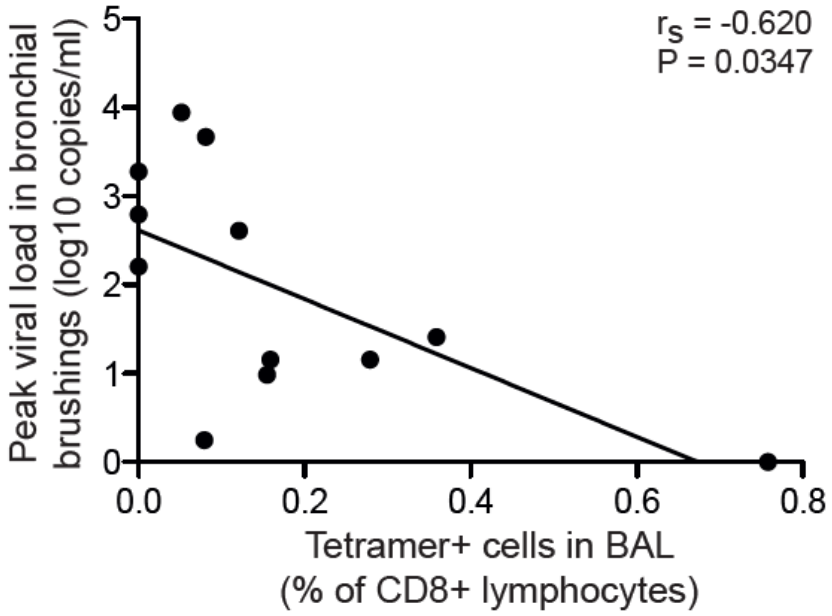
RSV-specific memory CD8+ T cells correlate inversely with disease

Symptoms



Viral load



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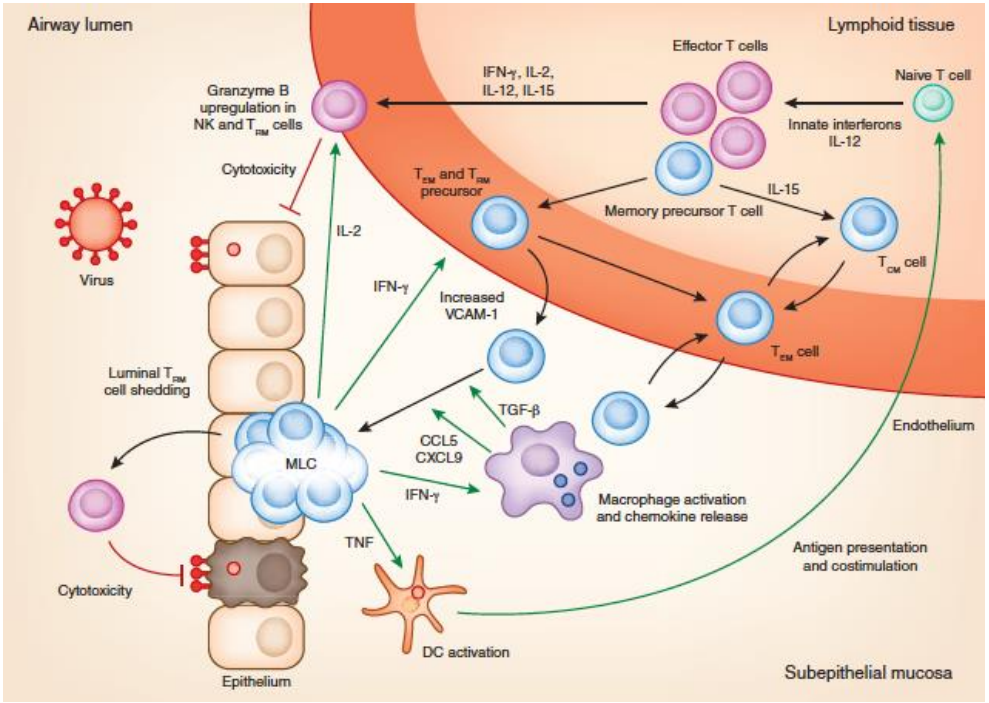
Resident memory T cells

- Tissue-resident memory T cell subset
  - Do not recirculate
- Possibly same precursors as effector memory T cells
- CD8+ Trm cells express CD103 & CD69
- In mice, lung Trm cells preferentially protect against influenza



Chiu & Openshaw, Nat Immunol 2015

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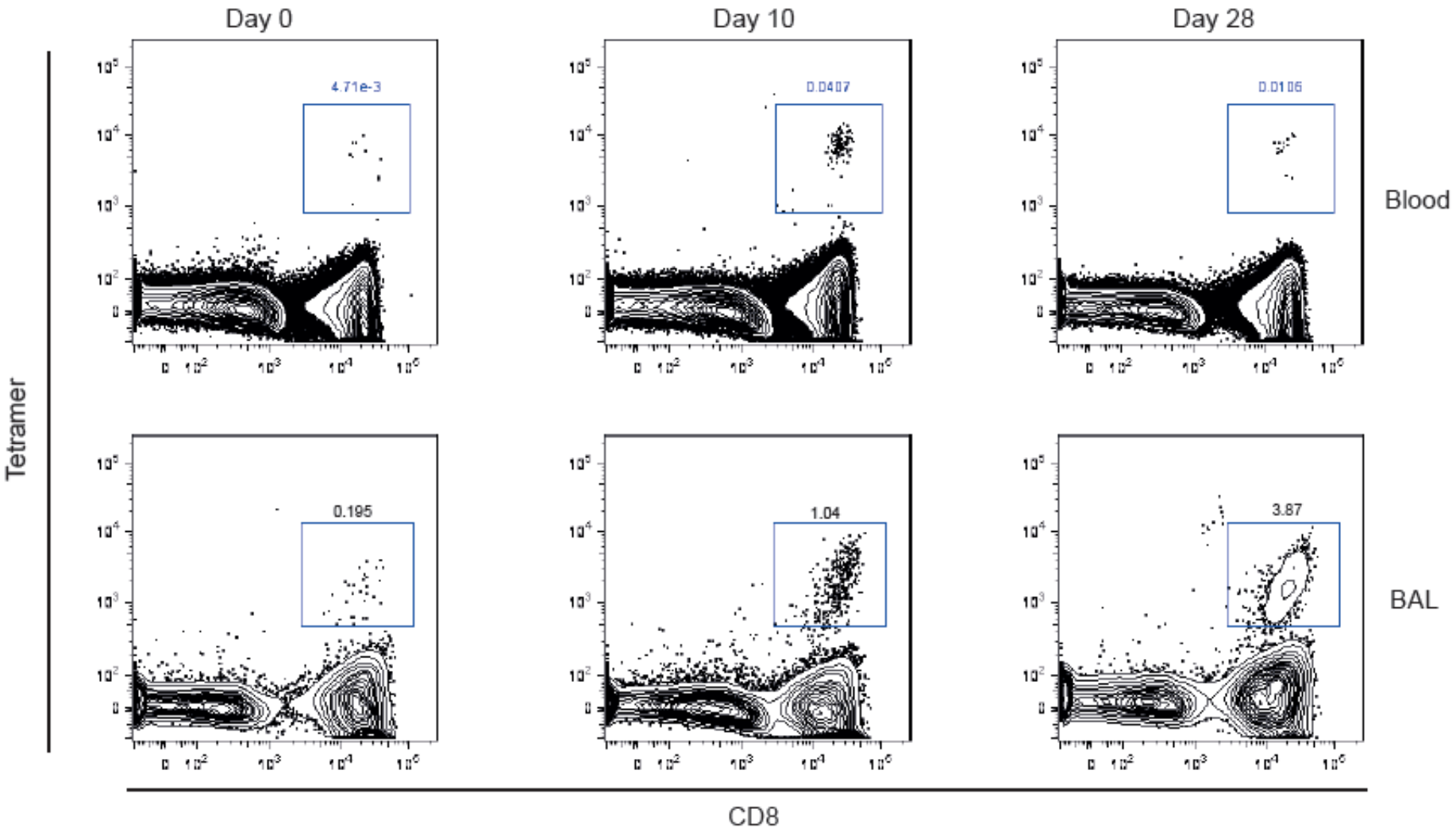
RSV-specific CD8+ T cells in blood vs BAL



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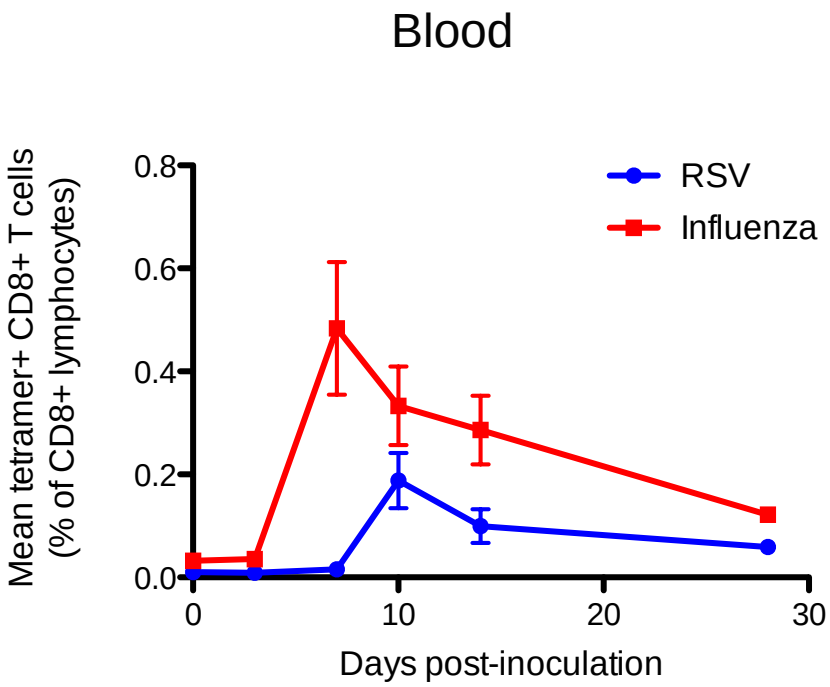
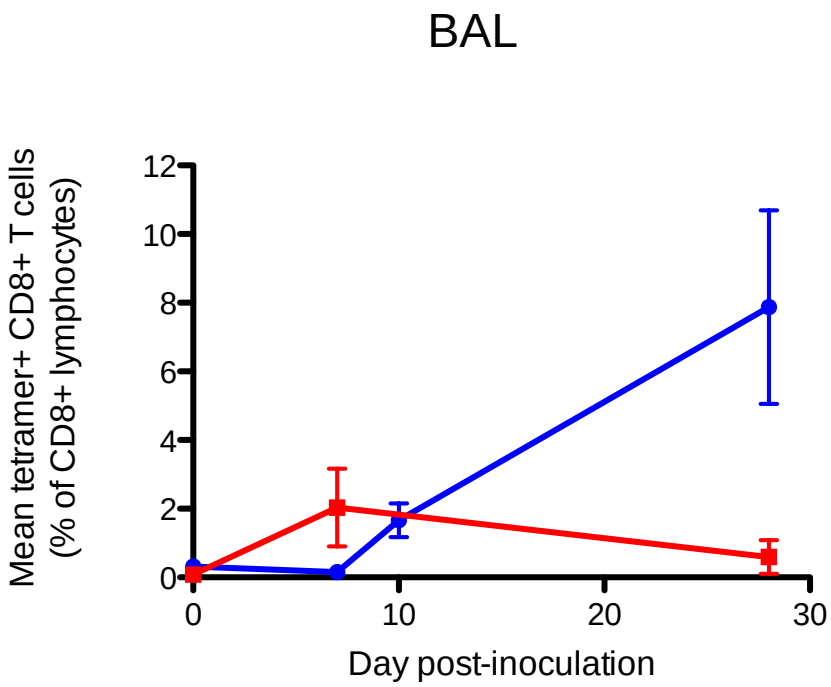
What drives accumulation of RSV-specific Trm cells?





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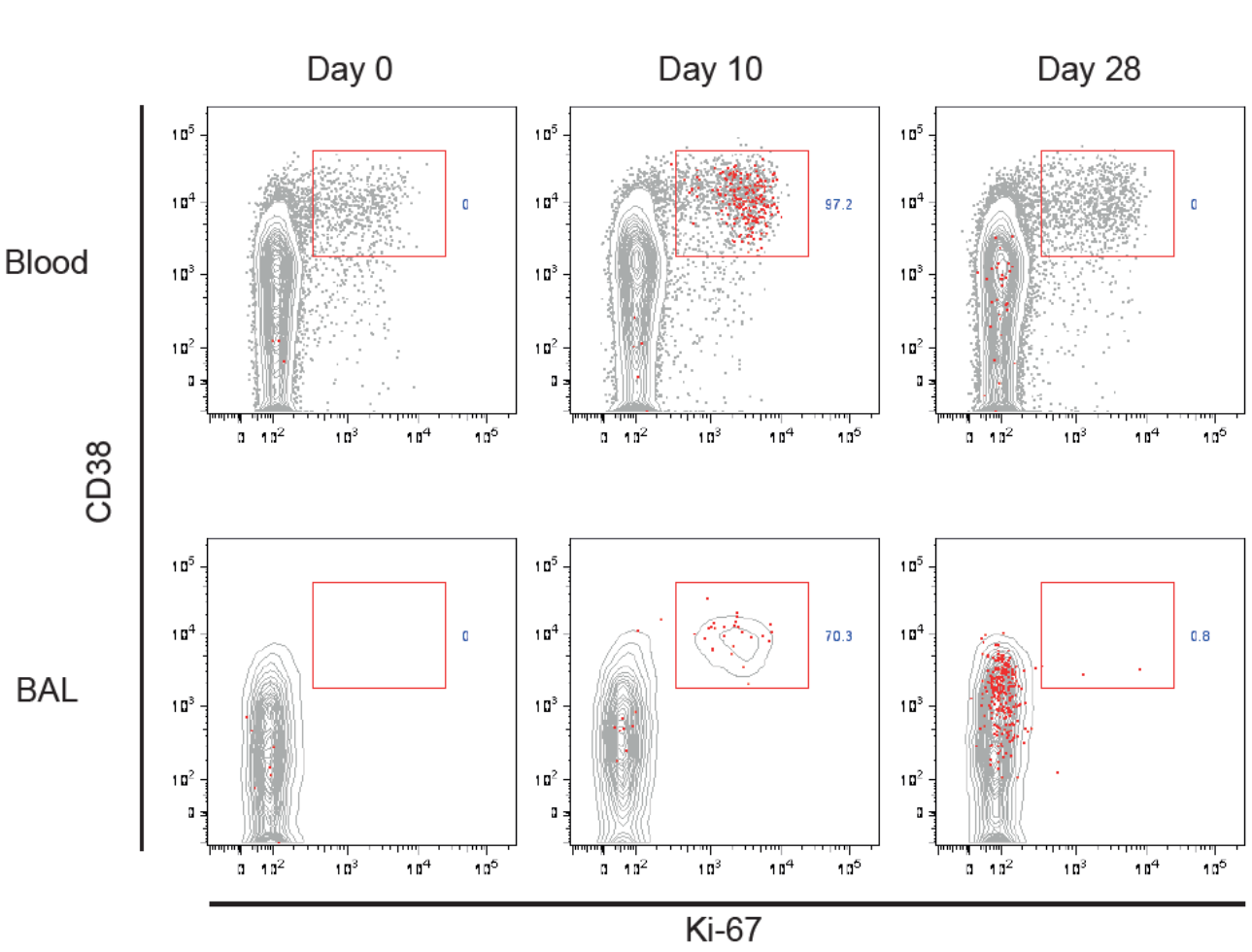
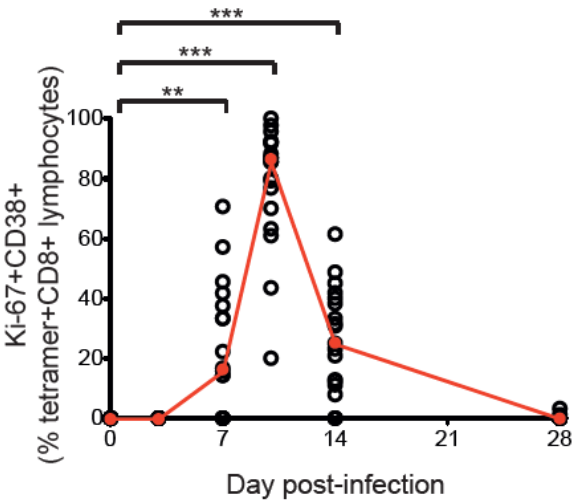
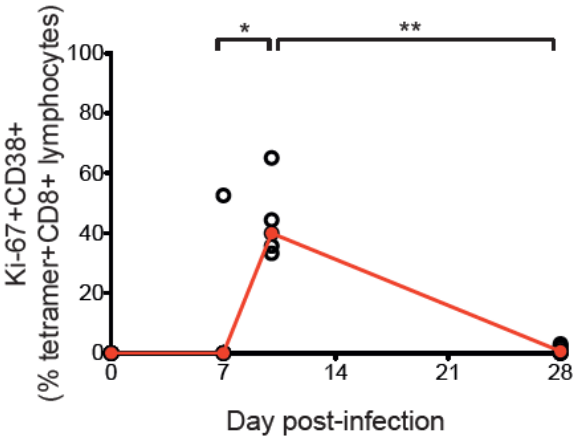
Trm accumulation is not driven by proliferation







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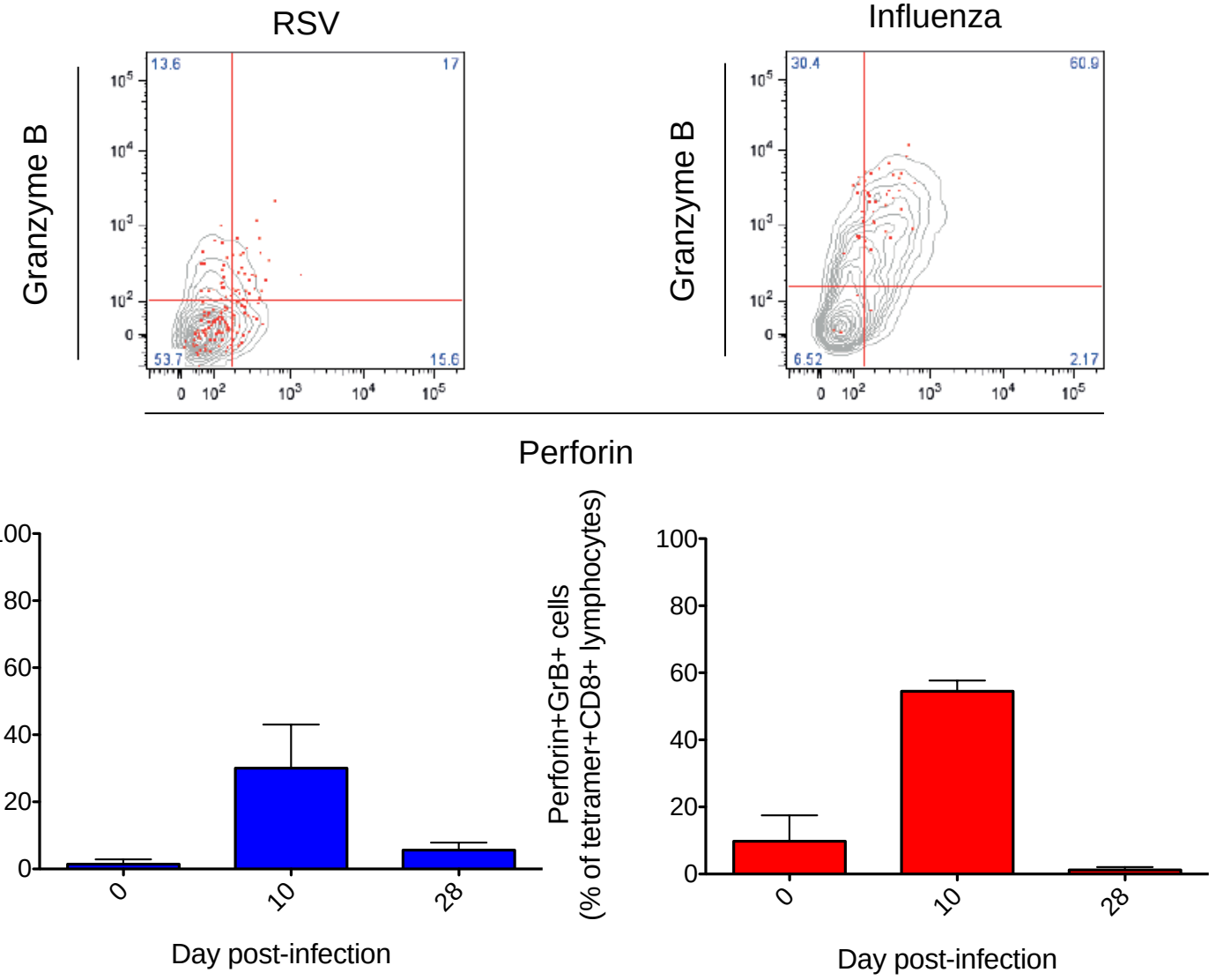
"Quality" of Trm cells following RSV vs influenza



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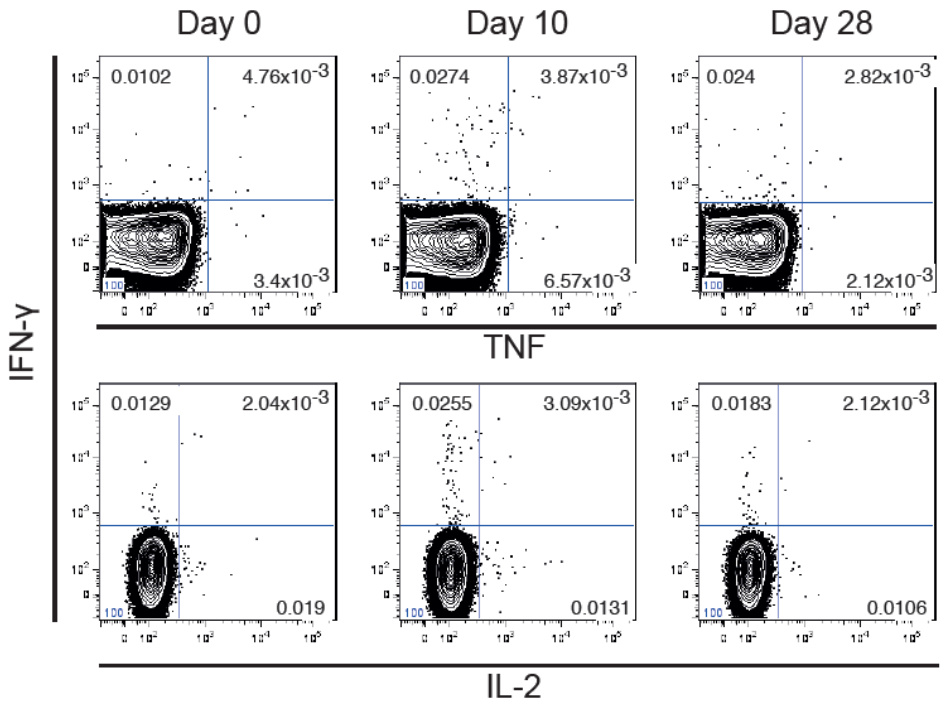
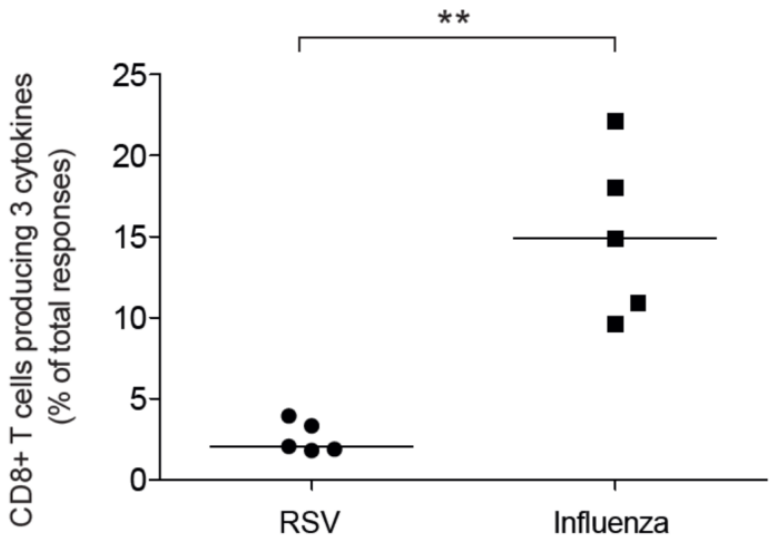
Impaired functionality of RSV-specific CD8+ T cells





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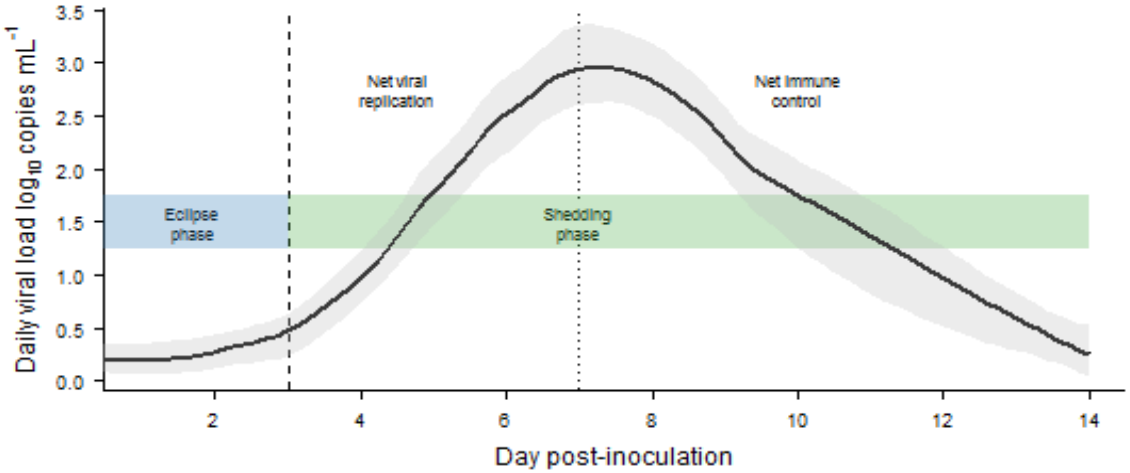
"Eclipse" phase is immunologically active



Nasosorption using SAM

Nasal curettage using a Rhino-probe

Ross *et al.* BMJ Open 2015

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Conclusions

- Experimental human infection bridges observational study & pre-clinical models
- Layers of protection against infection and/or disease
  - Pre-existing protective/immune mechanisms
    - Antimicrobial peptides
    - Secretory IgA
    - Systemic IgG if at high enough (supraphysiological?) level
  - Mucosal immunity
    - Resident memory T cells
  - Immediate/early antiviral responses during pre-symptomatic phase

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Mun Lim
Iris Vlachantoni
Suzie Paterson
Jake Dunning
Peter Openshaw

Hiromi Uzu
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John Sidney
Rafi Ahmed
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MRC Medical Research Council

wellcome trust

NHS National Institute for Health Research

Platform foR European Preparedness Against (Re-)Emerging Epidemics PREPARE

BIOVACSAFE

efpia

imi Innovative Medicines Initiative