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Immune cross-protection within emm-clusters following group A Streptococcus skin infection: broadening the scope of type-specific immunity

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Background: The group A streptococcus (GAS) is an important human specific pathogen causing a range of clinical phenotypes, including impetigo which is particularly prevalent in developing nations in Oceania. The GAS M protein, by which strains are differentiated into >220 different *emm*-types, is the most immunogenic GAS virulence factor. A major obstacle for vaccine development is that immunity following infection has traditionally been thought to be restricted to single *emm*-type immunity. However, recent evidence has led to the hypothesis of immune cross-reactivity between M proteins, and the advent of the *emm*-cluster typing system provides a useful framework for the investigation of cross-protective immunity between functionally similar M proteins within *emm*-clusters.

Material/methods: We investigated the human serological response to GAS impetigo in 457 Fijian school children, focusing on 3 major clusters (E4, E6 and D4). Pre- and post-infection sera from participants with a single episode of GAS impetigo were assayed by ELISA with N-terminal M-peptides and bactericidal assays, against the infecting-type strain, *emm*-cluster-related strains and non-related strains.

Results: A total of 53 participants had a single infection from an *emm*-type belonging to cluster E4, E6 or D4. Of these, 17 paired sera demonstrated a ≥4-fold increase in antibody titre against the infecting-type. When tested against all cluster-related M-peptides and non-cluster related M-peptides, we observed that 9/17 (53%) paired sera also demonstrated a ≥4-fold increase to cluster-related strains. When grouped by cluster, the average fold-change to cluster-related *emm*-types in E4 and E6 was >4-fold, (5.9-fold and 19.5-fold respectively) but for D4 was <4-fold (3.8-fold). The mean differences in average fold-change between cluster-related and non-related strains were: E4 cluster 4.8 (95% CI: 8.0 to 1.5); E6 cluster 17.5 (95% CI: 42.2 to -7.1); D4 cluster 1.1 (95% CI: 7.0 to -4.9). This indicates much higher levels of antibody cross-reactivity within a cluster than outside a cluster for the E4 and E6 clusters. The 17 paired sera with a ≥4-fold increase in antibody titre to the infecting type were used in bactericidal assays against selected cluster-related and non-related strains. Numerous instances of cross-reactive killing were observed, however the responses were variable. Percentage killing values were grouped by cluster and the mean differences between cluster-related and non-related killing were in favour of cross opsonisation for the E4 cluster 27.6% (95% CI: 51.4 to -3.7) but not for the E6 cluster (-5.4%; 95% CI: 11.3 to -22.0) and the D4 cluster (1.8%; 95% CI: 12.2 to -8.6).

Conclusions: These data confirm the existence of M-type specific immunity, but also suggest that cross-reactive immune responses occur following skin infection in endemic countries, and that these responses frequently align with *emm*-clusters. These results raise new hopes for multivalent vaccine with broad coverage.