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## Review

## Do parasite infections interfere with immunisation? A review and meta-analysis

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## ABSTRACT

Immune responses to vaccination are heterogeneous between individuals; the same vaccine that provides protection in one circumstance may be ineffective in another. One factor that could influence the response to vaccination is concurrent or prior infection with unrelated parasites. Here, we review both the experimental and epidemiological literature on parasite-vaccine interactions, and present a meta-analysis of the published data. In total, our review returned 101 relevant articles, 50 of which met criteria for meta-analysis. Parasite factors potentially affecting vaccination include the type of parasite involved, the stage of infection, and the timing of infection relative to vaccination. Vaccine factors affecting likelihood of interference by parasites include vaccine formulation, route of administration, and the type of immune response required to provide protection against the target antigen. Our meta-analysis of these data show three key things: (1) parasite infections at the time of vaccination result in worse immunisation outcomes, (2) chronic helminth infections are more likely to negatively impact immunisation than acute helminth infections, and (3) thymus-dependent vaccines are more susceptible to parasite interference than thymus-independent vaccines. Our findings highlight the importance of considering and mitigating parasite infections: by taking parasites into account, it should be possible to more effectively immunise individuals and populations.

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## 1. Introduction

Vaccination is an enormously important public health measure that saves and improves the quality of lives of humans and animals worldwide [1]. Effective vaccination relies on the production of a robust, appropriate, and long-lasting immune response. However, not everyone reacts immunologically to vaccination in the same way. Many different factors shape the immune response mounted by an individual when they are vaccinated. The nature of the vaccine itself is important: vaccine antigens differ in their immunogenicity and in the type of immune response that they stimulate, and vaccine formulation can also influence success of immunisation [2–4]. The state of the host at the time of vaccination is of equal importance: host genetic makeup, physiological status, and infection history can all influence the way an individual responds to vaccination [5–8].

Since the 1960s, there has been a steady stream of studies indicating that parasite infections (unrelated to the vaccine target) could be influencing immunisation. These empirical studies have reported, for example, that individuals infected with helminths [9], protozoa [10], bacteria [11], and viruses [12] respond differently to vaccination compared with uninfected individuals. The effects of enteric viruses on poliovirus vaccine effectiveness have been previously reviewed [13], but no such review exists of how, in general, parasites (broadly defined to include helminths, protozoa, bacteria, and viruses) impact immunisation. We wanted to fill this gap and discover overarching patterns, so we reviewed the existing literature to develop a meta-analysis that examines parasite-vaccine interactions to determine whether, when, and how parasite infections might influence immunisation.

## 2. Methods

### 2.1. Literature search and inclusion criteria

We searched the literature on parasite-vaccine interactions up to February 2019 using PubMed, Science Direct, and Web of Science. Our search included combinations of the following terms, plus their variants: *vaccine*, *interaction*, *interference*, *facilitation*, *infection*, *concurrent*. The bibliographies of all retrieved articles were further searched for additional relevant studies, which were also included in our analysis. Our criteria were intentionally kept broad to include all mammalian hosts, and parasites were defined broadly to include helminths, protozoa, bacteria, and viruses.

Studies were included in the review if they: (1) Compared the response to vaccination between an infected group (i.e. infected with a parasite other than the vaccine target) and an uninfected control group, and (2) Measured the response to vaccination in some way (e.g. antibody titres, measure of cell mediated immunity, seroconversion rate, rate of resistance or survival in the face of a post-vaccination challenge with the vaccine target). Studies were included in the meta-analysis if they met the above criteria and if: (1) Individuals in the infected group were infected at the time of vaccination, and (2) Data suitable for meta-analysis were available (i.e. information was provided on the number of individuals in the different treatment groups, and measures of mean and variance were provided for numeric data). Studies that involved a different timing of infection (i.e. infected post-vaccination), or that treated individuals for parasites as part of the study were excluded from the meta-analysis but included in the review. In all, we reviewed 101 studies, 50 of which were included in our

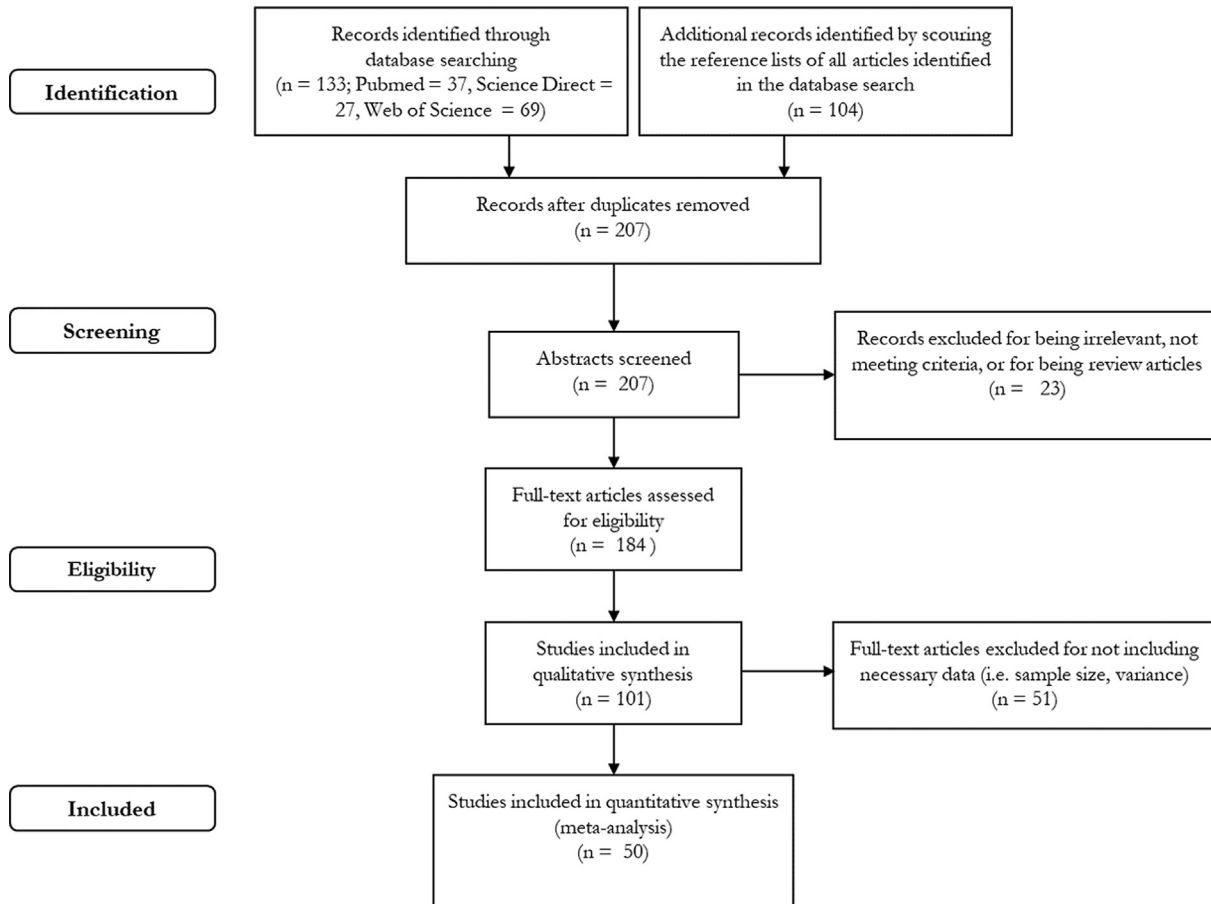


Fig. 1. PRISMA diagram of study selection process.

meta-analysis. Our search and screening process is depicted in the PRISMA flow diagram in Fig. 1.

## 2.2. Extraction and preparation of data

Summary data were collected from the text, tables, and figures of included studies. WebPlotDigitizer, Version 4.2 was used to digitally extract data from figures. Two datasets were collected and analysed separately: an immune dataset, based on immunological responses to vaccination, and a challenge dataset, based on how infected vs uninfected groups fared when challenged with the vaccine target post-vaccination.

Data were standardised for comparison by calculating Hedges' *g* index of effect size with 95% confidence intervals. Hedges' *g* quantifies the standardised mean difference between the effect of a treatment relative to a control group (in our case, we compared groups that were infected at the time of vaccination vs uninfected controls), and is weighted by sample size and the pooled standard deviation [14]. In the context of our meta-analysis, an effect size of 0 implies that parasites have no effect on immunisation, an effect size >0 implies that parasites positively affected the efficacy of immunisation, and an effect size <0 implies that parasites negatively affected immunisation.

Hedges' *g* was calculated directly for numeric data (e.g. on immune response to vaccination or infection intensity post-challenge). For binary data (seroconversion in response to vaccination, or survival rates and absolute ability to block an infection post-challenge), a log odds ratio was first calculated and this was then converted to Hedges' *g* (the standardised mean difference) for comparison [15,16].

Where more than one immunological parameter was measured, the parameter most closely linked to the desired effector outcome for the vaccine target was chosen. Our choice for each study was guided by the authors of those studies, and by searching for information on the immune response required to combat each of the vaccine targets. For example, vaccine-specific cytophilic antibodies or % vaccine-specific T cells were often considered the best measures of vaccine-induced immunity [17,18]. For studies that measured the same variable at multiple time-points [19,20], the effect size was calculated for each time-point and these were then averaged to provide a single effect size for that variable/study. Several studies resulted in multiple effect sizes as they independently investigated more than one vaccine [21–23], more than one parasite [9,24], or reported on more than one independent experiment [25,26].

In addition to effect sizes, information was collected from each study on a range of different parasite, vaccine and other relevant

factors (Table 1). Some of these factors were stated explicitly in the papers, and other were extrapolated based on knowledge of the parasites and vaccine targets involved: For each study, for example, we classified the immune response required for immunisation as being either in agreement or mismatch with the immune response induced by the concurrent infection, based on the T-helper (Th)1/Th2 paradigm [27] – under this paradigm, different and mutually inhibitory immune responses are required for macroparasites (e.g. helminths, cleared by Th2 responses) vs. microparasites (e.g. bacteria or protozoa, cleared by Th1 responses), so an example of a mismatch would be a study investigating the effects of roundworm infection on measles vaccination. We also classified each immune response as being either Thymus Dependent or Thymus Independent based on whether immunisation for the vaccine target in question relies on help from T lymphocytes [28].

## 2.3. Analysis and publication bias

Following extraction, data were graphed and analysed using R version 3.6.0 in RStudio. The pooled effect size and 95% confidence intervals for each type of parasite were estimated using a random effects model in the R package “metafor” to account for between-study heterogeneity. We used one-way and two-way ANOVAs (with study ID as a random effect to account for between-study heterogeneity and non-independence of multiple observations from a given study) to identify relationships between the response to vaccination and many of the factors presented in Table 1, including the broad groups of both parasites and vaccine target, the stage of infection, and the type of immune response required for immunisation.

We performed two tests to account for the possibility of publication bias in this meta-analysis. Firstly, we made funnel plots of the two data sets and performed Egger's test to determine whether or not publication bias was present. We then ran Rosenthal's Failsafe-*n*, which estimates the number of unpublished non-significant studies that would need to exist in order to negate any significant meta-analytical patterns [29]. A Failsafe-*n* larger than  $5n + 10$  (where *n* is the number of studies included in the meta-analysis) is conventionally considered large enough that publication bias can be safely ignored [29].

## 3. Results and discussion

Altogether, the extracted immune dataset comprised 72 effect sizes from 40 studies, and the challenge data comprised 14 effect sizes from 11 studies. Additionally, 7 of the effect sizes for the challenge dataset had a corresponding measure in the immune dataset,

**Table 1**

Information on a range of parasite, vaccine, and other relevant factors were extracted from all included studies.

Parasite factors	<ul style="list-style-type: none"> <li>Parasite species</li> <li>Broad parasite group (Helminth, Protozoa, Virus, Bacteria)</li> <li>Stage or type of infection (Acute or Chronic)</li> </ul>
Vaccine factors	<ul style="list-style-type: none"> <li>Vaccine target (target species, toxin, or model antigen)</li> <li>Vaccine target class (Virus, Bacteria, Helminth, Toxin, Protozoa, Model Antigen)</li> <li>Vaccine type (Live attenuated, Inactivated, Subunit, etc.)</li> <li>Route of administration (oral, subcutaneous, etc.)</li> <li>Is immunisation Thymus Dependent or Thymus Independent?</li> </ul>
Other factors	<ul style="list-style-type: none"> <li>Host species (Human, Mouse, Rat, Cattle, Sheep, Pig)</li> <li>Study design (Experimental or Epidemiological)</li> <li>Agreement or Mismatch in type of immune response required for immunisation vs type of immune response stimulated by parasite (e.g. under the Th1/Th2 paradigm)?</li> </ul>

**Table 2**

Pooled effect sizes for different types of parasitic infection on the immune response to vaccination (immune dataset) and on the resistance and survival of individuals who were challenged with the vaccine target post-vaccination (challenge dataset), calculated using a random effects model to account for between-study heterogeneity and repeated measures.

	Effect Size (Hedges' <i>G</i> )		
	Parasite group	n	Pooled effect size (95% CI)
Immune dataset	Helminth	49	-0.40 (-0.58, -0.23)
	Protozoa	10	-0.87 (-1.16, -0.57)
	Virus	12	-0.36 (-0.56, -0.16)
	Bacteria	1	0.56
Challenge dataset	Helminth	10	-1.48 (-2.60, -0.36)
	Protozoa	3	-2.95 (-3.98, -1.92)
	Virus	1	0.00

allowing us the opportunity to compare immunological and functional measures of immunisation for those studies. The full immune and challenge datasets are available as a [supplementary material](#).

### 3.1. Publication bias

Our funnel plots (not shown) visually indicated the presence of publication bias in both the immune and challenge datasets, and this was confirmed by Egger's test ( $p < 0.005$  for both datasets). However, our Rosenthal's Failsafe- $n$  calculations indicated that we could safely ignore publication bias, as the Failsafe- $n$ 's for both the immune and challenge datasets were much larger than the stipulated  $5n + 10$ , indicating that publication bias alone does not account for our meta-analytical results (immune dataset:  $n = 72$ , Failsafe- $n = 2908$ ,  $p < 0.0001$ ; challenge dataset:  $n = 14$ , Failsafe- $n = 306$ ,  $p < 0.0001$ ). That is, although the data suggest that studies finding an effect of parasite infection on vaccination are more likely to be published than those finding no effect, the number of unpublished studies that would be required to alter the conclusions of this meta-analysis is very large. Furthermore, when we divided the immune dataset based on the study design (Experimental or Epidemiological), we only found evidence of bias for the Experimental subset (Epidemiological immune studies:  $n = 23$ , Eggers test  $p = 0.3875$ ; Experimental studies:  $n = 49$ , Eggers test  $p < 0.001$ ), and again found that a very large number of studies would be needed to negate the meta-analytical results for these low-sample size experimental studies (Experimental studies:  $n = 50$ , Failsafe- $n = 997$ ,  $p < 0.0001$ ).

Overall, our meta-analysis showed that parasitic infections at the time of vaccination were associated with worse vaccination outcomes (Table 2). Immune responses to vaccination were on average weaker for groups that were infected with helminths, protozoa, and viruses at the time of vaccination when compared with uninfected controls. Furthermore, individuals who were infected with helminths, protozoa or viruses at the time of vaccination were less likely to resist or survive infection by the vaccine target pathogen when challenged post-vaccination. Only one paper investigating the effects of bacterial infection on immunisation met our meta-analysis inclusion criteria [30], so we cannot draw any conclusions regarding bacterial infections from the meta-analysis. Several other studies that we reviewed reported that bacterial infections negatively impact immune responses and ability to resist the targeted infection post-vaccination [11,31,32]. There have also been a number of studies on the role of the microbiome in influencing response to vaccination – some have shown that certain microbiome components improve immunisation [33–35], while others have shown no significant effect [36].

In the sections below, we discuss the roles of parasite factors, vaccine factors, and study design (outlined in Table 1) in determining the impact of infection upon immunisation. The findings from our meta-analysis are interspersed with discussion, focusing on ideas and examples from our review. But first: our meta-analysis has several limitations, which we'll acknowledge here. Because we asked a very broad question (do parasites in general, no matter their taxonomic differences, impact immunisation), and because we had wide inclusion-criteria (any mammalian host, experimental or epidemiological study design, varied vaccine formulations and schedules, etc.), there is a lot of heterogeneity in the studies, and it is therefore difficult to pinpoint the immunological mechanisms behind our findings. Secondly, although we made considerable effort to optimise our search strategy, it is possible that we missed relevant papers. Finally, there is probably bias inherent in which studies have been undertaken (let alone published) on this subject: it seems likely that researchers would investigate scenarios in which they think parasite-vaccine interactions might be of

practical importance. Nonetheless, our results offer interesting and important insights into a major constraint on the world of vaccine-induced immunisation.

### 3.2. Parasite factors

Many parasite factors could be involved in determining the outcome of parasite-vaccine interactions. One important factor is the type of parasite involved, since parasite taxa stimulate or discourage the immune system in divergent ways: e.g. interference with a vaccine could be the result of parasite-induced systemic immunosuppression, a qualitative mismatch in the type of immune response required to combat the parasite vs immunise against a vaccine target. Additionally, since different immune profiles are present in chronic vs acute infections, the timing of infection relative to vaccination could also play an important role in determining the outcome of an interaction. We discuss these in turn, with examples, in the following paragraphs.

Some parasites induce systemic immunosuppression in their hosts, thus inhibiting immune responses to other infections and to vaccines. In some cases, this immunosuppression is achieved via depletion of immune cells [37,38], and in other cases it's achieved via upregulation of tolerance or anti-inflammatory mechanisms [39,40]. Systemic immunosuppression due to lymphopenia has been shown to interfere with immunisation in HIV infected individuals, for example [18,41,42].

In other cases, the outcome of a parasite-vaccine interaction could be determined by whether there is mismatch or agreement between the type of immune response stimulated by a parasite and the type of response required to protect against the vaccine target. For example, if cell mediated immunity (often promoted by Th1 cells) is necessary for effective immunisation, but a host is infected with a parasite that skews the immune system towards a Th2 response, infection would be predicted to interfere with immunisation. Conversely, if a concurrent parasite stimulates the same branch of the immune system as required for immunisation, this immunological environment would be predicted to facilitate immunisation. These ideas are similar to well documented interactions that occur during parasite co-infections [39,43–45]. Our review included several studies showing that Th2-inducing parasites can interfere with immunisation by vaccines requiring a Th1 type response for protection [43,46–50]. However, other mechanisms must be invoked in some cases: for example, a decrease in vaccine efficacy in the presence of helminth infection, which was reversed by anthelmintic treatment and was associated with an increase in Th1 cytokines, but not a counterbalancing decrease in Th2 or T-regulatory cytokines, indicates that simply clearing the helminths can facilitate immunisation, even if helminth-induced T-helper responses persist [51]. We didn't find any examples of a Th1 bias impairing Th2 immunisation, probably due to the low number of vaccine target species that require a Th2 response for clearance. Overall, our meta-analysis didn't reveal a statistically significant relationship between agreement/mismatch in immune response and immunisation (Immune dataset: Agreement:  $n = 18$ , Mismatch:  $n = 54$ ,  $F = 1.66$ ,  $p = 0.202$ ; Challenge dataset: Agreement:  $n = 3$ , Mismatch:  $n = 11$ ,  $F = 0.01$ ,  $p = 0.917$ ), but we may not have had sufficient power to answer this question, given that the majority of the studies involved helminth infections and microparasite vaccine targets (i.e., immunological mismatches).

High levels of immunological similarity between the infecting parasite and the vaccine target could also potentially interfere with immunisation via original antigenic sin [52], whereby the existence of immune memory against a closely related parasite prevents the production of a new, more specific, immune response against a new parasite or antigen. Several studies have investigated the potential for non-polio enteroviruses to interfere with polio

vaccination, and non-tuberculous *Mycobacteria* to interfere with BCG vaccination – some have found evidence of interference [53,54], while others have not [55–57]. Given the almost endless potential for different combinations of parasites and vaccines, it is perhaps unsurprising that multiple interference mechanisms might be involved. Our meta-analysis doesn't have the power to shed much light on these mechanisms, but we do, importantly, show that whatever the mechanism, the outcomes of parasite-vaccine interactions tend to be negative.

Indeed, our meta-analysis indicates that parasite-vaccine interactions are overall negative for immunisation (Table 2), although only a few studies have investigated the facilitative effects of heterologous infection on vaccination outcome. Conceptually, such facilitation should be possible if an infecting parasite upregulates the same pathways required for effective immunisation for a given vaccine. This principle is one basis for vaccines that use live bacterial vectors [58]. We found three studies that demonstrated correlations between certain parasites and upregulated humoral vaccine responses: an epidemiological study found that malaria-infected individuals produced higher geometric mean titres in response to a human papilloma virus vaccine [59], and *H. pylori* infection was associated with higher seroconversion rates to a *Salmonella typhi* vaccine [30], and to an oral cholera vaccine [60]. None of these studies measured cytokine or leukocyte profiles, however, and these higher antibody titres could also be explained by cross-reactive antibodies. More studies are needed if we want to understand the mechanism behind such facilitative interactions.

For chronically infecting parasites, different immune profiles are sometimes present during the acute and chronic stages of infection, and so these different stages of infection could interact differently with the same vaccine. Several vaccine trials have investigated the differential effects of acute versus chronic infection on vaccination efficacy. For mice experimentally infected with *Schistosoma japonicum* and then vaccinated for Hepatitis B, chronic but not acute infections were associated with reduced humoral immunity [43]. Similarly, mice infected with *Schistosoma mansoni*

and then vaccinated with tetanus toxoid at different time points post-infection showed no difference compared to uninfected controls if vaccinated 1–6 weeks post-infection, but lower titres when vaccinated 9 or 12 weeks post-infection [26]. In contrast, when mice were experimentally infected with *Trichinella spiralis*, acute infection impaired humoral response and lymphocyte proliferation, while chronic infection did not [61], and mice vaccinated 7 days post infection with *Strongyloides ratti* had worse outcomes than those vaccinated 14 days post infection [62]. In cattle experimentally infected with *Trypanosoma congolense* and then vaccinated for *Brucella abortus*, both acute and chronic infections were associated with an impaired humoral response [63].

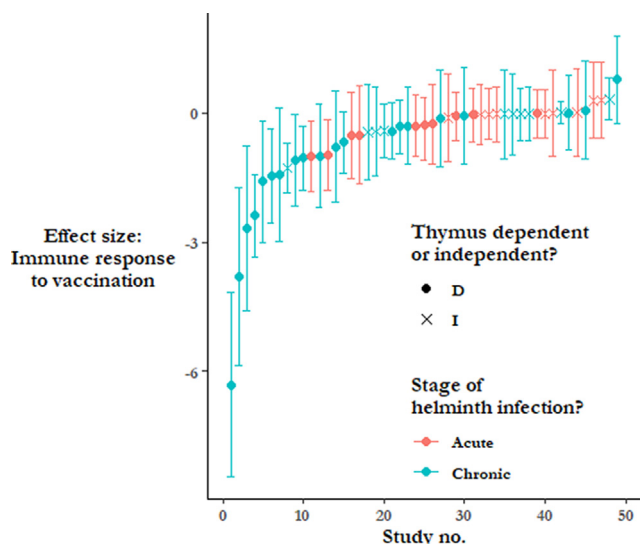
Interestingly, despite these complexities, our meta-analysis points to a relationship between stage of infection and immunisation for helminth infections: chronic helminth infections ( $n = 30$ ) were associated with worse immunisation outcomes than acute helminth infections ( $n = 19$ ) (Fig. 2,  $F = 4.05$ ,  $p = 0.05$ ). No associations were found between immunisation outcome and stage of viral, protozoal, or bacterial infection, possibly due to the smaller number of studies that investigated these types of infection (Table 2).

Most studies of parasite-vaccine interactions have investigated the effects of infection at the time of vaccination on vaccine outcome (hence why this was the focus of our meta-analysis), but some have looked at the effect of infections following vaccination on immune protection and memory. Two studies found that individuals infected with an unrelated parasite post-vaccination lacked protection when subsequently challenged with the vaccine target [21,64]. Another study found evidence that post-vaccine infection with the vaccine target itself could erase vaccine-induced memory – vaccination allowed mice to survive challenge, but rather than boosting immunity, this challenge purged vaccine-induced memory B cells, such that post-challenge vaccinated mice were as immunologically susceptible to subsequent infection as unvaccinated controls [65]. However, most studies have found only transient effects [66], or no effect, of post-vaccination infection on vaccine induced protection to challenge [67,68] or memory [69,70]. A great deal of further research will be required to determine causes of such divergent outcomes.

### 3.3. Vaccine factors

Many vaccine factors are likely involved in determining whether and how parasites could interact with a given vaccine. These include the vaccine type, formulation, and the route of administration. Vaccines that are already less immunogenic (for any reason) than other vaccines may be more susceptible to interference from infecting parasites. What exactly makes for a strongly immunogenic vaccine remains somewhat of a mystery, but there is no doubt that such variation in immunogenicity exists [4]. The vaccine target antigen itself could also play a role in determining whether or not a vaccine is susceptible to interference by parasite infections – historically, viruses and toxins have been the easiest vaccine targets, while it is notoriously difficult to develop effective vaccines against metazoan parasites [71].

Vaccine type could also be important in determining the outcome of a parasite-vaccine interaction. Vaccines based on live attenuated organisms are conventionally considered to be more effective than other vaccines types due to the fact that they can replicate in the vaccinated individual, increasing antigen exposure, and because they are capable of inducing both cell-mediated and humoral immunity [72]; similarly, whole-organism inactivated vaccines are thought to be more effective than vaccines directed against a small number of specific epitopes [73]. Vaccines with increased effectiveness could also be less susceptible to parasite interference. There is some evidence supporting this in the



**Fig. 2.** Effect of helminth infection stage and thymus dependence on immunisation. Studies of individuals with chronic helminth infections at the time of vaccination had worse immunisation outcomes (more negative effect sizes when compared with uninfected controls) than studies of acute helminth infections (ANOVA:  $F = 4.61$ ,  $p = 0.04$ ). Thymus dependent vaccines also had worse immunisation outcomes than thymus independent vaccines in helminth-infected individuals (ANOVA:  $F = 17.38$ ,  $p = 0.0001$ ). However, there was no statistically significant interaction between the stage of helminth infection and thymus dependency (Two-way ANOVA:  $F = 1.44$ ,  $p = 0.23$ ).

literature – in one study, helminth infection interfered with immunisation by a DNA subunit vaccine, but not by a vaccine comprised of live attenuated sporozoites [74]. However, our meta-analysis did not find any associations between vaccine type and the strength or direction of parasite-vaccine interactions, neither when vaccine types were divided at a fine scale, nor when we compared live attenuated vaccines ( $n = 16$ ) with all other types ( $F = 0.027$ ,  $p = 0.87$ ).

Adjuvants, by increasing vaccine immunogenicity, may also be able to help override parasite interference with immunisation – one study showed that the negative effects of parasite-interference could be overcome when the vaccine was formulated with the right adjuvant [48].

Thymus dependence is another immune factor that seems important in determining whether a parasite will interfere with immunisation – that is, the outcome of a parasite-vaccine interaction may depend on whether or not T lymphocytes are required for immunity against the vaccine target species [75]. Our meta-analysis indicated that parasite infections are more likely to interfere with thymus dependent ( $n = 44$ ) than thymus independent ( $n = 28$ ) vaccines ( $F = 9.75$ ,  $p = 0.003$ ), implying that T-lymphocyte modulation may be a key mechanism underlying parasite-vaccine interactions. This effect emerged even when we analysed helminth infections alone and controlled for whether the infection was acute ( $n = 19$ ) or chronic ( $n = 30$ ) at the time of vaccination (Fig. 2,  $F = 6.99$ ,  $p = 0.011$ ). This effect also emerged when we further analysed those studies involving experimental helminth infections (Acute:  $n = 19$ , Chronic:  $n = 22$ ,  $F = 6.10$ ,  $p = 0.018$ ), though no thymus-dependency pattern was observed for the small number of epidemiological helminth infection studies ( $n = 8$ ,  $F = 0.956$ ,  $p = 0.373$ ).

Finally, the route of vaccine administration could play a role in determining whether or not parasite-vaccine interactions influence immunisation. Oral vaccines are used primarily when mucosal immunity – mediated by IgA – is essential for protection, but are also used for wildlife vaccine trials where immunisation relies on the uptake of vaccine baits from the environment. Orally administered vaccines also come into direct contact with gastrointestinal parasites, whereas gastrointestinal parasites and parenterally administered vaccines interact primarily via the immune system. A study of *M. tuberculosis* interference with HIV vaccination found that tuberculosis negatively impacted immunisation when the vaccine was administered by the intramuscular but not by the intranasal route [31]. However, few studies have compared

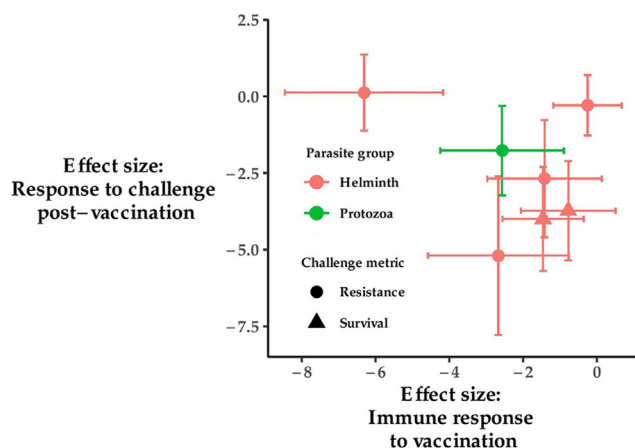
parasite-vaccine interactions for different routes of administration. Our meta-analysis found no difference between vaccines administered parenterally vs orally ( $F = 2.34$ ,  $p = 0.131$ ), however 66/72 of the immune effect sizes were for parenterally administered vaccines, and so more varied studies are probably required to answer this question.

### 3.4. Study design

Studies hoping to investigate the influence of parasite infection on vaccine-induced immunity face several challenges. They must choose the time scale on which to study – acute vs chronic infections, and the timing of infection relative to vaccination – and they must decide on the best correlate of immunity for the vaccine in question, and on when to take measurements of immunity.

Many published studies in this field have simply measured vaccine specific antibodies at a single timepoint, but this might not always be the best correlate of protection. The most convincing studies are arguably those that not only measure vaccine-induced immunity but also challenge subjects with the vaccine target post-vaccination. A small subset of studies in our meta-analysis provided both immune and challenge data (Fig. 3). There appears to be qualitative agreement between the immune and challenged effect sizes for 6/7 studies – that is, parasitic infections that resulted in weaker vaccine specific immune responses (negative effect sizes), also negatively impacted resistance (absolute ability to avoid infection) and survival when individuals were experimentally infected with the vaccine target. However, our review also uncovered some studies that found a discrepancy between the immune response measured and how individuals fared when actually challenged with the vaccine target. For example, mice with pre-existing orthopoxvirus immunity produced depressed humoral and cell-mediated responses to influenza vaccination, but when challenged with influenza the infected mice fared just as well as controls [76]. Of more concern are the cases where immune measurements imply protection that isn't there – in one study, pigs infected with Porcine reproductive and respiratory syndrome virus in-between primary and secondary vaccination for swine influenza virus (SIV) had identical serological profiles to uninfected vaccinated pigs, but had worse pathology (microscopic and macroscopic lesions), and higher viral shedding when subsequently challenged with SIV [68]. These complexities suggest that it is of the utmost importance to undertake studies of the robustness of vaccine protection in the context of a variety of infections, especially those likely to jointly affect health of the target host species. The ideal study of parasite-vaccine interactions would measure multiple immune factors (humoral and cell mediated immunity), at multiple time-points, and would challenge subjects post-vaccination, or monitor their exposure to the vaccine target species, if epidemiological.

The choice between performing an experimental or epidemiological study could also influence whether or not a study finds evidence of parasite-vaccine interactions: experimental studies have the upper hand in terms of the ability to manipulate and control, but epidemiological studies usually allow for increased sample sizes. However, our meta-analysis didn't find a statistically significant difference in immunisation outcome for experimental ( $n = 49$ ) vs epidemiological ( $n = 23$ ) studies of parasite-vaccine interactions ( $F = 3.18$ ,  $p = 0.0784$ ), though we might have expected more noise in cross-sectional epidemiological studies. When we ran analyses within these subsets, the Experimental immune dataset supported our main findings from the combined dataset: chronic helminth infections ( $n = 22$ ) were associated with more negative outcomes than acute helminth infections ( $n = 19$ ) ( $F = 4.96$ ,  $p = 0.03$ ), and thymus dependent vaccines ( $n = 34$ ) were also more likely to be associated with worse immunisation than



**Fig. 3.** Relationship between immune response to vaccination and protection when challenged post-vaccination. For the most part, when parasites negatively affected vaccine-induced immune responses, they also negatively impacted the ability of hosts to resist (absolutely block infection) or survive infectious challenge with the vaccine target.

thymus independent vaccines ( $n = 15$ ) ( $F = 6.10$ ,  $p = 0.018$ ). The Epidemiological immune dataset, however, showed no relationship between thymus dependency and immunisation (Thymus dependent:  $n = 10$ , Thymus independent:  $n = 13$ ,  $F = 0.643$ ,  $p = 0.432$ ), or between stage of infection immunisation (Acute:  $n = 6$ , Chronic:  $n = 17$ ,  $F = 0.076$ ,  $p = 0.786$ ), and this lack of significance remained when it was further subset to only include epidemiological studies involving helminth infection.

Finally, parasite removal experiments, involving anti-parasitic treatment before or after vaccination, constitute another study design that has been used to identify parasite-vaccine interactions. We excluded these studies from our meta-analysis because some didn't test for parasitic infection prior to assigning individuals to treated or untreated groups, and because evidence exists that the effects of parasitic infection can last even long after those infections are treated or resolved [19]. However, these parasite removal experiments do provide evidence of parasite interference with immunisation, and they point to the possibility of using anti-parasitic treatment as a public health measure to aid immunisation campaigns [50,77]. They also provide some insight into how such campaigns should be designed. For example, de-worming of individuals prior to vaccination appears to improve immunisation outcomes, but deworming post-vaccination has no beneficial effect [78]. De-worming far in advance of vaccination may also be preferable to de-worming at the time of vaccination – in laboratory mice, antibody titres were stronger the longer the interval between de-worming and vaccination, and antibody titres were still significantly lower in mice that were vaccinated 16 weeks post-de-worming compared with mice that were never infected [43].

#### 4. Conclusions

Parasite-vaccine interactions can negatively impact immunisation. Though the mechanisms involved will vary for different combinations of parasite and vaccine, it seems clear that vaccinologists, medical professionals, and public health officials ought to account for parasites and their potential to obstruct immunisation. These considerations are of particular importance in populations with endemic parasite infections: vaccine campaigns in regions with neglected tropical diseases may be less likely to succeed than those in regions with fewer endemic parasites. Similarly, vaccines that are trialled in regions with parasites may fail and therefore not proceed further due to parasite obstruction rather than to a failure in vaccine design. With all this in mind, an increased awareness of parasite-vaccine interactions, and when, where, and how they might impact immunisation, could help us to more effectively administer vaccines to individuals, and to better implement vaccination campaigns for at-risk populations.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2020.06.064>.

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