



Immune cross-opsonisation within *emm*-clusters following group A streptococcus skin infection

Broadening the scope of type-specific immunity

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Group A Streptococcus



Large range of clinical manifestations

- Non-Invasive
- Invasive
- Post-streptococcal sequelae



infantigo.xyz

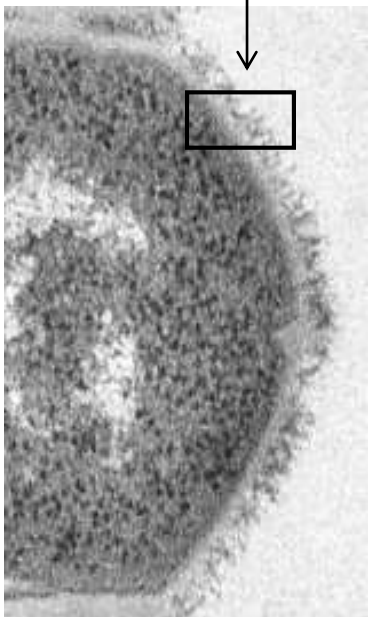


James Heilman, MD

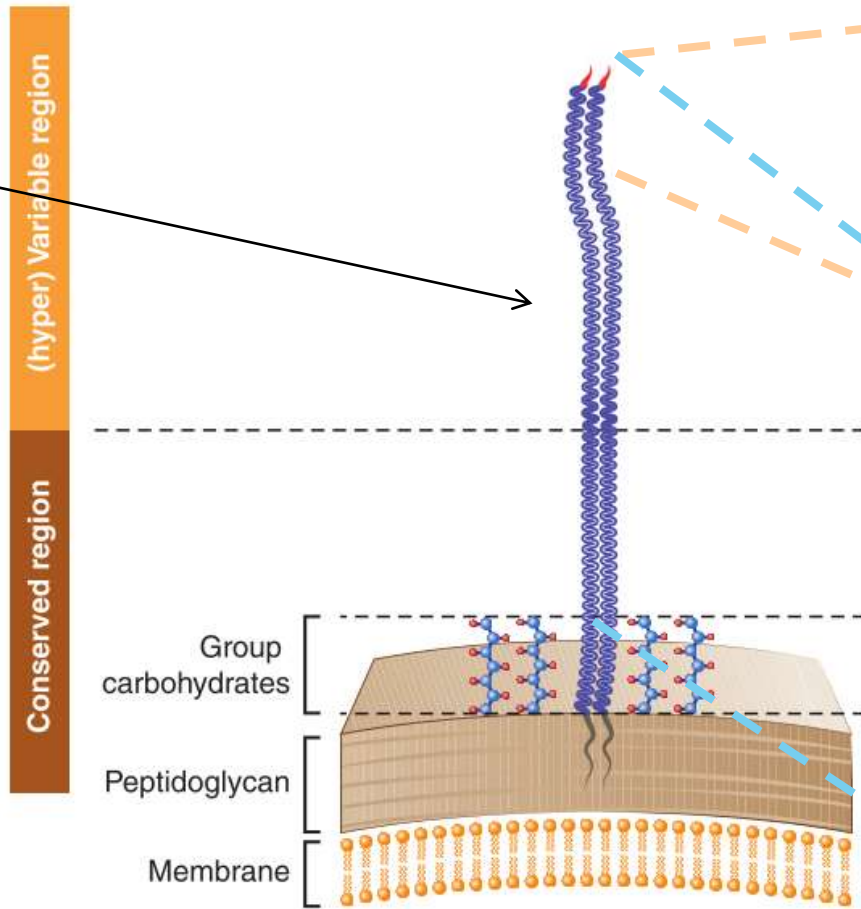
Significant global disease burden

- Each year:
 - >111 million cases of impetigo
 - >616 million cases of pharyngitis
 - >660,000 cases of invasive GAS disease causing >160,000 deaths per year
- Between 15 and 19 million people living with rheumatic heart disease causing between 230,000 to 290,000 deaths per year

The GAS M protein



M protein



McMillan et al., 2013 CMI

emm-typing:

Beal, JCM, 1996

223 *emm*-types defined on:

- the sequence of the 180 nucleotides encoding for the 50 first amino-acids of the mature M protein

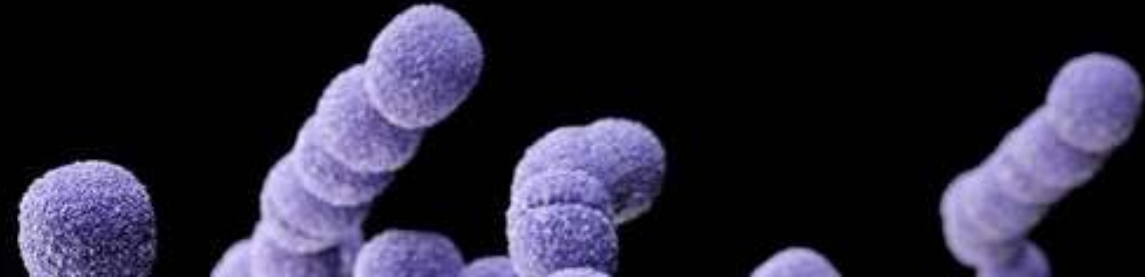
emm-clusters:

Sanderson-Smith, JID, 2014

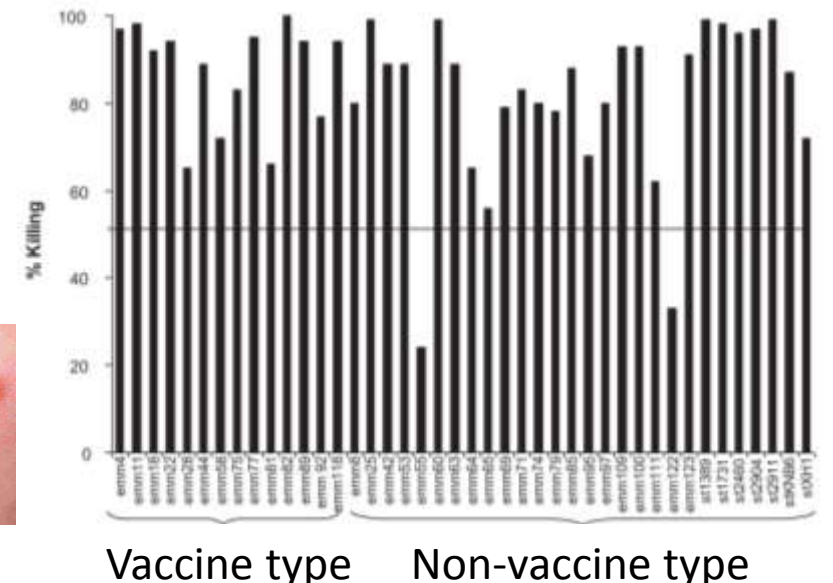
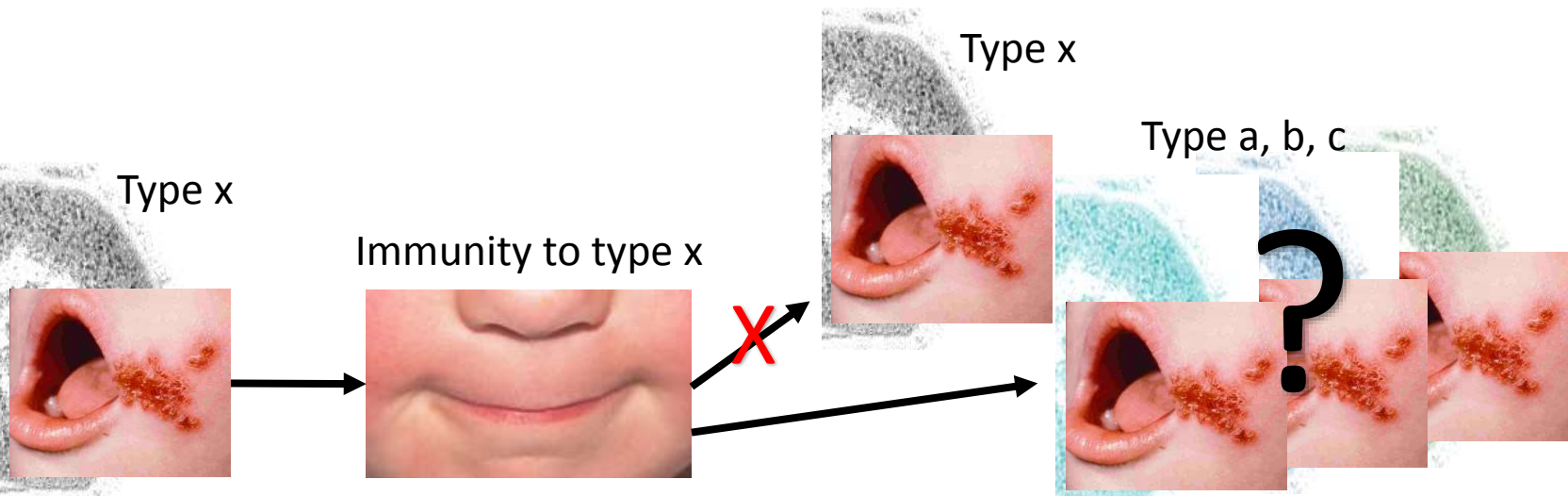
48 *emm*-clusters defined on:

- the entire sequence of the mature M protein
- the M protein binding capacities to 6 host serum proteins (IgG, IgA, C4BP, Fibrinogen, Plasminogen and Albumin)

Immunity and Vaccines



- Vaccine candidates target immunogenic but variable regions or conserved but less immunogenic regions of the M protein
- *emm*-type-specific immunity develops from infection but are >200 *emm*-types
 - However where there is more strain diversity there is lower genetic diversity
- Leading vaccine is 30-valent but also opsonised 38 of 47 non-vaccine types
 - Dale et al., Vaccine 2011 and 2013



A background image showing a series of purple, spherical particles, likely representing virus particles, arranged in a diagonal line from the top left towards the bottom right. The particles have a textured, bumpy surface. The background is black.

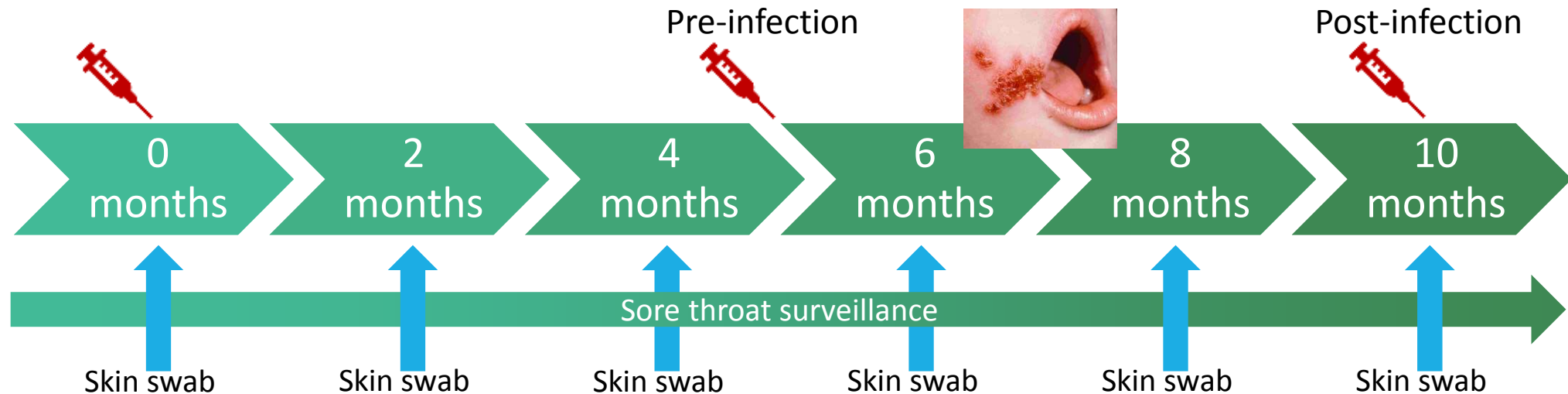
Investigating immune cross-protection in an endemic setting

Study design and results

Study design and samples



- 2006: large prospective cohort study of GAS infections in Fijian school children
 - Steer et al, PIDJ 2009; Steer et al, PLoS NTD 2009



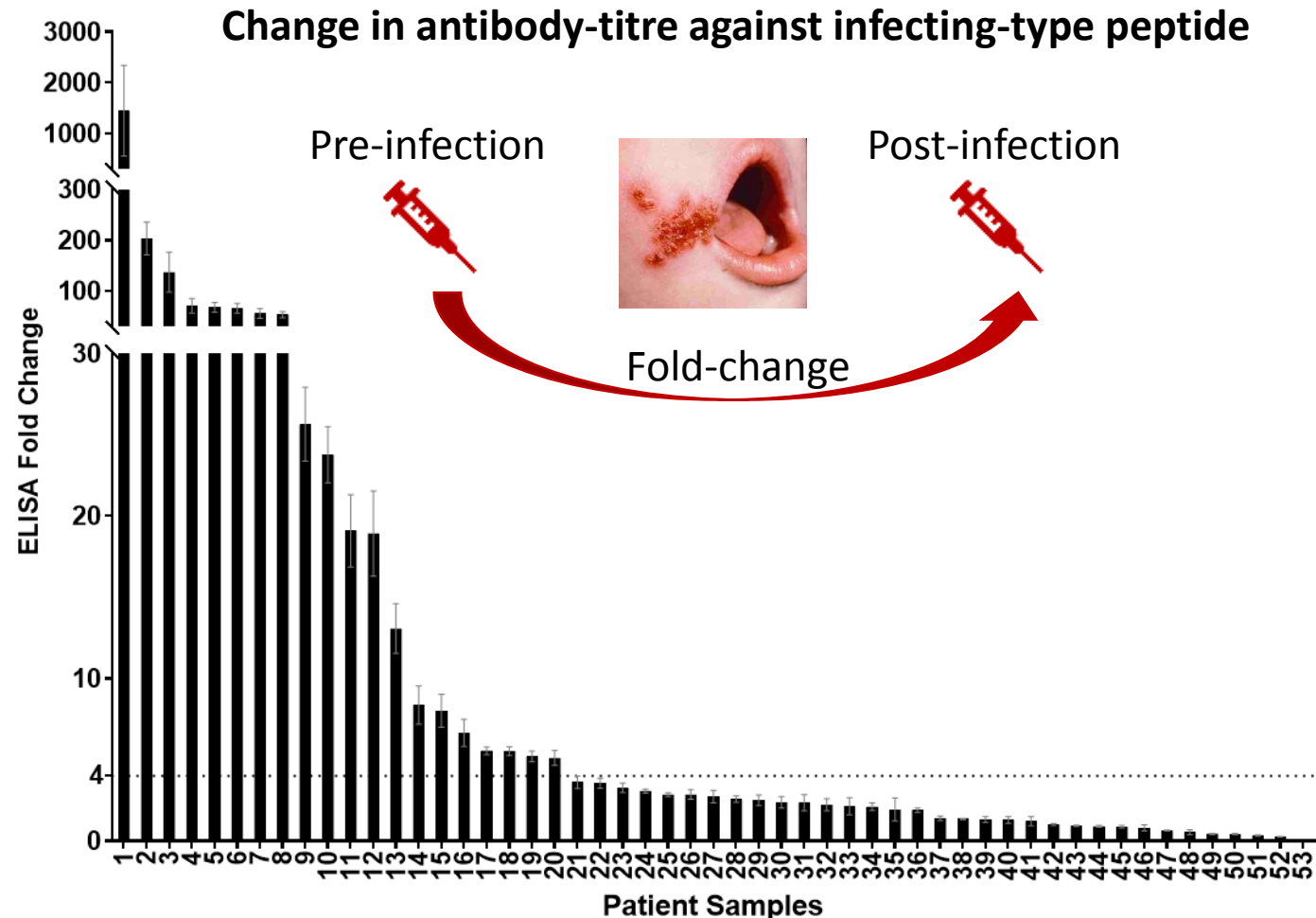
- Comparison of pre-infection and post-infection sera

Infecting *emm*-type ELISA



Sample selection

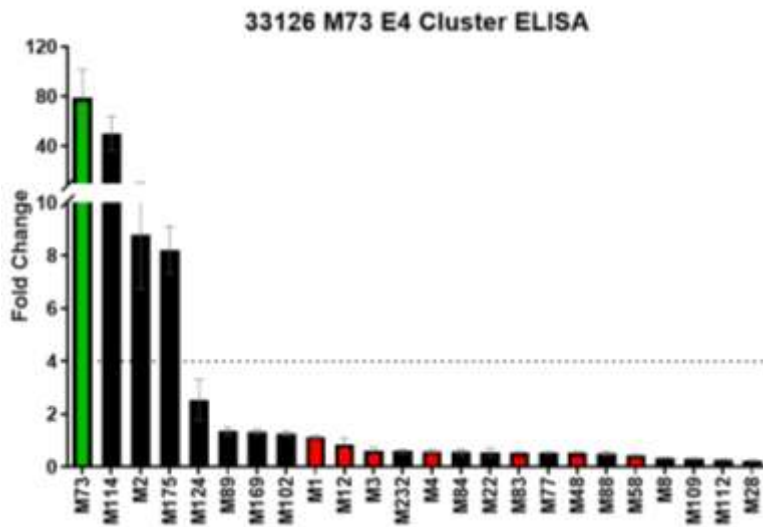
- Clusters E4, E6 and D4
 - 67 *emm*-types
 - >35% of GAS infections worldwide
 - Different binding properties, epidemiological characteristics and performance in 30-valent vaccine
- 53 samples with one infection only between time points
 - E4 (13), E6 (16), and D4 (24)



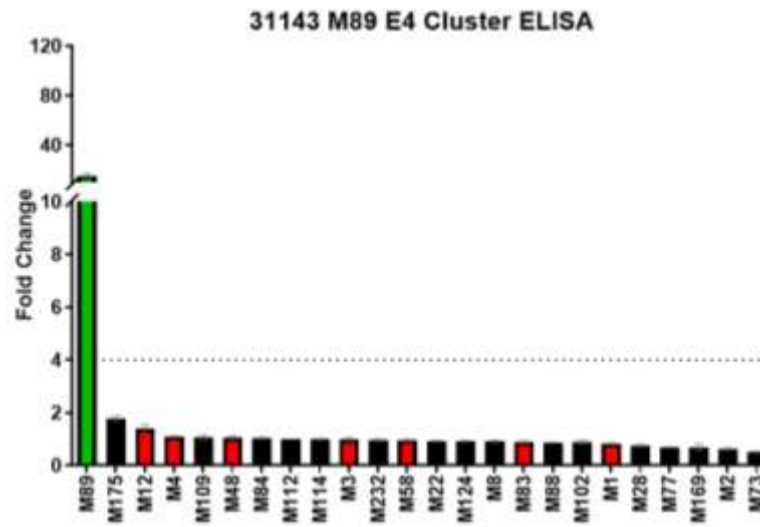
Cluster-related *emm*-type ELISA



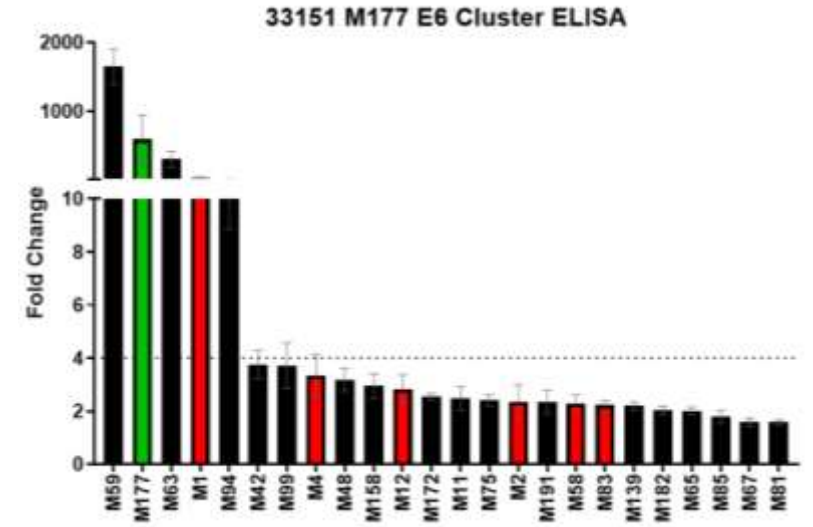
- 3 response patterns defined from individual's antibody responses



A) high response to infecting-type and *emm*-cluster-related peptides



B) high response to infecting-type peptide only



C) high response to infecting-type, *emm*-cluster-related and non-cluster-related peptides

Green = infecting-type peptide

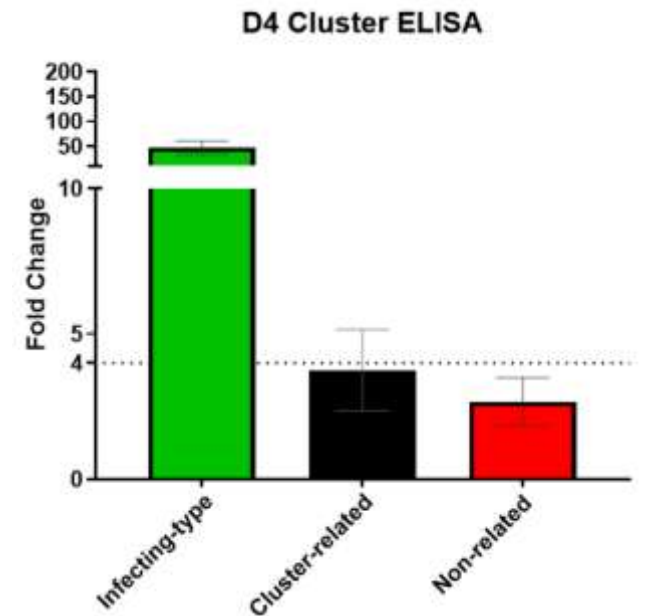
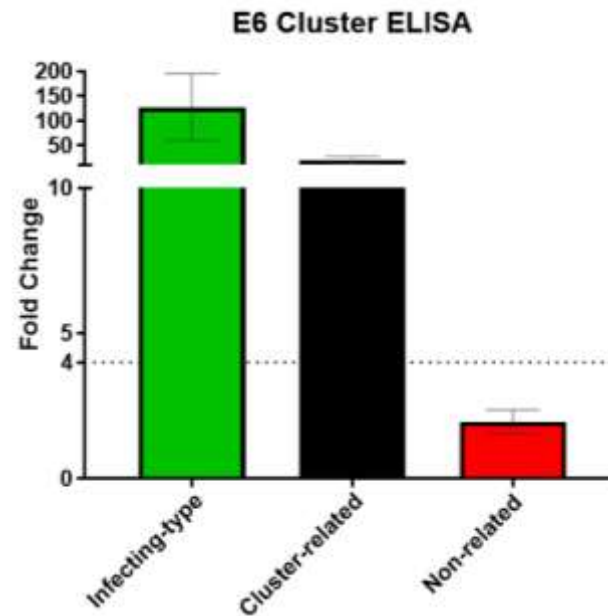
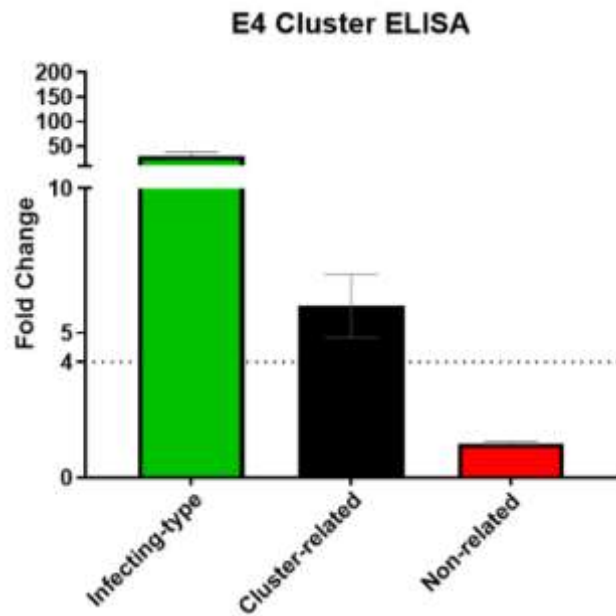
Black = *emm*-cluster-related peptide

Red = non-cluster related peptide

ELISA results by cluster



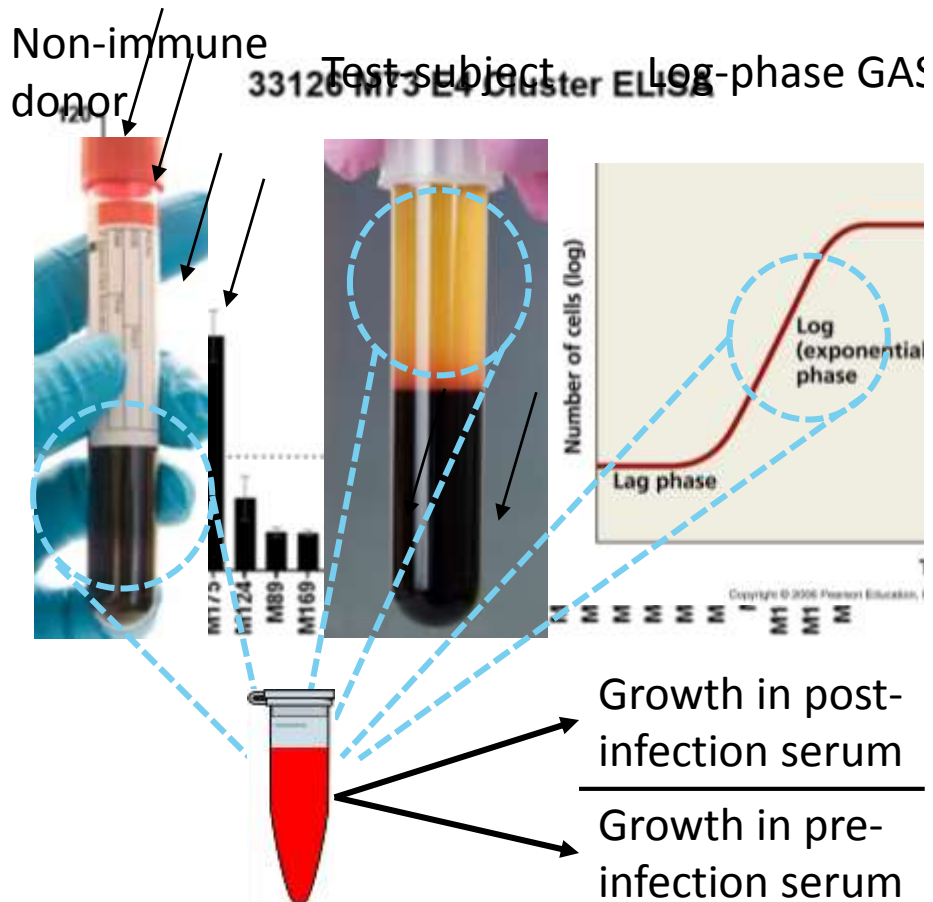
- Pooling responses shows a difference between cluster-related and non-related for E4 and E6 clusters but not D4 cluster



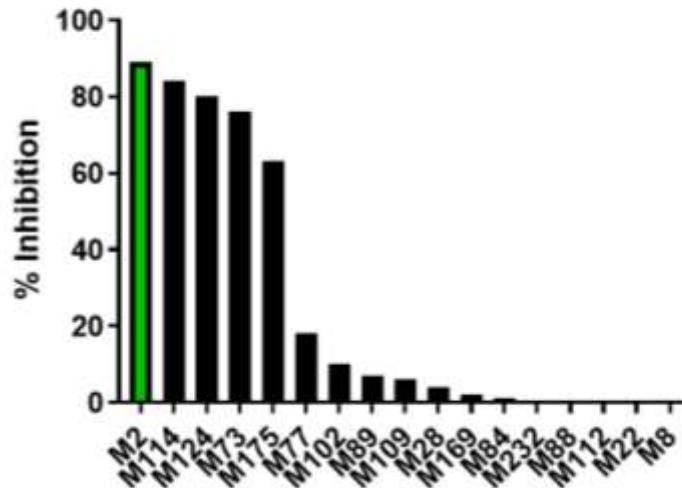
Green = infecting-type peptide
Black = *emm*-cluster-related peptide
Red = non-cluster related peptide

Functional studies of cross-reactive antibodies

Bactericidal assays



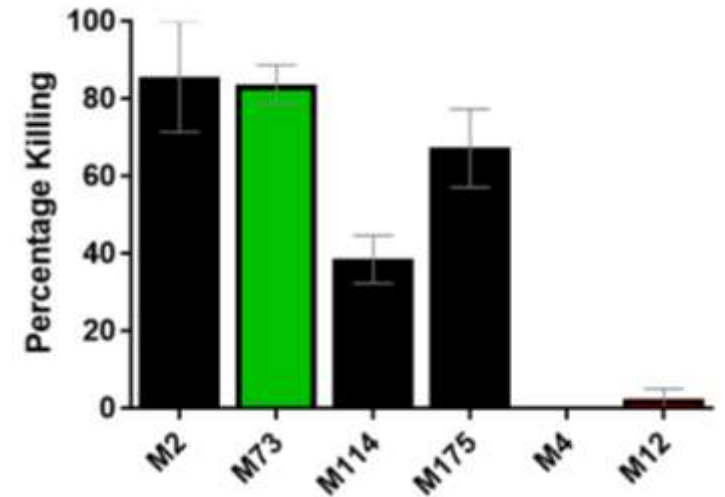
Competitive inhibition ELISA from synthetic M2 vaccine vs. E4 peptides



Data from Dale et al., 2016 Vaccine

Percentage Killing

33126 M73 Bactericidal Assay

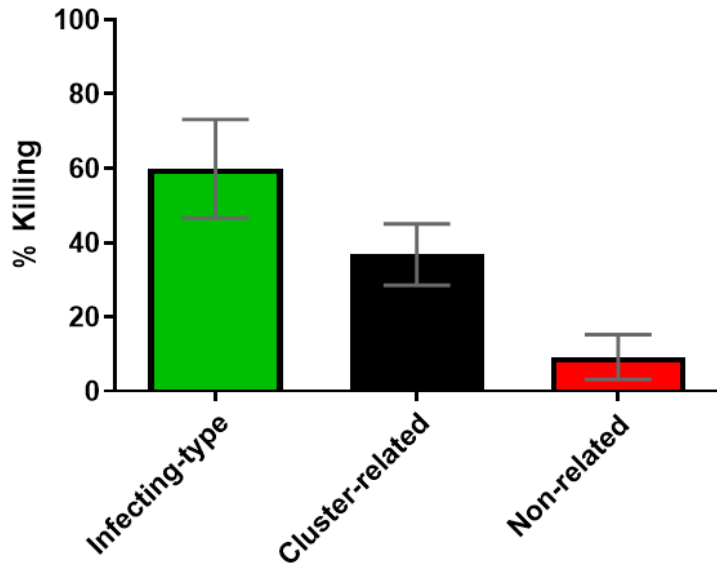


Green = infecting-type bacteria
 Black = *emm*-cluster-related bacteria
 Red = non-cluster related bacteria

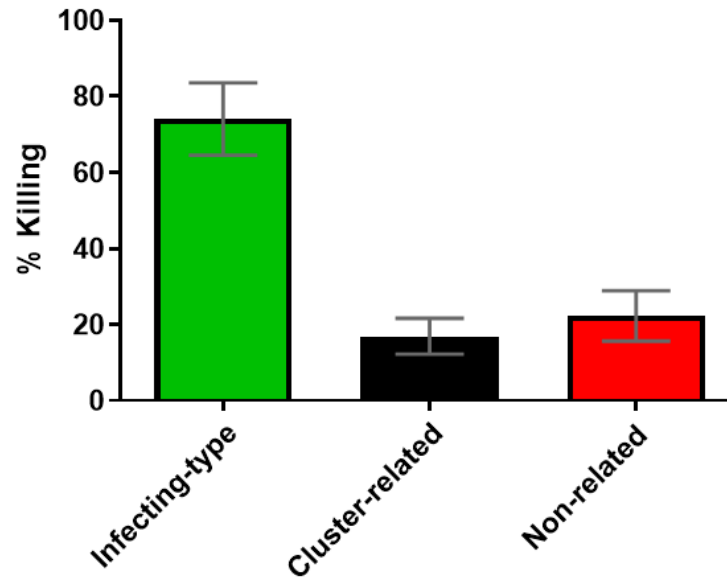
Bactericidal results by cluster



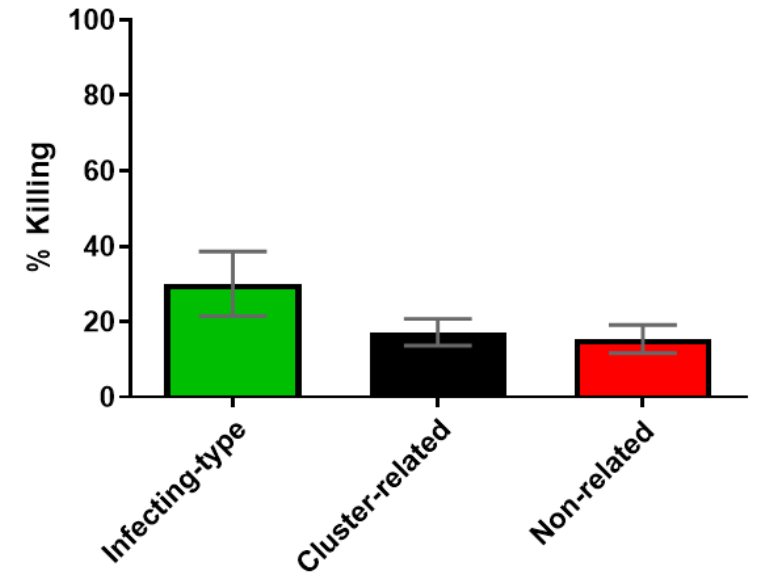
E4 Bactericidal Assay Results



E6 Bactericidal Assay Results



D4 Bactericidal Assay Results



Green = infecting-type bacteria

Black = *emm*-cluster-related bacteria

Red = non-cluster related bacteria

Summary and implications



- For E4 and E6, higher antibody titres observed against cluster-related *emm*-types than non-cluster related
- For E4, cross-reactive antibodies also cross-opsonise some cluster-related *emm*-types
- Immunity following GAS skin infection in endemic settings appears to be a combination of type specific and cluster related immunity
- Cross-protective immunity would allow broader coverage from multivalent vaccines than previously predicted

Acknowledgements

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