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Psychological Interventions as Vaccine Adjuvants: a systematic review

Running title: Psychological vaccine adjuvants

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Abstract

Objectives: The effectiveness of vaccines is known to be altered by a range of psychological factors. We conducted a systematic review to evaluate the effects of psychological interventions on the ability of vaccines to protect against disease, as measured by antibody responses.

Methods: Electronic databases (EMBASE, Medline, PsychINFO, CINAHL) were searched from their inception to 6th February 2018.

Results: The search yielded 9 eligible trials conducted with 1603 participants and four broad categories of intervention: meditation/mindfulness (n=3), massage (n=3), expressive writing (n=2) and cognitive behavioural stress management (n=1). Some evidence of benefit on the antibody response to vaccination was observed in 6/9 of all trials and in 4/7 of randomised controlled trials. However, effects on antibody levels were often mixed, with only 3 of 6 trials showing benefit demonstrating an improvement in all antibody outcomes and at all time points assessed. Trials demonstrating benefit also provided direct or indirect evidence of adequate adherence with the intervention; and in 50% of these trials, there was also evidence that the intervention was effective in changing the mediating psychological constructs targeted by the intervention.

Conclusions: This literature is characterised by considerable heterogeneity in terms of intervention type, vaccine type, age of participants and the temporal relationship between vaccination and intervention. We conclude that there is early evidence to suggest that psychological interventions may enhance the antibody response to vaccination. However, the effects are inconsistent, with the greatest likelihood of benefit seen in trials evidencing adequate adherence with the intervention. Future work would benefit from rigorous

intervention development that focuses on achieving adequate adherence and large well-controlled randomised trials with a focus on an agreed set of outcomes.

Keywords: vaccinations; antibodies; psychological interventions

Introduction

The Centres for Disease Control stated that vaccination is among the ten most significant health achievements ever documented[1]; and for many conditions they have been an enormous success (e.g., smallpox). However, vaccinations are not universally effective, with multiple factors related to the vaccine and the vaccine recipient known to influence efficacy [2, 3]. With regard to the latter, there are several populations in whom the evidence for vaccine effectiveness is equivocal. These include populations with underlying immune impairment due to advancing age [3, 4] and/or the presence of co-existing diseases (e.g., cancer) [5]. As a consequence, vaccines may be most likely to fail in those they most seek to benefit [6, 7].

This has prompted research into strategies to enhance the immune response to vaccination, so called vaccine adjuvants. The aim of such interventions is to optimise the response of the immune system to the vaccine antigens and, in so doing, increase the likelihood that the vaccine confers protection. Within this context, there has been a growing interest in the potential for non-pharmacological factors to act as vaccine adjuvants. This is borne out of a literature which has demonstrated that psychological and behavioural factors such as mood, diet and physical activity can modulate aspects of functional and enumerative immunity [8], including responses to vaccination [9, 10]. For example, a meta-analysis of 13 studies examining the relationship between psychological stress and antibody responses following influenza vaccination reported evidence of a significant negative relationship, such that greater levels of stress (regardless of how it was measured) were associated with lower levels of antibody [9]. Similarly, a review of cross-sectional, observational and randomised controlled studies investigating the relationship between chronic and acute exercise and immune responses to vaccination concluded that the immune response appears to be augmented by exercise [11]. Comparable evidence also exists for a range of dietary factors. For example, both vitamin D and zinc have been shown to modulate the functioning of the immune system [12, 13] .

This systematic review aims to provide a comprehensive evaluation of the effects of psychological interventions on the human antibody response to vaccination; with a view to informing the debate as to whether they could be used to optimise vaccine efficacy. We sought to be inclusive in this review. Thus, the term psychological was used to capture any treatment that could be broadly considered to be aiming to improve the vaccine response by targeting a psychological construct or process known to effect immunity (e.g., mood, relaxation, pain, etc.), but we did not require the intervention to draw on psychological theory. This was necessary to ensure a comprehensive assessment of the relevant literature, given that this is a field known to be characterised by a relative absence of theory driven enquiry [14]. We examined the evidence from all eligible trials conducted with human participants that measured the effects of a psychological intervention on the antibody response to standard dose vaccinations.

Furthermore, although a range of immunological outcomes have been reported in the literature, we chose to focus this review on the antibody response only. Vaccines contain live, attenuated, modified, or killed microorganisms (or their toxins) and, when administered, they stimulate an immune response, the nature of which depends on the type of microorganism administered. However, most often the cascade of immune activity following vaccination ends with the production of antibodies. Thus, antibody responses can be accepted as a surrogate and universal marker of an effective immune response to vaccination.

It is worth noting that there are two classes of vaccine that stimulate B cells to produce antibodies: thymus-dependent (i.e. T cell-dependent) or thymus-independent (i.e. T cell-independent) vaccines. Psychological factors have been shown to influence the response to both in comparable ways [15]. Thus, we had no *apriori* reason to expect that the effect of the non-pharmacological interventions considered in this review would affect these two classes of vaccines differently.

Systematic Review Methods

Search strategy and selection criteria

We searched electronic databases (EMBASE, Medline, PsychINFO, and CINAHL) from their inception to 6th February 2018 (see Appendix 1 for details of the search strategy). Our search was constructed to identify all non-pharmacological interventions and identified three broad types of intervention: psychological, physical activity/exercise and dietary/nutritional interventions. However, given the diversity in types of intervention within and between each category, the results from the physical activity/exercise and dietary/nutritional interventions are to be the subject of separate manuscripts. Hereafter, we use ‘k’ to denote number of articles and ‘n’ to denote number of participants in this manuscript:

No language restrictions were applied. Only primary studies published in peer-reviewed journals were considered for inclusion. Review articles were excluded, but their reference lists were examined for relevant papers. We also hand-searched reference lists of included papers and contacted subject experts for additional relevant papers. The following study inclusion criteria were applied: (1) human adult, child and infants receiving any type of vaccine; (2) studies explicitly concerned with evaluating the therapeutic (i.e., beneficial) effects of an intervention on the immune response to the vaccine; (3) the intervention targeted a psychological construct known to effect immunity (e.g., mood, relaxation, etc.) but was not required to explicitly draw on psychological theory; (4) studies in which participants received standard doses of vaccine; (5) comparative studies (randomised and non-randomised); (6) studies providing a quantitative assessment of the antibody response to the vaccination and (7) examined the association between the intervention and the antibody response. To be included, studies had to meet all 7 criteria.

Antibody responses are typically quantified in absolute levels, as captured by titres, or binary outcomes that capture a change in antibody levels: with the outcomes 'seroresponder/responder' and 'seroconversion' used most commonly. Typically, seroresponding following vaccination is defined as a rise in serum antibody of a particular magnitude (e.g., a four-fold increase or greater). Seroconversion refers to the presence of antibody specific to the vaccine antigens in the blood. All approaches to quantifying the antibody response were included in this review.

It is usual in reviews of this kind to specify the primary outcome in advance. In the case of the present body of work this might have included a focus on a specific type of antibody measure (e.g., absolute antibody levels) and a specific time-point following vaccination (e.g., 4 weeks post-vaccination). However, this was not possible in this review because common practice in this field has been to report multiple antibody outcomes; measure these on more than one occasion post-vaccination and not always specify the primary or secondary outcomes. The absence of a consistent approach to measuring the effects of psychological interventions on the antibody response to vaccination led us to operationalise 'an improvement in the antibody response' as a statistically significant ($p \leq 0.05$) enhancement in one or more antibody outcome, at any time point post-vaccination, i.e., evidence of improvement across all outcomes and all times post-vaccine was not required. Although this approach is symptomatic of the extant literature, it does increase the risk of bias. Thus, in our summary table we describe all antibody outcomes reported in each trial, and in the manuscript comment on the proportion of outcomes, relative to the total outcomes measured, exhibiting an improved antibody response.

The titles and abstracts of the papers were initially assessed against the inclusion criteria by two independent reviewers who removed those that did not meet the criteria. Full text papers were retrieved and read in full by both reviewers. Disagreements at each stage of the selection process were resolved through discussion between the reviewers. For example, at title and abstract review it was not always clear if a vaccine had been administered or antibodies measured. This was resolved by review of the full-text. The search procedure can be seen in Figure 1.

INSERT FIGURE 1 ABOUT HERE

Data extraction and assessment of risk of bias

Data were extracted by two reviewers directly from the papers into tables. These data included the sample size, characteristics of the participants, a description of the intervention, type of vaccine administered, the primary outcome, number of follow-ups and a summary of the major findings.

Risk of bias for individual studies was assessed independently by two reviewers using the Cochrane Collaboration's risk of bias tool [16]. The tool refers to seven items that assess: method of randomisation, allocation concealment, blinding of participants, study personnel, outcome assessments, how missing data were handled and evidence of selective reporting.

All discrepancies between reviewers were resolved through discussion. For example, there was some discrepancy regarding what could be considered selective reporting. Discussions led to reviewers agreeing that this could only be determined if a published protocol was available containing the relevant details. All agreed ratings are reported in Table 1.

INSERT TABLE 1 ABOUT HERE

Effect Sizes

Between group effect sizes (Hedges' g) were calculated for all antibody outcomes using Comprehensive Meta-Analysis (Version 3): Englewood, NJ; Biostat: https://www.meta-analysis.com/). These were calculated using post-vaccination means, standard deviations and sample size for continuous outcomes and number of events per group used for dichotomous outcomes. In two cases [17, 18], where these statistics were not reported in the published manuscript, effect sizes were calculated on the basis of reported inferential tests assessing between group differences in changes from pre-vaccination antibody levels. In the case of the Davidson et al. trial [17] this was because no other data were available. In the case of the Vedhara et al trial [18], the measure presented was seroconversion and thus was, in effect, 'change from baseline'.

For five studies, insufficient statistics of any kind were published to calculate effect sizes. Authors of all 5 studies were contacted and two provided additional data, thus allowing us to calculate effect sizes for 6/9 articles in total (see Table 2).

Effect sizes were interpreted in line with guidelines for Cohen's d (small = .2, medium= .5, large= .8 [19], with positive values interpreted as the intervention having enhanced antibody responses compared to controls. However, due to the heterogeneous nature of the trials identified (in terms of vaccinations used, intervention type, and method of antibody measurement) we did not meta-analyse these data.

Results

Summary of findings

The search yielded nine eligible papers reporting nine trials which covered four broad categories of intervention: meditation/mindfulness (k=3), massage (k=3), expressive writing (k=2) and cognitive behavioural stress management (k=1). We elected to include the massage trials in this review of psychological interventions for two main reasons. First, they met our criteria of 'interventions targeting a psychological construct known to effect immunity' in that the massage in these trials was designed to reduce pain or enhance mood. Second, we considered these interventions to be wholly different from the exercise/physical activity based interventions identified in our searches, all of which were concerned with participants actively engaging in some form of physical activity. This contrasts with massage where subjects are the passive recipients of some degree of physical manipulation.

Seven randomised controlled trials were identified, one study used matched controls, and another used waiting-list controls. All studies provided data on at least one measure of adherence or effects on a mediating mechanism. The total sample size across all studies was 1603 (range: 40-413). The average age of participants ranged from 2 months to 80 years. Two trials were conducted with infants (2-6 months), five with adults (21-60 years), and two in older adults (75-80 years). Five trials focussed on responses to seasonal influenza vaccination, two to hepatitis B vaccinations, and two to diphtheria/tetanus/pertussis (DTP) vaccination. Four trials targeted groups who could be considered to be at potential risk of vaccine failure: two with young infants [20, 21] and two with older adults [18, 22]. The length of the interventions ranged from single sessions of 1 minute [20] to 3 x 1 hour sessions per week for 20 weeks [22]. Five trials administered their vaccination post-intervention; two before or at the first intervention session and two during the intervention.

Two-thirds of all trials (k=6/9), and over half of all RCTs (k=4/7), reported some evidence of a statistically significant improvement in the antibody response to vaccination [17, 18, 20, 22-24]; two showed no benefit [21, 25] and one showed evidence of an impaired antibody response in the intervention group [26]. Intervention effect sizes ranged from g=-0.73 to g=1.13 (see Table 2). Trials showing evidence of an improved immune response to vaccination, and in which effect sizes could be calculated, typically exhibited moderate to large effects [17, 18, 24].

When examining the six trials that showed some evidence of benefit in more detail, it was clear that there was variability in both the number of outcomes reported (ranging from 1-25) and the proportion of these that exhibited evidence of a statistically significant improvement in the antibody response. For 50% of these trials (k=3) all antibody outcomes reported improved significantly in the intervention group compared with the control group [17, 18, 24]. In contrast, the study by Hsu [20], considered 5 outcomes over 5 time points, only 12 of which (48%) attained significance in the expected direction. Two outcomes showed significantly greater antibody levels in the control arm (both at 2 months post-vaccine) and the direction of the non-significant comparisons indicated higher antibody levels in the control arm for 7/11 outcomes.

The study by Yang [22], reported 6 between-group comparisons, 2 of which (33%) attained statistical significance in the expected direction. The direction of all the non-significant between group comparisons in this study were in the expected direction (i.e., greater antibody levels or protective titres observed in the intervention arm). Finally, the post-hoc analysis by Stetler [23] which showed evidence of improved antibody responses, did so for only 1 out of 3 viral strains (33%). The results for the other viral strains were not presented in the manuscript and so we could not determine the direction of these non-significant comparisons.

There appeared to be no systematic differences in intervention effects based on the nature of the vaccine (influenza, hepatitis B and DTP vaccines used in trials showing benefit/impairment and not); or the timing of the vaccination relative to the intervention (i.e., whether vaccination occurred pre, during or post-intervention). Trials showing no benefit/impairment also did not appear to differ markedly in their duration, from those that did show benefit (median total number of intervention days: 4 versus 6 respectively). However, they did appear to differ in intensity (i.e., median number of minutes engaged in formal intervention sessions): with median intensity (not including unsupervised intervention practice) over the intervention period of 180 minutes for trials showing no benefit/impairment versus 280 minutes for trials reporting benefit. They also differed in sample size: with trials showing no benefit/ impairment typically being larger than the trials showing some evidence of benefit (medians n=149 and n=49 respectively). Although this latter observation may be attributable, in part, to a single very large trial of 413 participants [21].

In considering this literature in more detail, we next give consideration to findings according to intervention type and methodology

Intervention Type and Methodology

No single intervention approach was examined in more than three trials. Thus it is not yet possible to consider the relative benefits of each intervention approach in the context of such a modest evidence base. However, some early patterns emerge if we consider aspects of intervention methodology, relating in particular to (a) adherence with the interventions (indicated by the number of intervention sessions attended); (b) intervention effects on purported mediating mechanisms i.e., whether it had a beneficial effect on constructs targeted by the intervention (e.g., improved mood) and (c) characteristics of participants at baseline (i.e., could they be considered to be at risk of vaccination failure).

Intervention adherence: Only three trials formally reported on intervention adherence [18, 22, 26], but it is possible to infer levels of adherence from other details (e.g., degrees of freedom) presented in a further three trials [20, 23, 24]. All six of these trials evidenced adequate to good adherence, as measured by participants attending >75% of intervention sessions, and all but one [26] reported evidence of an enhanced antibody response to vaccination in the intervention group compared with the control group. In contrast, of the three trials that did not provide data on adherence [17, 21, 25], only one reported evidence of an improved vaccination response.

Mediating mechanisms: Nearly all trials (k=8/9) reported evidence relating to one or more hypothesised mediating mechanism: mood [17, 18, 23, 24, 26]; brain activity [17]; cognitive change [23-25]; pain and other vaccine related adverse events [20, 21]. Of these, three trials were characterised by the intervention having no effect or an adverse effect on their hypothesised mechanisms [21, 25, 26]; and all three showed no evidence of a beneficial effect on vaccine effectiveness. In contrast, three out of the five trials reporting evidence of a beneficial effect on vaccine effectiveness showed that the purported mechanisms had also been changed in the expected direction [17, 23, 24]. The remaining two trials showing benefit observed no effect of their intervention on their hypothesised mechanism (mood: [18]) or an adverse effect (pain and fever: [20]).

Participant characteristics: Four out of nine trials were conducted with individuals at risk of vaccine failure due to their age [18, 20-22]. All but one of these trials [21] reported a beneficial effect of their intervention on the antibody response to vaccination. However, evidence of an enhanced immune response to vaccination following interventions conducted in healthy adults was also not uncommon, with three out of five of these trials reporting benefit [23-25].

Discussion

This review identified nine trials in which the effects of psychological interventions on the antibody response to vaccination were examined. This literature was modest in size and characterised by considerable heterogeneity in terms of the type of intervention, age of participants, vaccine type, intervention duration and intensity and approaches to assessing the antibody response to vaccination. When examining the evidence according to the less stringent criterion of 'a statistically significant ($p \leq 0.05$) enhancement in one or more antibody outcome at any time point post-vaccination', we observed that two-thirds of trials reported some evidence of benefit in the antibody response to vaccination, and in those where an effect size could be calculated, the results suggested evidence of a moderate to large effect. However, a closer examination of these trials suggests that caution should be exercised when interpreting these findings. For example, only 50% of trials reported a significant improvement across all antibody outcomes and at all time points; while for the remaining trials, evidence of improvement was seen only for between 33-48% of outcomes and time-points considered.

The weight of the evidence offers early support for the view that psychological interventions may help to prevent disease through their ability to improve the antibody response to vaccinations and thus make vaccines more effective. Furthermore, the data suggest the effect could be generalizable across a range of vaccinations and at all stages of the immune response: evidenced by the fact that intervention effects were unrelated to vaccine type or the timing of the intervention relative to the vaccine. However, this conclusion should be tempered by several caveats.

First, while our outcome measure (i.e., antibody responses) is widely used as a surrogate for protection from disease [27], vaccine effectiveness is more accurately determined in studies that report laboratory confirmed disease [28]. Such trials, do however, require longer follow-ups, are likely to be more costly and thus are rarely undertaken in the context of psychological interventions.

Second we wish to acknowledge that the way we determined if there was evidence of an enhanced immune response to vaccination, and thus improved protection from disease, lacked precision and could have increased the risk of bias. We considered an improvement in at least one immune outcome (not necessarily all immune outcomes), at any time point, as evidence of an enhanced response to vaccination i.e., improvement across all outcome measures and at specific times was not required. This was necessary because of variability in the literature in the ways that the antibody response has been measured; at what time points; and the failure in many trials to specify primary or secondary outcomes. The former poses a particular problem for this field because it is well known that findings from different immunological methods and outcomes do not correlate well [29, 30]. Thus, it is perhaps not reasonable, for example, to expect improvements in absolute antibody levels to translate into improved rates of seroprotection. Similarly, the optimal timing of antibody outcomes is influenced by whether the focus is on a primary or secondary immune response (a primary response is slower than a secondary response) [31-34]; and whether the focus is on the peak antibody response or long-term persistence in immunity (again the former would be measured earlier than the latter). In addition, the choice of primary outcome may also be influenced by the nature of the vaccine itself [35]. These considerations have contributed to capriciousness in outcome assessment in this literature which, in turn, serves only to impede attempts to synthesise the evidence. We suggest that future research in this area would benefit from the development of an agreed set of outcomes as is advocated by the COMET initiative [36]. COMET seeks to achieve agreement on the minimum outcomes that should be measured and reported in clinical trials with a view to facilitating comparisons between trials and evidence synthesis. The initiative is typically focussed on single disease entities. However, the principles of COMET are of relevance to this field. In addition, we would recommend greater uptake of pre-registration of trial designs and analysis plans as this would alleviate concerns regarding 'researcher degrees of freedom' [37] which can also lead to false-positive results.

The third caveat relates to the potential for the significance of these findings to be influenced by the 'file drawer effect' or publication bias. This phenomenon, now widely recognised in the psychological and medical sciences, refers to the likelihood of positive findings being more likely to appear in the published literature than null findings. Some estimates of the size of the file drawer problem suggest that there may be 3 times more negative trials than those found in the published literature. For example, in a now classic study, Smart [38] examined publications in psychological journals and reported that while studies with negative findings typically accounted for 9% of published papers, negative findings were reported in 20.5% of abstracts of papers presented at a mainstream psychological conference in a single year and 30.2% of dissertation abstracts from the same year. These findings support the view that research is much more likely to be published if the results are positive.

A host of factors are known to drive the file drawer effect [39], but the implications for reviews like the present one are clear: it can lead to an over-estimation of the size of the treatment effect. Like many authors, we sought to mitigate this risk by contacting known authors in the field to enquire about data from unpublished trials (none were reported). We also sought to be as inclusive as possible in our identification of the literature by not restricting ourselves to studies in which the intervention explicitly drew on psychological theory. Indeed, we are somewhat reassured that this review reflects the extant literature by the fact that three of the nine included studies reported null findings or evidence in support of a psychological intervention impairing the antibody response. Furthermore, while we were unable to locate and include any unpublished studies, there is a contrasting view that this could be a strength of the present work because unpublished research is not without bias (e.g., due to potentially being of lower quality, not having been subjected to peer review etc.). Indeed, a recent simulation study concluded that selective publication (as opposed to publishing everything) results in a more accurate estimate of effect sizes [40].

The debate on the file drawer effect is likely to continue for some time to come. But in the context of this nascent field, typically characterised by modest sample sizes, we strongly encourage authors to always seek to publish their findings regardless of observed effects so that the scientific community can arrive at an informed view on whether psychological interventions represent a viable means for enhancing vaccine effectiveness.

Further observations arising from this review worthy of comment include, first, that we cannot yet determine what type of intervention (e.g., mindfulness versus CBT) might be most effective in enhancing vaccinations and reducing disease risk because no single intervention has been examined in more than 3 studies. Second, that observations regarding intervention methodology pointed towards effective interventions being more likely to involve treatments that were more intensive (reflected by the median time spent in receipt of formal intervention sessions), although not necessarily of a longer duration, and where the intervention was effective in modifying the psychological constructs being targeted. We also observed some potentially interesting findings in relation to intervention adherence and effects on the antibody response. For six of the nine trials, adherence data were reported (or could be inferred) and the majority of these (k=5/6) showed evidence of both adequate adherence and an improved antibody response to vaccination. For the remaining three trials it was not possible to determine if adequate adherence had been achieved, but two of these failed to show evidence of benefit on the antibody response. We cannot of course assume that the absence of adherence data is indicative of poor adherence. But the findings hint at this possibility and, at the very least, highlight the need for more rigorous reporting of trial methodology.

Third, we did not observe any clear patterns in relation to the age of participants and the likelihood of psychological interventions enhancing the antibody response to vaccination: with some degree of improvement reported in trials with the very young, the elderly and healthy adults.

Fourth, we suggest that the heterogeneity evident in this literature regarding intervention type and populations assessed may be a consequence of the absence of theory driven enquiry in this field. The theoretical context for much of this work comes from the biopsychosocial model [41] which proposes that health and disease are a function of not only biology but the complex psychological and social influences that surround an individual. Although this framework has been influential, critics argue that its lack of specificity has meant that it does not make clear predictions or hypotheses that can be tested [14]. This lack of specificity is reflected in the literature reviewed here where both the populations under investigation (ranging from the very young to the very old) and the mechanisms targeted by the interventions were broad (ranging from mood, cognitive change and brain activity to pain). At this stage we have not achieved a clear understanding of which psychological factors may be the most influential in modifying immunity or how these relationships vary according to factors such as participant age and contextual factors such as the nature and type of stressor. Greater clarity on these issues would enable us to focus research effort on developing interventions that could optimise, rather than just improve, the effectiveness of vaccinations.

An additional consequence of the varied literature examined here is that it necessarily precluded a meta-analysis and also impacted on the conclusions we could draw in this narrative synthesis. We also observed that studies where the intervention methodology was less robust (e.g., no data on intervention adherence) were less likely to find evidence of benefit. This makes it difficult to determine whether an absence of effect was due to the interventions per se, or the rigour with which they were implemented.

Taken together, some clear directions for future research are evident. In particular, we would suggest that there is a need for more trials to examine the potential for psychological interventions to prevent disease by enhancing the effectiveness of vaccines; for these trials to be larger and conducted with a focus on an agreed set of outcomes; for authors to publish trial protocols in advance and be mindful of the consequences of publication bias. It would also be advantageous for this work to adopt a clearer theoretical framework so that we can move towards a better understanding of which psychological influences on immunity are preeminent; and develop interventions that target these specifically whilst also maximising participant adherence.

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Table 1: Risk of Bias Assessments

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Davidson	2003	?	?	H	?	?	?	L
Hayney	2014	L	L	H	L	L	?	L
Hsu	1995	?	?	H	?	?	?	L
Huang	1999	?	?	H	?	?	?	L
Loft	2012	L	?	H	?	?	?	L
Petrie	1995	?	?	H	?	?	?	L
Stetler	2006	?	?	H	?	?	?	L
Vedhara	2003	H	H	H	?	L	?	H
Yang	2008	H	H	H	?	L	?	L

L = low risk; ? = Unclear risk; H = High risk

Table 2 Summary of Studies

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]+
Davidson et al. (2003) USA Randomised controlled trial	Intervention: n=25 Control: n=16 Healthy adults Mean age 36 years 12 male, 29 female	Intervention: mindfulness meditation program; sessions lasting 2.5 – 3 hours, once a week, over 8 weeks; 7 hour silent retreat; unsupervised sessions 1 hour 6 days a week for 8 weeks Control: wait-list control Adherence: not reported Mediating mechanisms: intervention group, compared with controls showed a reduction in negative affect and increased left sided brain activity. Vaccination administered after the 8 week intervention period	Influenza Hemagglutination inhibition assay 3-5 weeks & 8-9 weeks post-vaccination Change in HI antibody titres (composite of viral strains)	Compared with control group, intervention participants displayed a significantly greater increase in HI antibody titres between 3-5 and 8-9 weeks post-vaccine.	g= 0.64 [.01, 1.27]

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]+
Hayney et al. (2014) USA Randomised controlled trial	Control group n= 51 Exercise group n= 47 MBSR/meditation group n= 51 Adults ≥ 50 years: no previous/current experience of meditation; moderate exercise ≥ 2 times a week; any intense exercise Control group: mean age 59, 10 male, 41 female MBSR group: mean age 60, 9 male, 42 female Exercise group: mean age 59, 8 male, 43 female	Mindfulness-based stress reduction (MBSR) group: 8-week meditation intervention, weekly 2.5hr group sessions and 45mins home practice per day. Exercise group: 8 weeks in length, weekly 2.5hr group sessions, 45mins daily home practice Waiting list control group: no intervention Adherence: not reported Mediating mechanisms: measures of mindfulness and exercise completed at 1 and 8 weeks post-intervention indicate no between group differences in mindfulness and a difference in exercise between the exercise and control group at 1 and 8 weeks post-intervention Timing: Vaccine given to all participants during week 6 of intervention	Influenza Hemagglutination inhibition assay; Baseline (pre-vaccine), 3 and 12 weeks post-vaccine HI titres: Mean fold increase from baseline to 3 weeks (by viral strain); geometric mean titre (by viral strain); seroprotection rates - titres ≥ 40 (by viral strain and by number of strains); seroconversion rates – 4-fold increase in titres (by viral strain and by number of strains)	No significant differences between groups for any immune outcome at any time point.	<u>Meditation vs Control</u>+ Mean fold Increase: g= .08 Geometric Mean Titre 3 weeks: g= -.51 Geometric Mean Titre 12 weeks: g= -.34 Seroprotection: g= -.42 Seroconversion: g= -.13 <u>Exercise vs Control</u>+ Mean fold Increase: g= -.07 Geometric Mean Titre 3 weeks: g= .23 Geometric Mean Titre 12 weeks: g =.03 Seroprotection: g= -.15 Seroconversion: g= .04 <u>Meditation vs Exercise</u>+ Mean fold Increase: g= .06 Geometric Mean Titre 3 weeks: g= -.73 Geometric Mean Titre 12 weeks:g= -.38 Seroprotection: g= -.27 Seroconversion: g= -.17 *+Average Hedges' g across viral strains and number of strains reported, as a total of 72 effect sizes could be reported. Effect sizes by viral strains and number of strains available at request.*

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]⁺
Hsu et al. (1995) Taiwan Randomised controlled trial	Intervention: n=175 Control: n=152 Infants recruited through routine vaccine programme 2 months of age n= 125; receiving first vaccine dose); 70 male, 55 female 4 months of age n=100; receiving second dose; 44 male, 56 female 6 months of age n=102; receiving third dose; 48 male, 54 female	Intervention: 1-minute light circular massage over injection site Control: no treatment Adherence: not reported, but intervention was a single session of supervised massage. Mediating mechanisms: examined parents' reports of local (e.g., pain) and systemic (e.g. fever) adverse reactions. Greater percentage of parents in intervention arm reported local pain and fever. But effects on fever not significant when examining fevers >39^{o}C. Vaccination administered immediately prior to intervention.	Diphtheria, tetanus, pertussis Diptheria: neutralisation assay; tetanus: indirect hemagglutinin test; pertussis: elisa measuring antibody to filamentous hemagglutinin (anti-FHA); antibody to pertussis toxin (anti-PT) microagglutination assay for pertussis agglutinin 2 (pre-vaccine), 6, 7, 18, & 19 months of age Antibody titres (log transformed)	Compared with controls, the intervention group exhibited higher diphtheria titres at 6 and 7 months, but no significant between group differences at 18 or 19 months. At 2 months titres were significantly higher in the control group. No significant between group differences in tetanus titres at any time point. Compared with controls, the intervention group exhibited significantly higher anti-FHA at 2, 6 and 7 months; significantly higher anti-PT at all time points and significantly higher pertussis agglutinin titres at 18 and 19 months, but with greater levels in the control group at 2 months.	Insufficient details available.

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]⁺
Huang & Huang (1999) Taiwan Randomised controlled trial	Intervention: DTPw n=293 (of which 107 provided a blood sample for antibody measurement); DTPa n= 107 (of which 99 provided a blood sample for antibody measurement); Control: DTPw n=297 (of which 108 provided a blood sample for antibody measurement); DTPa n= 111 (of which 99 provided a blood sample for antibody measurement). Infants recruited through routine vaccine programme 2-6 months	Intervention: 2 minute massage immediately after vaccination and application of warm towel on injection site for 30 minutes in the evening of the vaccination day Control: no treatment Adherence: not reported, but first part of intervention was a single session of supervised massage. Adherence to warm towel application not reported. Mediating mechanisms: examined parents' reports of local (e.g., pain) and systemic (e.g. fever) adverse reactions. Found no differences between groups for DTPa but evidence of increased, rather than decreased adverse reactions (pain and induration) in intervention children receiving DTPw. Vaccination administered immediately prior to intervention.	Diphtheria, tetanus, & whole-cell pertussis combined vaccine (DTPw) & diphtheria, tetanus and acellular pertussis combined vaccine (DTPa) Diptheria: neutralisation assay; tetanus: indirect hemagglutinin test; pertusus: microagglutination assay 2 (pre-vaccine) and 7 months of age Antibody titres (log transformed)	No significant between group differences between the intervention group and controls in antibody titres of diphtheria, tetanus, and pertussis antibodies in response to the DTPw or DTPa vaccines.	Insufficient details available.

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]⁺
Loft et al. (2012) New Zealand Randomised controlled trial	Intervention: n=35 Control: n=35 Undergraduate medical students Mean age 21 years 34 male, 36 female	Intervention: 45-minute body massage received once a week for 4 weeks. Control: no treatment Adherence: all intervention participants attended all treatment sessions. Mediating mechanisms: no effect of intervention on measures of emotional distress Vaccination administered after intervention	Hepatitis B (single, primary dose) Microparticle enzyme immunoassay 0 (pre-vaccine), 2 & 6 weeks post-vaccination Total serum (IgM & IgG) anti-HB antibody titres	Compared with controls, the intervention group exhibited significantly lower anti-HB antibody titres at 2 weeks and 6 weeks post-vaccination.	At 2 weeks: g= -.68 [-1.16, -.21] At 6 weeks: g= -.40 [-.87, .07]
Petrie et al. (1995) New Zealand Randomised controlled trial	Intervention: n=20 Control: n=20 Undergraduate medical students Mean age 21 years 21 male, 19 female	Intervention: writing about traumatic event or events over 4 consecutive days Control: emotionally neutral writing about activities in recent days over 4 consecutive days Adherence: not reported, but degrees of freedom data indicate 100% adherence Mediating mechanisms: text analysis of written material showed intervention group's writing was more emotional and showed greater cognitive change Vaccination administered on the day after the 4th day of writing	Hepatitis B (triple vaccine schedule) Microparticle enzyme immunoassay 0 months (after intervention/pre-vaccine), 1, 4, & 6 months Anti-HB antibody titres (log transformed)	Compared with the control group, the intervention group had increasingly higher levels of anti-HB antibody titres over time. This effect became non-significant when individuals (n=5) who were seropositive at baseline were excluded from the analyses.	All participants at: 1 month: g= .06 [-.55, .67] 4 months: g= .43 [-.18, 1.05] 6 months: g= .42 [-.19, 1.04] Excluding seropositive at baseline participants: 1 month: g= -.21 [-.86, .44] 4 months: g= .41 [-.24, 1.07] 6 months: g= .37 [-.28, 1.03]

Authors (year of publication); setting & trial design	**Sample size per condition & participant characteristics**	**Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination**	**Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination**	**Authors' main immune findings relating to vaccine response**	**Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]⁺**
Stetler et al. (2006) Canada Randomised controlled trial	Intervention: n=26 Control: n=22 Healthy students Mean age 27 years Intervention group: 2 male, 24 female Control group: 3 male, 19 female	Intervention: writing about personal experiences of racism for 20 minutes over 3 days (day 1, day 1 + 5-7 days; day 2 +5-7 days) Control: emotionally neutral writing about activities 20 minutes over 3 days (day 1, day 1 + 5-7 days; day 2 +5-7 days) Adherence: not reported, but degrees of freedom data indicate 100% adherence Mediating mechanisms: intervention participants were less positive and more negative after each intervention session Vaccination administered within one week of the 3rd day of writing	Influenza Hemagglutination inhibition assay 0 (pre-vaccine), 30 and 90 days Hemagglutination inhibiting antibody slopes/change over time (log transformed, regressed on time since vaccination) analysed separately by viral strain (A/New Caledonia H1N1; A/Moscow H3N2, B/Sichuan)	Compared with the control group, the intervention group had lower antibody slopes/change over time for the A/New Caledonia H1N1 and A/Moscow H3N2 viral strains. No significant between group differences in antibody slopes/change over time for the B/Sichuan viral strain. Post-hoc analysis of the intervention group only showed greater antibody slopes/change over time for the A/New Caledonia H1N1 strain in participants who attributed greater certainty their experiences were explained by racism, compared with those who showed expressed less certainty. No such relationships were observed for the other two viral strains.	A/New Caledonia H1N1: 30 days: g= -.14 [-.70, .42] 90 days: g= -.12 [-.68, .44] A/Moscow H3N2: 30 days: g= -.21 [-.77, .35] 90 days: g= -.28 [-.85, .28] B/Sichuan: 30 days: g= .10 [-.46, .66] 90 days: g= .10 [-.45, .66]

Authors (year of publication); setting & trial design	Sample size per condition & participant characteristics	Description of intervention/control arms; adherence; effects on mediating mechanisms & timing in relation to vaccination	Type of vaccine; assay methods; timing of immune measures & immune outcomes relating to vaccination	Authors' main immune findings relating to vaccine response	Effect Sizes (Hedges' g) for between condition differences [95% Confidence intervals]⁺
Vedhara et al. (2003) UK Matched control design	Intervention: n=16 Carer controls: n=27 Non-carer controls: n= 27 Chronically stressed older adults (spousal carers and non-caregiving controls) Mean age 75 years (carers); 71 years (controls) 32 males, 38 females	Intervention: Cognitive-behavioural stress management intervention; sessions 1 hour a week over 8 weeks Control: no treatment Adherence: all intervention participants attended at least 6/8 intervention sessions Mediating mechanisms: no change in emotional distress between groups Vaccination administered 2-3 weeks after final intervention session	Influenza Enzyme-linked immunosorbent assay 0 (pre-vaccine), 2, 4, & 6 weeks Seroresponse: 4-fold increase in IgG antibody titres to at least one viral strain	Significantly more carers in the intervention group were classed as seroresponders compared with carers in the control group. Seroresponder rates did not differ significantly between intervention carers and non-carer controls. Significantly more non-carer controls were classed as seroresponders compared with carer controls.	Intervention vs Carer Controls: g= 1.13 [.41, 1.83] Intervention vs Non-carer Controls: g= .43 [-.19, 1.06] Carer Controls vs Non-carer controls: g= -.59 [-1.15, -.02]
Yang et al., (2008) USA Waiting-list control design	Intervention: n=27 Control: n=23 Older adults Intervention group: mean age 80 years; 6 male, 21 female Control group: mean age 75 years; 7 male, 16 female	Intervention: combined Taiji/Qigong meditation; 3 x 1 hour sessions per week for 20 weeks Control: waiting-list control Adherence: mean attendance of intervention sessions 80.5% Mediating mechanisms: no relevant data reported. Vaccination administered during first week of intervention/control period	Influenza Hemagglutination inhibition assay 0 (pre-vaccine), 3, 6 & 20 weeks Hemagglutination inhibiting antibody titres (composite of all viral strains) and seroprotection rates (titre > 40) analysed separately by viral strain	Compared with the control group, intervention group had higher hemagglutination inhibiting antibody titres at 3 and 20 weeks post-vaccination, but not at 6 weeks. Compared with baseline levels: antibody levels were significantly greater at 3, 6 and 20 weeks post-vaccination in the intervention group; in the control group, antibody levels were significantly greater at 3 and 6 weeks only. No significant differences between groups in seroprotection rates for each viral strain.	Insufficient details available.

MBSR= Mindfulness-based stress reduction; HI= Hemagglutination inhibiting; DTPw= Diphtheria, tetanus, & whole-cell pertussis combined vaccine; DTPa= diphtheria, tetanus and acellular pertussis combined vaccine; IgG= Immunoglobulin serotype G; IgM= Immunoglobulin serotype M; anti-HB= anti-hepatitis B. [+] Positive effect sizes should be interpreted as the trial arm listed first (typically the intervention) having enhanced antibody responses compared to the trial arm listed second (typically the control). Negative effect sizes indicate reduced antibody responses in the same manner

Figure Captions

Figure 1: PRISMA summary of search procedure

Appendix 1: Medline search matrix as example of search strategy

Each group of search terms were combined with the Boolean AND operator within each bibliographic database.

Population (vaccine)

Conjugate OR Haemophilus Vaccines OR Human OR Influenza OR Influenza vaccines OR Vaccin OR Vaccines OR Viral vaccines

Intervention

Acupressure OR Acupuncture OR Adaptation OR Affect OR Alternative medicine OR Alternative therapy OR Anxiety OR Autogenic training OR Behavior change OR Behaviour change OR Behavior modification OR Behaviour modification OR Behavior therapy OR Behaviour therapy OR Biofeedback OR Biofeedback training OR Breathing exercises OR Client education OR Cognition OR Cognitive behaviour therapy OR Cognitive behavior therapy OR CBT OR Cognitive performance OR Cognitive restructuring OR Cognitive therapy OR Cognitive techniques OR Complementary therapy OR Coping behavior OR Coping behaviour OR Counseling OR Counselling OR Depression OR Diet OR Education OR Emotional adjustment OR Emotional disclosure OR Emotional expression OR Emotions OR Exercise OR Exercise therapy OR Expressive writing OR Group counseling OR Group counselling OR Health education OR Health promotion OR Home practice OR Hypnosis OR Hypnotherapy OR Illness behavior OR Illness behaviour OR Interventional studies OR Lifestyle changes OR Massage OR Meditation OR Meditation retreat OR Mind body therapies OR Mind body therapy OR Mindful meditation OR Mindfulness OR Motivation OR Narration OR Nutrition OR Optimism OR Patient counseling OR Patient counselling OR Patient education OR Perceived stress OR Physical activity OR Physical education OR Physical education training OR Physiological OR Pilates OR Preventative medicine OR Promotion campaign OR Psychoeducation OR Psychology OR Psychological OR Psychological intervention OR Psychotherapy OR Rehabilitation OR Relaxation OR Relaxation therapy OR Relaxation training OR Self-help groups OR Sleep OR Sleep techniques OR Social adjustment OR Social network OR Social care OR Social skills training OR Social support OR Stress OR Stress appraisal OR Stressor appraisal OR Stressors OR Stress OR Stress management OR Stress reduction OR Support groups OR Tai chi OR Tai ji OR Visualisation OR Yoga

Outcome

Antibodies OR Antibody OR Antibody formation OR Antibody maintenance OR Antibody-producing cells OR Antibody status OR Antibody titer OR Antigens OR Anti-idiotypic OR Autoantibodies OR B-Lymphocytes OR Bacterial OR Cellular OR Cytokines OR Dendritic Cells OR Hemagglutination inhibition OR Humoral OR Humoral responses OR OR IgA OR IgM OR IgD OR IgE OR IgG OR Immune response OR Immune tolerance OR Immunity OR Immunoglobulin OR Immunologic memory OR Immunosorbent assay OR Immunosuppression OR Immunosuppressive agents OR Innate OR Lymphocytes OR Memory cells OR Primary antibody response OR Regulatory OR Secondary antibody response OR Seroconverted OR Seronegative OR Seropositive OR Seroprotection OR Seroprotective responses OR T-Lymphocytes OR Titres OR Viral