HelmSys: The impact of helminth infections on vaccine outcomes in humans: a systematic literature review

Project type

☒ interdisciplinary pilot project ☐ cross-sector project ☐ global health postdoc fellowship

Research areas involved

☒ Biomedical sciences ☒ Public health
☐ Social sciences and humanities ☐ Engineering and other sciences

Project duration

01.2022 – 01.2023

Project team

Name	Organization	Discipline(s)
Clarissa Prazeres da Costa	Technical University of Munich	Immunology Global health
Marrium Habib	Technical University of Munich	Public health Global health
Meral Esen	University Clinic Tübingen	Clinical studies Immunology
Judith Flügge	University Clinic Tübingen	Clinical studies Immunology
Alex Siebner	University Clinic Tübingen	Clinical studies Immunology
Stefanie Klug	Technical University of Munich	Epidemiology Public health
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Case study

Introduction and background

The importance of safe and effective vaccination throughout life is paramount for global public health. Vaccination has significantly reduced childhood morbidity and mortality worldwide, primarily through initiatives like the Expanded Program on Immunization (EPI) set up by the WHO to combat deadly diseases of childhood. However, vaccine-preventable diseases (VPDs) remain a significant cause of morbidity and mortality, particularly in low- and lower-middle-income countries (LMICs), highlighting the necessity of maintaining vaccine efficacy.

Effective vaccination relies on generating robust and long-lasting immune responses in individuals. However, factors unrelated to the vaccine, such as parasitic infections like helminths, can influence vaccination outcomes. Helminths induce immunomodulatory responses in hosts, affecting not only the response to helminth-derived antigens but also to bystander antigens like vaccines.

Experimental evidence, particularly form mouse models, has suggested that helminths utilize enzymes and excretory/secretory proteins to manipulate host tissues; employ various strategies to evade host immune responses, including inducing Th2 cytokines like interleukin (IL)-4 and IL-13, which promote alternative activation of macrophages and the production of immunomodulatory molecules like IL-10 and TGF-. This causes T cell hypo-responsiveness and the generation of regulatory T and B cells, facilitating helminth survival and reproduction within the host.

The burden of helminth infections, classified as neglected tropical diseases (NTDs), is substantial, particularly in regions like sub-Saharan Africa. Helminths have complex life cycles and can persist in the host for decades, causing chronic and debilitating diseases. Their prevalence overlaps with other infectious diseases, posing significant challenges to public health efforts.

Mass drug administration (MDA) programs aim to control helminth infections, potentially reversing the immunomodulatory effects and improving vaccine responses. Albendazole, commonly used in MDA, has shown promise in enhancing vaccine responses in some studies. However, clinical trials investigating the effects of helminth treatment on vaccine efficacy have yielded mixed results, highlighting the complexity of interactions between helminths and vaccines.

Given the inconclusive evidence from individual studies, there is a need for systematic reviews to comprehensively analyze the impact of helminth infections on vaccine responses in the framework of vaccine immunogenicity, efficacy and effectiveness.

Summary of project

The *Helmsys* project aimed to investigate whether helminth infection and antihelminthic treatment affects immunogenicity, efficacy, and effectiveness of vaccines in humans in two distinct parts:

Part 1 investigated if the immunogenicity, efficacy and effectiveness of a given vaccine differ in persons infected with helminths compared to persons not infected with helminths? And part 2 investigated if anti-helminthic treatment alter the immunogenicity, efficacy and effectiveness of a given vaccine in persons infected with helminths versus those given a placebo.

This is, to the best of our knowledge, the first systematic review on this topic, and aims to analyze and address the identified gaps of the variety of study designs, often small sample, choice of study sample size, choice of study design, selection bias, complexity of population characteristics, type of vaccines under study and the complex interplay of all these factors that have contributed to no clear evidence being established yet in humans.

Summary of findings

Within the systematic search, 9214 studies were identified, from which, after screening of first the title and abstract and then screening the full texts, discarding irrelevant studies at both levels, **34 studies** were included. Of the study designs, out of the total, there were **25 observational studies** and **9 randomized controlled trials** (RCTs).

From the 9 RCTs, 3 studies each investigated BCG and Cholera vaccines; 8 studies investigated populations infected with soil-transmitted-helminths (STH); 4 studies looked at adult populations whilst 3 studies looked at populations of schoolchildren. 5 studies investigated only humoral immunogenicity outcomes and 4 studies investigated cellular immunogenicity outcomes. No RCT investigated efficacy or effectiveness.

From the 25 observational studies, 36% (9 studies) investigated tetanus vaccines, whilst 28% (7 studies) investigated BCG vaccine. 60% of the studies investigated populations infected with STH and 64% studies looked at adult populations whilst 60% studies looked at populations of schoolchildren. 52% studies investigated only humoral immunogenicity outcomes and 24% studies investigated both humoral and cellular immunogenicity outcomes. Only one observational study mentioned efficacy outcomes and no study investigated effectiveness.

Quality for RCTs was assessed by the Cochrane Risk-of-Bias 2.0 (RoB 2.0) tool and no RCT scored a low RoB; 5 RCTs scored a partial RoB and 3 scored a high RoB. Quality assessment for observational studies was assessed by the Newcastle-Ottawa Scale (NOS) which we modified to suit our quality parameters. Only 20% of observational studies scored low RoB and 52% scored partial RoB whilst 28% scored a high RoB. Taken together, 53% of our total studies scored a partial risk of bias.

For all possible studies, the outcome parameters were converted to means and standard deviations and then standardized mean differences (SMDs) were estimated using the Hedges' g, which includes a correction factor for small sample size bias. Corresponding 95% confidence intervals (CIs) were also estimated. No pooled estimate was calculated because of the high heterogeneity in outcomes and time points across studies. All analyses were conducted in R.

SMDs and 95%CIs were visualized using a forest plots for BCG and cholera RCTs. Overall, there was only a significant positive large effect of the treatment on cholera-specific antibodies from only 1 out of 3 studies but a positive effect of the treatment across multiple components of the immune system related to the BCG vaccine. There is one RCT each for tetanus, meningococcal and influenza; will be analyzed qualitatively.

The quantitative analysis for observational studies is also being performed in R and will be available in the published manuscript ca. summer 2024 along with all qualitative analyses and summary of results.

Materials and publications

We would like to highlight two manuscripts (both in preparation) here:

Marrium Habib, Alex Siebner, Vanesa Osmani, Judith Flügge, Meral Esen, Stefanie J. Klug, Clarissa Prazeres da Costa

The impact of helminth infections on vaccine response in humans: a systematic literature review

Planned submission ca. May/June 2024

Alex S. Siebner, Marrium Habib, Ayola Akim Adegnika, Minka Breloer, Christian Bogdan, Alison Elliott, Anahita Fathi, Greet Hendrickx, Justin Nono Komguep, Roland Lang, Johannes Mayer, Benjamin Mordmüller, Esther Ndungo, Vanesa Osmani, Ulrike Protzer, Maria Yazdanbaksh, Stefanie J. Klug, Clarissa Prazeres da Costa, Meral Esen

Interdisciplinary Symposium on Global Challenges and Opportunities in Vaccine Research: A Comprehensive Exploration

Planned submission: ca. May/June 2024

Lessons for GLOHRA/ Global health community

The team set out on the project with the ambition that the results of such a review could lead to the generation of knowledge translation resources to help inform clinical and public health practice guidelines, set research agendas including the basis for the design of new studies with proper study design, size of study sample and high quality conduct on this important public health topic and eventually formulate scientific consensus statements.

Within this framework, the HelmSys consortium were also successful in winning GLOHRA funding for a their scientific workshop entitled 'Challenges and Opportunities for Vaccines' taking place 30th Nov to 1st Dec 2023 near Munich, Germany. With thirteen key speakers across thematic areas such as (1) compromised vaccine immunogenicity due to underlying infections, (2) new vaccine targets and the potential of human challenge models, (3) the overarching challenges of vaccine trials, and (4) conceptualizing vaccine confidence in low and high resource contexts; the consortium tried to highlight the challenges of vaccine research from an inter- and multi-disciplinary approach. There was also an effort to discuss the challenges arising from the analysis of the first results of the HelmSys systematic review and discuss an 'ideal' study investigating impact of helminth co-infection on vaccine response in humans; as a basis for a shared grant in the future e.g. EDCTP II.

Impressions of the project

The HelmSys project team along with M. Cook-Deegan at the workshop 'Challenges & Opportunities for Vaccines' on 30th November, 2023, at Kloster Bernried (near Munich), Germany

Picture courtesy: M. Habib

From L to R: A. Siebner, V. Osmani, M. Habib & J. Flügge, junior scientists on the HelmSys project team, at the project workshop in Tübingen in summer 2022

Picture courtesy: M. Habib

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