The impact of chronic whipworm infection on vaccine mediated immunity

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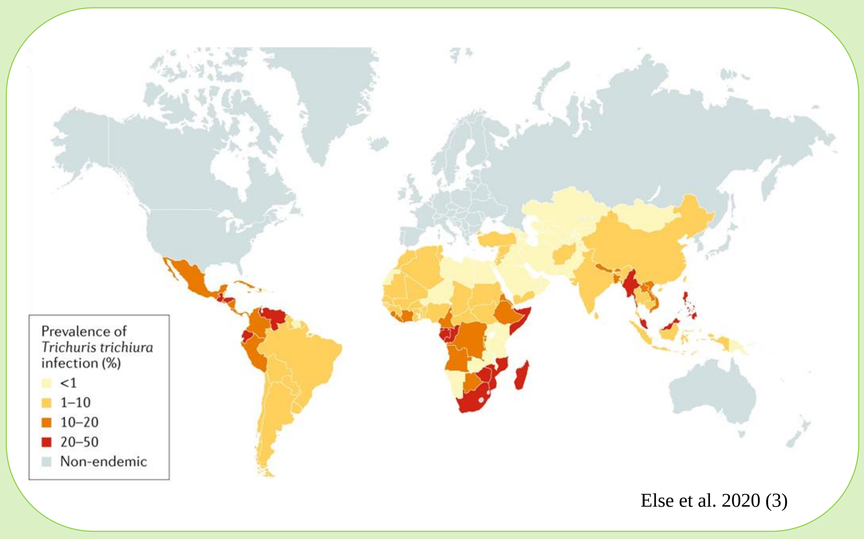
Background

- *Trichuriasis* affects **~465 million people worldwide** resulting from infection with *T. trichiura*, (whipworm).
- **The low effectiveness of drugs** currently used to control *T. trichiura* has driven the search for alternative treatments including **anti-*Trichuris* vaccines**.
- The ability of some parasites to dampen vaccine-mediated immune responses of their hosts (1-2) poses a challenge for vaccine design.
- To be considered as viable alternatives these novel vaccines may need to work in the context of pre-existing worm infections.



Else et al. 2020 (3)

Experimental Design

To investigate the ability of *Trichuris spp.* to dampen vaccine mediated immunity in their hosts here we employ a crude vaccine composed of excretory/secretory products against the *Trichuris* mouse model, ***T. muris***, in **C57BL/6 mice**.

Experimental Groups

A. Mice vaccinated with 100µg of E/S in alum via subcutaneous injection and then challenged with 30 *T. muris* eggs (a low dose infection).

B. Mice vaccinated with PBS in alum and then challenged with a low dose *T. muris* infection.

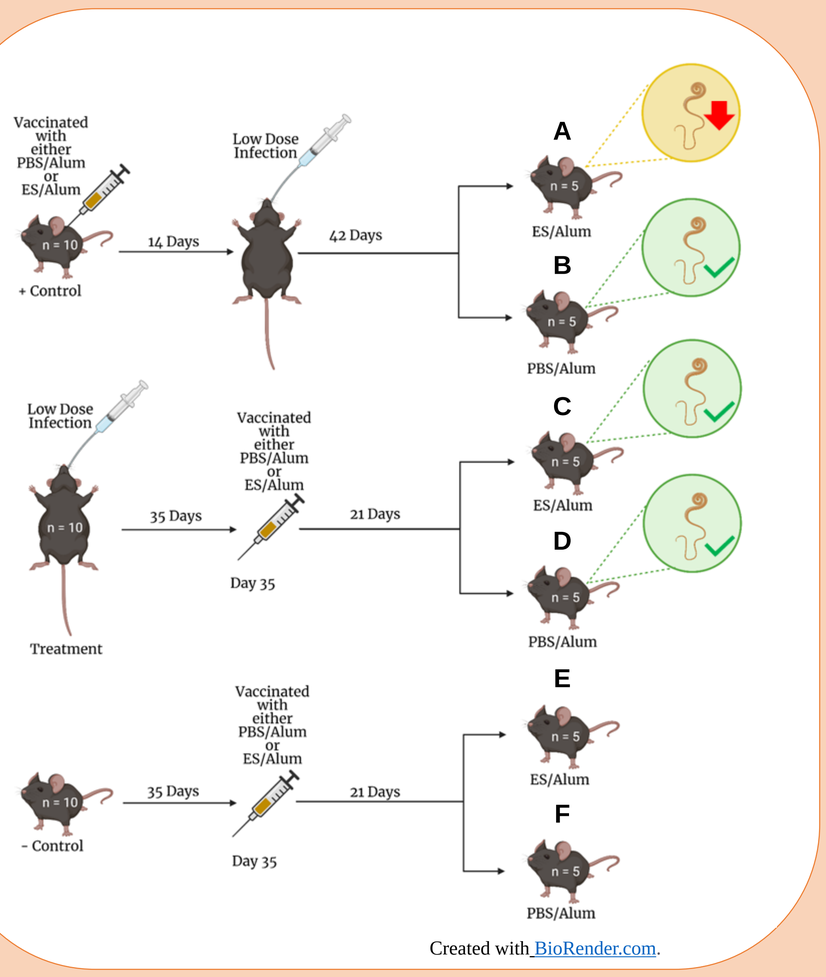
C. Mice received a low dose *T. muris* infection and then vaccinated with E/S in alum.

D. Mice received a low dose *T. muris* infection and then vaccinated with PBS in alum.

E. Mice were vaccinated with ES in alum and received no infection.

F. Mice were vaccinated with PBS in alum and received no infection.

Following euthanasia the large intestine, serum, and mesenteric lymph node (MLN) were harvested. MLN cells were subsequently restimulated with E/S over 48hrs. Worm burdens were counted from the large intestine. Relative quantities of E/S specific serum IgG1 and IgG2c antibodies along with IFN-γ produced by MLN cells were determined via **ELISA assays**. Other cytokines of interest produced by MLN cells were quantified via **cytometric bead array (CBA)**. All statistical differences were confirmed via the Kruskal–Wallis non-parametric ANOVA statistical test.



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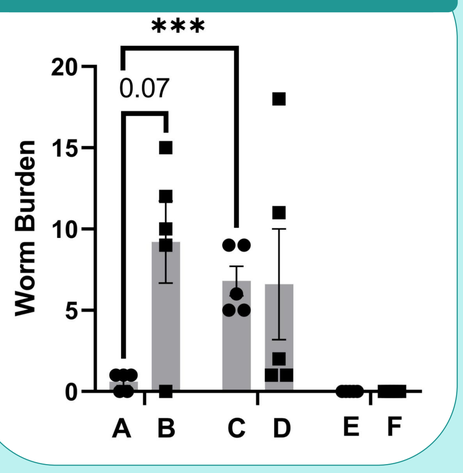
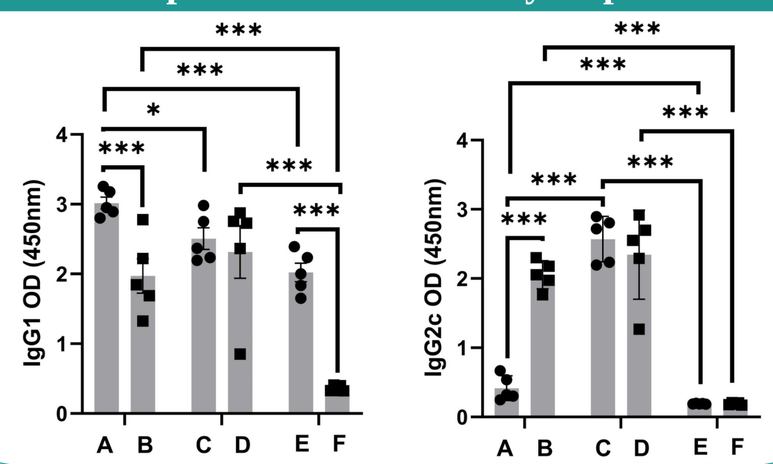
Results

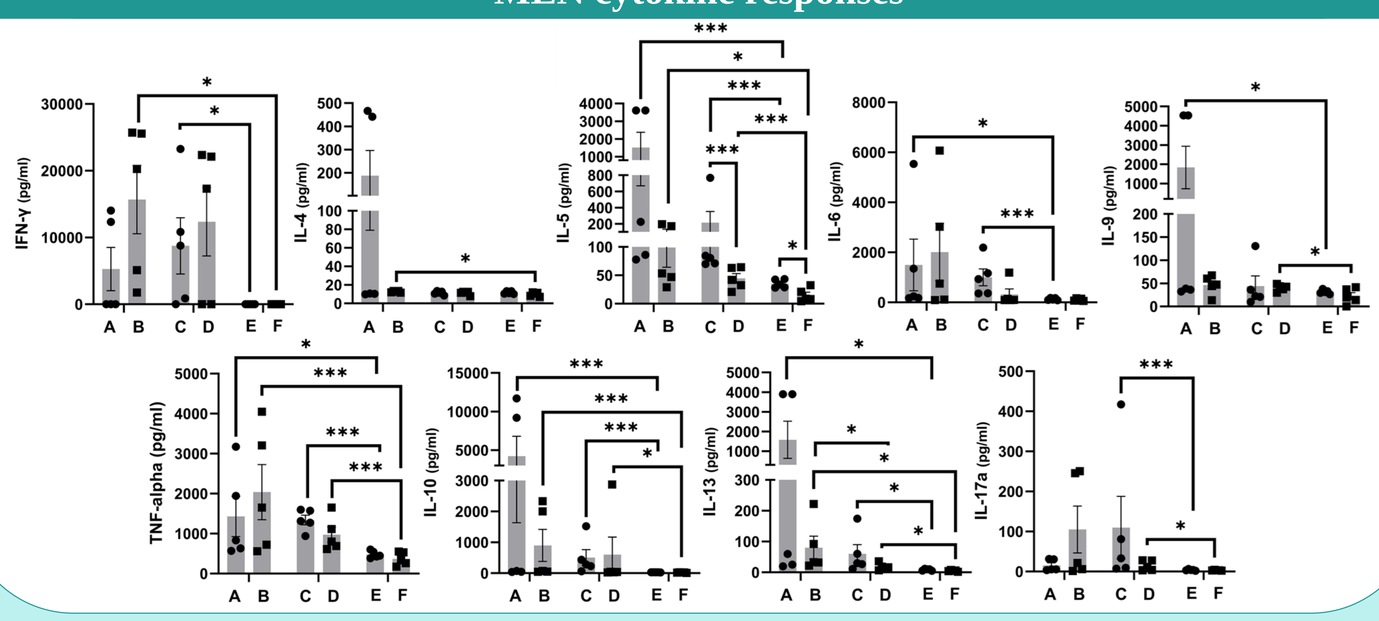
Worm Burden



E/S specific serum antibody response



MLN cytokine responses



Key Findings

1. **Mice vaccinated with E/S prior to low dose *T. muris* challenge infection display a resistant phenotype with low worm burdens or sterile immunity (GROUP A) (4).**
   - As illustrated by a biologically significant reduction in worm burden, high-levels of E/S specific IgG1 serum antibodies accompanied by relatively low levels of IgG2c, and a general skewing of the local immunity (e.g. MLN cells) towards a Th2 immune response, when compared to PBS vaccinated counterparts.

2. **Mice chronically infected with a low dose *T. muris* infection and then vaccinated with E/S exhibit a susceptible phenotype with high worm burdens (GROUP C).**
   - Exemplified through their high levels of IgG1 and IgG2c E/S specific serum antibodies, generally mixed Th1 and Th2 local immune responses, and harbouring similar worm burdens to mice in the PBS vaccinated treatment group. However, the MLN cells of these mice did express significantly more IL-5 compared to PBS vaccinated counterparts.

Conclusions

1. **E/S vaccination in C57BL/6 mice that canonically results in sterile immunity or significant reduction in worm burden against subsequent *T. muris* infection is incapable of protecting against a pre-existing *T. muris* infection.**

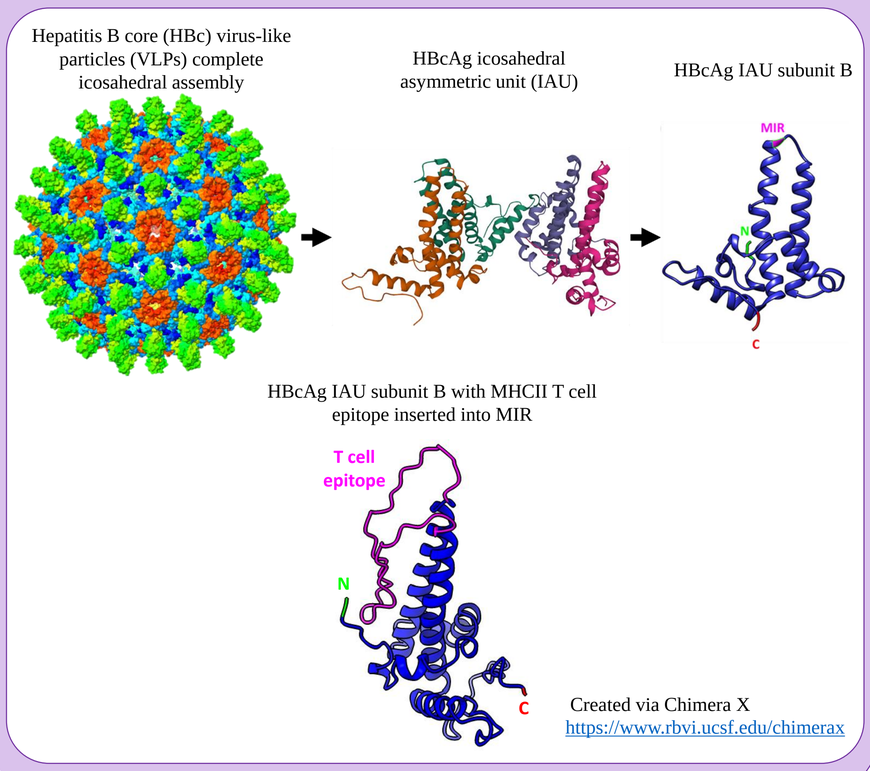
2. **Whether this results from the parasite priming the host's immune system towards a susceptible phenotype (e.g. Th1 oriented) or other factors remains unclear.**

A potential barrier to vaccine mediated immunity in *T. trichiura* endemic areas

If this lack of efficacy against pre-existing chronic infections extends to vaccines targeting *T. trichiura* it will have **implications on the development and delivery of such vaccine candidates as the majority of *T. trichiura* infections in the field are chronic** and result from exposure to low doses of eggs (5). For instance, novel anti-*T. trichiura* vaccines may have to be administered within existing paediatric programmes prior to the exposure and subsequent infection with the parasite.

Future Work

- **To modify the anti-*T. trichiura* vaccine candidate developed by Zawawi et al. (6)** to increase vaccine efficacy above the 50% reduction in worm burden that it currently provides and test efficacy in the context of pre-existing infections.
- This vaccine candidate is comprised of an even mix of four Hepatitis B core (HBc) virus-like particles (VLPs) which have had an MHCII T cell epitope pertaining to separate *T. trichiura* antigens of interest genetically fused into their major immunodominant region (MIR).



Created via Chimera X
https://www.rbvi.ucsf.edu/chimerax

References

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