

Effects of Non-Pharmacological Interventions as Vaccine Adjuvants in Humans: a systematic review and network meta-analysis

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Abstract

Introduction: Psychological and behavioural factors influence the effectiveness of vaccines. This has led to interest in the potential for non-pharmacological treatments, which modify these factors, to enhance vaccine effectiveness. We conducted a systematic review and network meta-analysis (NMA) to examine the effects of non-pharmacological adjuvants on vaccine effectiveness, as measured by antibody responses to vaccination.

Areas covered: Electronic databases (EMBASE, Medline, PsychINFO, CINAHL) were searched from inception to 6th February 2018. This yielded 100 eligible papers, reporting 106 trials: 79 interventions associated with diet and/or nutrition; 12 physical activity interventions and 9 psychological interventions.

We observed that over half (58/106, 55%) of the trials reported evidence of non-pharmacological interventions enhancing the antibody response to vaccination across one or more outcomes. The NMA considered the evidence for the comparative effects between all intervention types, control and placebo for antibody titres (48 studies), seroconversion (25 studies) and seroprotection (23 studies) separately. The NMA provided only weak evidence in support of nutritional formulae and probiotics in increasing antibody titres.

Expert opinion: This review offers a comprehensive summary of the available literature on non-pharmacological interventions as vaccine adjuvants. The evidence is characterised by considerable heterogeneity but provides early evidence of nutritional formulae and probiotic interventions being associated with enhanced antibody responses to vaccination. The absence of evidence for other treatments may be the consequence of limited and unreliable evidence on these treatments. Large, well-designed studies which include consistent core outcomes and measures of intervention adherence and fidelity are required.

Keywords: vaccinations; antibodies; diet; stress; physical activity; psychological interventions

The Centers for Disease Control and Prevention regard vaccination to be among the ten most significant health achievements ever documented ("Ten great public health achievements—United states, 1900-1999.," 1999), 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 its recipient known to influence efficacy (Jefferson et al., 2005; Osterholm, Kelley, Sommer, & Belongia, 2012). 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 (Osterholm et al., 2012; Mauro Provinciali, 2009) and/or the presence of co-existing diseases (e.g., cancer) (Hoffman, Rice, & Sung, 1996). As a consequence, vaccines may be most likely to fail those whom they most seek to benefit (Herbert & Cohen, 1993; Roberts, 1999).

This has prompted research into strategies which could enhance the immune response to vaccination, so called vaccine adjuvants. The aim of such treatments 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. In view of evidence that non-pharmacological factors such as mood, diet and physical activity can modulate aspects of functional and enumerative immunity (Pedersen, Zachariae, & Bovbjerg, 2009), including responses to vaccination (Pascoe, Fiatarone Singh, & Edwards, 2014; Vedhara et al., 1999), there has been growing interest in these as potential vaccine adjuvants.

This systematic review and network meta-analysis (NMA) aims to provide a comprehensive evaluation of the effects of these non-pharmacological interventions on the human antibody response to vaccination; with a view to informing the debate as to whether they could be used to optimise the clinical effectiveness of vaccinations. In keeping with our aim to provide a comprehensive overview of the entire corpus of the evidence we did not restrict this review by vaccine type, population or type of non-pharmacological intervention, but we did conduct subgroup

analyses for these factors where possible. We also limited our focus to trials which measured antibody responses to vaccination. Although a range of immunological outcomes have been reported in the literature, we focussed on antibody responses because, regardless of the type of vaccine used (i.e., inclusion of live, attenuated, modified, or killed microorganisms (or their toxins)), the cascade of immune activity following vaccination most often ends with the production of antibodies. Consequently, antibody responses are widely accepted to be the best surrogate marker of clinical effectiveness.

It is also worth noting that there are two classes of vaccines that stimulate B cells to produce antibodies: thymus-dependent (i.e. T cell-dependent) or thymus-independent (i.e. T cell-independent) vaccines. T cell-dependent vaccines (usually protein antigens) require the presence of helper T lymphocytes to trigger a B lymphocyte response and usually lead to a long lived response and IgG production. Thymus-independent vaccines (usually polysaccharide antigens) can mount an antibody response in the absence of helper T lymphocytes and these are usually mostly of the IgM isotype and short lived. However, non-pharmacological influences have been shown to have comparable effects on thymus-dependent and thymus-independent vaccines (Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008). Thus, we had no *a priori* reason to expect that the effect of non-pharmacological interventions would affect these two classes of vaccines differently.

We undertook a network meta-analysis (NMA) because a standard pairwise meta-analysis is restricted to the comparison of just two interventions that have been evaluated in randomised controlled trials (RCTs) (Cooper, Hedges, & Valentine, 2009), whereas the literature targeted in this review is concerned with several differing interventions. NMA can accommodate this (Caldwell, Ades, & Higgins, 2005) as it allows the simultaneous estimation of the relative effects of multiple interventions that have been compared in RCTs, where the comparisons that have been made form a connected network of comparisons. NMA assumes that the direct and indirect estimates for a given comparison are consistent. This assumption must be checked (Dias et al., 2013), but as long as

consistency holds then pooled relative effects estimates can be obtained between any pair of interventions, even if they have not been compared directly. We have previously demonstrated that NMA methods can be used effectively in the evaluation of complex interventions, of the sort common in the target literature (Welton, Caldwell, Adamopoulos, & Vedhara, 2009).

We examined the evidence from all eligible trials conducted with human participants that measured the effects of a non-pharmacological intervention on the antibody response to standard dose vaccinations. In our evaluation of this literature, consideration was given to whether intervention effects varied according to (i) type of intervention and intervention categorisation; (ii) participant's age; (iii) whether participants could be considered to be at risk of vaccination failure due to factors other than age (e.g., through nutritional deficiency), (iv) vaccine type, (v) follow-up time, and (vi) risk of bias and study size.

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). 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 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 that were explicitly concerned with evaluating the therapeutic (i.e., beneficial) effects of an intervention on the immune response to the vaccine; (3) the target of the intervention was a non-pharmacological parameter known to effect immunity (e.g., diet, physical activity, mood); (4) studies in which participants received standard doses of vaccine; (5) comparative studies (randomised and non-randomised were included in the narrative

review, but note only randomised studies were included in the NMA); (6) studies that provided a quantitative assessment of the antibody response to the vaccination and (7) examined the association between the intervention and the antibody response.

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, which is a measure of achieving protective titre levels (seroprotection)). Seroconversion refers to the presence of antibody specific to the vaccine antigens in the blood. All approaches to quantifying the antibody response were included, but the outcomes (a) antibody titres, (b) sero-conversion, and (c) sero-protection were analysed separately in the NMA.

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 (SR, KS). 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. The inclusion of studies in the NMA involved discussion with the statistical co-authors (NJW, DMC). 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 (SR, KS). These data included the sample size, characteristics of the participants, a description of the intervention, type of vaccine administered, the antibody outcome(s) reported, number of follow-ups, and a

summary of the major findings. For the studies in the NMA, all data extractions were checked by a further reviewer (NJW).

Risk of bias for individual studies was assessed independently by two reviewers (SR, KS) using the Cochrane Collaboration's risk of bias tool (Higgins & Green, 2011). The checklist referred to seven items, which assessed the method of randomisation, allocation concealment, blinding of participants, study personnel, outcome assessments, how missing data were handled and evidence of selective reporting. Studies included in the NMA were also checked by two further reviewers (NJW, DMC). Discrepancies were resolved through discussion and agreed ratings are reported in Table 1.

INSERT TABLE 1 ABOUT HERE

Statistical Analysis

We used NMA to statistically combine results from the included studies. NMA allows for the simultaneous estimation of the relative effects of multiple interventions that have been compared in RCTs, where the comparisons that have been made form a connected network of comparisons. The method assumes that there are no important differences in factors that interact with the intervention effect (effect modifiers) between studies on different comparisons. This consistency assumption can be tested statistically when there are closed loops in the evidence network. As long as the underlying assumption is met, pooled relative effect estimates can be obtained between any pair of interventions, even if they have not been compared directly. We have used this method previously in the evaluation of complex interventions, of the sort common in the target literature (Welton et al., 2009).

The primary effectiveness outcome for the NMA was standardised mean difference (SMD) in antibody titre for specific antigens contained in the vaccines. There was a high degree of heterogeneity in the measures reported in the included studies (mean titre, geometric mean titre, log geometric mean titre, log-reciprocal geometric mean titre). All measures were converted to a

log-scale assuming a normal distribution on the log-scale (Appendix 1). Due to the high level of heterogeneity in the scale of the outcomes across studies and across antigens within study, evidence was pooled on the standardised mean difference scale. We used change from baseline measures, where reported. Where this was not reported, we used the measure reported at follow-up, which avoids making unverifiable assumptions about the correlations of the measures over time, but may introduce bias if there is an imbalance in baseline measures across the arms, as was the case in some of the trials. In all cases we used the longest follow-up time reported because the objective of vaccination is for long-term protection, although we acknowledge that time from vaccination may be a source of heterogeneity and explore the impact of this in a network meta-regression. The NMA model is based on the model used for standardised mean differences, reported in (Welton et al., 2009), extended to incorporate a hierarchical model allowing for variation in intervention effects on antigens within studies, as well as variation between studies in mean intervention effect across antigens. Positive SMDs indicate increased antibody titres, and thus greater vaccine response.

Some of the studies reported binary outcomes related to the magnitude of change in antibody. Definitions of these outcomes were not consistent between papers (see definitions, where given by the authors, listed in Tables 2-4). These outcomes could broadly be described as either achieving seroconversion or achieving protective titre levels. We also performed NMA for these binary outcomes, estimating intervention effects as log-odds ratios for the same hierarchical model for intervention effects as described above (see Appendix 1). Positive log-odds ratios (odds ratios greater than 1) indicate an increase in vaccine efficacy.

The interventions were coded using three different categorisations with differing levels of detail (Table 5). The coding for the dietary/nutritional interventions was done in consultation with authors with specific expertise in this area (VH, CMT). We explored the fit of each of the categorisations, and found that the detailed coding of the interventions (Categorisation 1) didn't improve model fit or reduce heterogeneity (Appendix 1, Table S1) and results were less precise.

Categorisation 3 was considered to be too broad to be useful, and we therefore report all results using Categorisation 2: 1=control, 2=placebo, 3=vitamins and/or minerals, 4=nutritional formulae, 5=probiotics, 6=fatty acids, 7=other dietary interventions, 8=physical activity, 9=psychological. Psychological interventions included any intervention that could be considered to be aiming to improve the antibody response to vaccination by targeting a psychological construct or process known to effect immunity (e.g., mood, relaxation, pain, etc.). We did not, however, require interventions 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. (McLaren, 1998) All results are reported relative to placebo.

Goodness of fit was measured by the posterior mean of the residual deviance. In a well-fitting model the residual deviance should be close to the number of data points (Spiegelhalter, Best, Carlin, & Van der Linde, 2002). Models were also compared using the Deviance Information Criterion (DIC), which is a combined measure of model fit and complexity. A difference of at least 3 or more points is considered meaningful on both the residual deviance and DIC scales. The consistency assumption was assessed by comparing the fit of an unrelated mean effects model with the consistency NMA model (Dias, Ades, Welton, Jansen, & Sutton, 2018). If the unrelated mean effects model gives a sufficiently better model fit or leads to a reduction in the between study variance and/or between antigen variance, then this suggests evidence of inconsistency and results are only reported narratively.

There was considerable heterogeneity in these data, and so only random effects models are presented. Heterogeneity was assessed by reporting the estimated between studies standard deviation and the between antigen within studies standard deviation. Heterogeneity was explored (where sufficient data available and adequate model fit) through pre-planned subgroup analyses for: (i) vaccine type; (ii) age (infants, children, adults, older adults) and (iii) whether participants were

deemed to be at high risk of vaccination failure. This latter subgroup was intended to capture risk factors other than age and included the following characteristics: institutionalisation in the target population (suggesting a degree of frailty not only dependent on age); or the presence of a clinical condition known to be associated with immunosuppression in the target population; or setting the study in an infant population from a lower income country in which malnutrition is highly likely. As with the data extraction and risk of bias assessments, the determination of risk of vaccine failure was made by two reviewers, with discrepancies resolved through discussion. We carried out sensitivity analysis to exclude studies at high risk of bias on any of the following domains: randomisation, allocation concealment, and blinding of assessors. We also conducted network meta-regression (Dias et al., 2018) to adjust for the differences in follow-up time between the studies and study size (where the covariate was the reciprocal of the square root of the average sample size per arm in a study). The network meta-regressions assumed the covariate effect was equal for each active intervention against control or placebo.

A Bayesian statistical approach was taken using WinBUGS1.4.3. All WinBUGS models were run with multiple simulation chains, and convergence assessed using the Brooks-Gelman-Rubin diagnostic tool. Once convergence was satisfactory, this “burn-in” sample was discarded, and a further simulation sample double the burn-in sample was obtained. All reported results are based on these further samples. Full details of the model are given in Appendix 1, and WinBUGS code is available by request from author NJW.

Results

Narrative Summary of Studies

The search procedure yielded 100 papers, reporting on 106 trials. Seventy-nine papers reported on interventions associated with diet and/or nutrition (Table 2); 12 on physical activity interventions (Table 3) and 9 on psychological interventions (Table 4). Hereafter we use ‘k’ to refer to number of studies and trials and ‘n’ to refer to number of participants. We identified 94 RCTs and

12 non RCTs. The total sample size across all studies was 15,514 (range: 10-1073). The average age of participants ranged from 12 hours old to 104 years. Thirty-six trials were conducted with neonates/infants/children (12hrs old to 13.8 years), thirty-eight with adults (18-65 years), thirty-one in older adults (65-89 years) and one in both adults and older adults (24-104 years). Twenty-five different vaccines were used, the most common was influenza, with 48 trials focussed solely on responses to seasonal influenza vaccine (see Appendices 2-4 for detailed summary of all trials).

The length of the interventions ranged from a single dose or session of 1 minute to daily supplements for 2 years. Fifteen trials administered their vaccination post-intervention; k=32 before or at the first intervention session, k=57 during the intervention, and k=2 were not clear in terms of when the vaccination was given in relation to the intervention. Over half of all trials, k=58/106 (55%) and 50/94 of all RCTs, reported evidence of a statistically significant improvement in the antibody response to vaccination across one or more outcome, but not necessarily all outcomes (see Appendices 2-4). (Ahmed, Arifuzzaman, Lebens, Qadri, & Lundgren, 2009; Akatsu et al., 2013; Akatsu et al., 2016; Albert MJ et al., 2003; Bahl R et al., 2002; Benn et al., 2002; Bhaskaram, Arun Jyothi, Visweswara Rao, & Narasinga Rao, 1989; Bhaskaram & Rao, 1997; Boge et al., 2009; Bosch et al., 2012; Chandra & Puri, 1985; L. E. Davidson, Fiorino, Snyderman, & Hibberd, 2011; R. J. Davidson et al., 2003; de Vrese et al., 2005; Duchateau, Delepesse, Vrijens, & Collet, 1981; Edwards et al., 2008; Edwards et al., 2007; Edwards et al., 2006; French & Penny, 2009; Gibson et al., 2012; Girodon, Galan, Monget, & et al., 1999; Hawkes, Gibson, Robertson, & Makrides, 2005; Heine et al., 2011; Hsu et al., 1995; Isolauri, Joensuu, Suomalainen, Luomala, & Vesikari, 1995; Karlsen et al., 2003; Marian L. Kohut et al., 2004; M. L. Kohut et al., 2005; Kukkonen, Nieminen, Poussa, Savilahti, & Kuitunen, 2006; Langkamp-Henken et al., 2004; Langkamp-Henken et al., 2006; Link-Amster, Rochat, Saudan, Mignot, & Aeschlimann, 1994; Maruyama et al., 2016; Meydani, Meydani, Blumberg, & et al., 1997; Negishi, Mori, Mori, & Yamori, 2013; Newton et al., 2007; Olivares et al., 2007; Osendarp et al., 2007; Paineau et al., 2008; Petrie, Booth, Pennebaker, Davison, & Thomas, 1995; M. M. Rahman et

al., 1999; Rizzardini et al., 2012; Roman, Beli, Duriancik, & Gardner, 2013; SCAGLIONE, CATTANEO, ALESSANDRIA, & COGO, 1996; Richard D Semba & West Jr, 1992; Soh et al., 2010; Stetler, Chen, & Miller, 2006; Udani, 2013; Udani, Singh, Barrett, & Singh, 2010; Vedhara et al., 2003; Vidal et al., 2012; Whitham & Blannin, 2003; Woods et al., 2009; Wouters-Wesseling et al., 2002; Yang et al., 2008; Youngster, Kozer, Lazarovitch, Broide, & Goldman, 2011); k=43/106 (41%) showed the intervention had no significant effect on the antibody response (Bahl et al., 1999; Benn et al.; Boge et al., 2009; Broome et al., 2004; Brown, Rajan, Chakraborty, & Aziz, 1980; Bunout et al., 2004; Bunout et al., 2002; Campbell et al., 2010; Cherian, Varkki, Raghupathy, Ratnam, & Chandra, 2003; Edwards et al., 2012; Fang, Elina, Heikki, & Seppo, 2000; Habib et al., 2015; Harman & White Miller, 1986; Hayney et al., 2014; Huang & Huang, 1999; Ivory et al., 2017; Jespersen et al., 2015; Darshan S Kelley, Taylor, Nelson, & Mackey, 1998; D. S. Kelley et al., 2000; Kriesel & Spruance, 1999; Kutukculer et al., 2000; Link-Amster et al., 1994; Long et al., 2013; Long et al., 2012; Namba, Hatano, Yaeshima, Takase, & Suzuki, 2010; Osendarp et al., 2006; Principi et al., 2013; M. Provinciali et al., 1998; Przemska-Kosicka et al., 2016; Mohammad M. Rahman et al., 1998; Ranadive et al., 2014; Remarque, Witkamp, Masurel, & Ligthart, 1993; Richard David Semba et al., 1997; Richard D. Semba et al., 1999; Soh et al., 2010; Stam, van Stuijvenberg, Garssen, Knipping, & Sauer, 2011; Türk S et al., 1998; Van Puyenbroeck et al., 2012; West et al., 2008; Yalçın et al., 2011) and k=6/106 (6%) showed evidence of a significantly impaired antibody response in the intervention group. In only k=59/106 trials (56%) was adequate adherence with the intervention reported, or could it be assumed due to the intervention being supervised/administered by the trial team and/or being a single session. Furthermore, assessments of intervention fidelity (i.e., did the intervention have the desired effects on the target mechanisms or processes) were reported in very few trials: k=25/106 (24%) trials reported data suggesting intervention fidelity and k=5/106 (5%) reported data which indicated the intervention had either not been delivered as intended and/or had not had the desired effect on target mechanisms or processes. In the remaining trials (k=76/106) no relevant data were reported.

INSERT TABLES 2-4 ABOUT HERE

Narrative Summary of Dietary/Nutritional Formulae Interventions

Seventy-nine papers, covering 85 trials (77 of which were RCTs and 8 non-RCTs) delivered a dietary or nutritional intervention (total sample size = 13,418, range 10- 1073). The average age of participants ranged from 12 hours to 104 years. The studies included k=41 examining effects of vitamin and/or mineral treatments, k=28 examined effects of probiotics; k=6 evaluated nutritional formulae; k=2 focussed on fatty acid interventions and the remaining k= 8 involved other types of interventions, most evaluated in only one trial. Thirty-two trials were classified as involving participants at risk of vaccine failure (see Table 2/Appendix 2)

Thirty four trials were conducted in children (12 hours old to 13.8 years old), of these three involved either giving the intervention to mothers during pregnancy (Osendarp et al., 2006), during pregnancy and to the neonates/infants post-delivery (Kukkonen et al., 2006), or giving the intervention post-delivery to both mothers and their neonate/infants. Twenty four were conducted in adults (18-65 years), k=26 in older adults (65-86.7 years), and k=1 with both adults and older adults (18yrs-104yrs) (Harman & White Miller, 1986).

Twenty-four different vaccines were used, the most common was influenza with k=38 focussed solely on responses to influenza vaccine. The length of the interventions ranged from a single dose intervention (Bahl et al., 1999; Bhaskaram et al., 1989; Bhaskaram & Rao, 1997; Brown et al., 1980; Cherian et al., 2003; Kriesel & Spruance, 1999; R. D. Semba et al., 1995; Richard D Semba & West Jr, 1992) to daily supplements for two years (Girodon et al., 1999). Three trials administered their vaccination post-intervention; k=28 before or at the start of the intervention, k=52 during the intervention period and k=2 were not clear in terms of when the vaccination was given in relation to the intervention.

Fifty-two percent of all trials (k=44/85), of which 53% (k=41/77) were RCTs, reported some evidence of a statistically significant improvement in the antibody response to vaccination in the

intervention vs control groups; k=36/85 (42%) showed the intervention had no significant effect on antibody response and k=5/85 (6%) showed evidence that their intervention significantly impaired/reduced antibody response.

Forty-two trials (49%) reported adequate adherence with the intervention or adherence could be assumed because the intervention was supervised/administered by the trial team and/or was a single session. However, in k=42/85 (49%) adherence was not reported and k=1 trial reported considerable variability in participant adherence (West et al., 2008).

Narrative Summary of Physical Activity Interventions

Twelve trials (9 randomised and 3 non or pseudorandomised) examined the effects of physical activity interventions (total sample size n=888 , range n=21-144; including two paired trials which reported different outcomes from the same subjects (Edwards et al., 2008; Edwards et al., 2006) (Marian L. Kohut et al., 2004; M. L. Kohut et al., 2005). All trials were conducted in healthy adults (n=7) or older adults (n=5) (Marian L. Kohut et al., 2004; M. L. Kohut et al., 2005; Long et al., 2012; Ranadive et al., 2014; Woods et al., 2009), with the average age of participants ranging from 20-72 years. A mix of interventions were tested ranging in duration from a single 15-minute session to 3 sessions a week of 45-60 minutes for 10 months. Six trials, all in younger adults, were laboratory based and used exercise regimes under the supervision of the study teams. The six remaining trials employed what might be termed lifestyle exercise at varying degrees of intensity. This ranged from a brisk walk just prior to vaccination (Long et al., 2012) to a 10-month supervised exercise programme (Woods et al., 2009). All of the studies had high levels of adherence as there was an element of supervision, either direct or indirect, in their design (see Table 3/Appendix 3).

Three different vaccines were used (influenza, pneumococcal and meningococcal), with the majority of trials (k=8) focussing on influenza. Seven trials administered their intervention before vaccination; k=2 post-vaccination and k=3 administered the vaccination during the intervention

period. Two-thirds of all trials ($k=8/12$) and RCTs ($k=7/9$) reported some evidence of an enhanced antibody response to vaccination in the intervention arm.

Narrative Summary of Psychological Interventions

Nine studies (7 RCTs, 1 matched control and 1 waiting list control) reported on four broad categories of intervention: meditation/mindfulness ($n=3$), massage ($n=3$), expressive writing ($n=2$) and cognitive behavioural stress management ($n=1$). 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), four 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. The length of the interventions ranged from single sessions of 1 minute (Hsu et al., 1995) to 3 x 1 hour sessions per week for 20 weeks (Yang et al., 2008). Five trials administered their vaccination post-intervention; two before or at the first intervention session and two during the intervention (see Table 4/Appendix 4).

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 and one showed evidence of an impaired antibody response in the intervention group.

Network Meta-Analysis (NMA) Results

The NMA combines results across the networks of intervention comparisons for the most common outcome types (i.e., antibody titres, seroconversion and protective antibody titres). We fitted NMA models for each of the intervention categorisations in Table 5, but found that using more detailed categorisations did not improve model fit or heterogeneity (Appendix 1, Table S1). Because Categorisation 3 was considered to be too broad to be useful and results below are based on Categorisation 2 (Table 5), however results for the more detailed Categorisation 1 and Categorisation 2 are provided in Appendix 1 (Tables S2-S3).

Antibody Titres

Forty-eight studies provided results on antibody titres for at least one antigen included in the vaccination given in that study, representing 325 data-points across studies, intervention arms and antigens. The network of evidence is shown in Figure 2a and reveals that the network is 'connected' (i.e., there is a path from any one intervention to any other) and so it is possible to fit an NMA model.

Combining all studies together in a network meta-analysis indicated some lack of fit (posterior mean residual deviance 343 which is higher than expected based on 325 datapoints) (Appendix 1, Table S4). There was a high level of heterogeneity, with a between antigen standard deviation of 0.29 95%CrI (0.22, 0.37), and between study standard deviation of 1.03 95%CrI (0.82, 1.30) on a standardised mean difference scale (Appendix 1, Table S4). However, there was no evidence that accounting for subgroups (vaccine type, risk of vaccine failure, or age-group) improved model fit or explained heterogeneity (Appendix 1, Table S4). Furthermore, excluding studies at high risk of bias on key domains did not lead to a better fitting model (given the lower number of data-points) nor reduce heterogeneity, and there was no evidence of small study effects (Appendix 1, Table S4). There was some evidence of effect modification by follow-up time, with an increase in SMD antibody titre of 0.027 per week (95%CrI (0.003, 0.051) (Appendix 1, Table S4). Excluding studies with poor model fit (Long et al., 2012; M. M. Rahman et al., 1999), reduced between antigen standard deviation to 0.086 (0.003, 0.160), however overall conclusions were unchanged. There was no evidence of inconsistency (Appendix 1, Table S4) based on the model fit or comparison of direct estimates and NMA estimates (where direct estimates were available) (Appendix 1, Table S5). All results from the subgroup analyses, sensitivity analyses, and meta-regressions are available in Appendix 1 (Tables S6-S8).

We present results using all data from the NMA model assuming consistency, but advise caution in their interpretation due to the high levels of heterogeneity and evidence of lack of fit.

Table 6 shows the estimated average (across antigen) standardised mean difference in antibody titre for each intervention compared with placebo. All estimates are very uncertain, with wide credibility intervals. There was some weak indication that probiotics (SMD 0.646, 95%CrI (0.059, 1.233)) and nutritional formulae (SMD 0.995, 95%CrI (-0.086, 2.083)) may have some benefit in increasing antibody titres. In subgroup analyses we found these effects were driven by studies conducted in individuals at high risk of vaccine failure for nutritional formulae and by studies in individuals at low risk of vaccine failure for probiotics (Table 7).

Seroconversion

Twenty-five studies provided results on the number of patients achieving seroconversion for at least one viral strain included in the vaccination given in that study, representing 127 data-points across studies, intervention arms and antigens. The network of evidence is shown in Figure 2b and reveals that, with the exception of fatty acids, the network is 'connected'. It was, therefore, possible to fit an NMA model for the 'connected' interventions.

Combining all studies together in a NMA indicated some lack of fit (posterior mean residual deviance 132.2 which is higher than expected based on 127 datapoints) (Appendix 1, Table S4). As observed with antibody titres, there was a high level of heterogeneity, with a between antigen standard deviation of 0.13 95%CrI (0.00, 0.34), and between study standard deviation of 0.73 95%CrI (0.51, 1.02). Neither accounting for subgroups (vaccine type, risk of vaccine failure, or age-group), accounting for follow-up time or sample size, nor excluding studies at high risk of bias improved model fit or explained heterogeneity (Table S4). However, one study (Rizzardini et al., 2012) was identified as an outlier. Excluding this study improved model fit (posterior mean deviance 108.2 compared with 115 data-points), and reduced heterogeneity (between antigen standard deviation of 0.078 95%CrI (0.003, 0.227) and between studies standard deviation of 0.378 (0.149, 0.635). There was no evidence of inconsistency (Appendix 1, Table S4) based on the model fit or comparison of direct estimates and NMA estimates (where direct estimates were available) (Appendix 1, Table S5).

All results from the subgroup analyses, sensitivity analyses, and meta-regressions are available in Appendix 1 (Tables S6-S8).

We therefore present results from the NMA model assuming consistency, based on all data except (Rizzardini et al., 2012). Table 6 shows the estimated average (across antigen) log-odds ratio for seroconversion for each intervention compared with placebo. There was no evidence that any of the interventions increased the odds of seroconversion. In subgroup analyses we found, however, that there was some evidence that probiotics (log odds ratio 0.769 95%CrI (0.101, 1.441)) may increase the odds of seroconversion in studies conducted in individuals at high risk of vaccine failure (Table 7).

Seroprotection

Twenty-three studies provided results on the number of patients achieving seroprotection for at least one viral strain included in the vaccination given in that study, representing 126 data-points across studies, intervention arms and antigens. The network of evidence is shown in Figure 2c. As with seroconversion, the network is 'connected' (apart from fatty acids). It was, therefore, possible to fit an NMA model for the 'connected' interventions.

The network meta-analysis model gave a good fit to the data (posterior mean residual deviance 115.7 compared with 126 datapoints) (Appendix 1, Table S4). As for the other outcomes, there was a high level of heterogeneity between studies, with a between study standard deviation of 0.52 95%CrI (0.28, 0.87), but lower between antigen standard deviation of 0.05 95%CrI (0.00, 0.16). Furthermore, accounting for subgroups (vaccine type, risk of vaccine failure, or age-group), follow-up time or sample size, or excluding studies at high risk of bias did not improve model fit or explain heterogeneity (Table 5). There was no evidence of inconsistency (Appendix 1, Table S4) based on the model fit or comparison of direct estimates and NMA estimates (where direct estimates were available) (Appendix 1, Table S5). All results from the subgroup analyses, sensitivity analyses, and meta-regressions are available in Appendix 1 (Tables S6-S8).

Table 6 shows the estimated average (across antigen) log-odds ratio for seroprotection for each intervention compared with placebo. All estimates are very uncertain, with wide credibility intervals, but show no evidence of any impact of any of the interventions on the odds of seroprotection compared with placebo. This conclusion was robust to subgroup analyses and excluding studies at high risk of bias (Appendix 1, Tables S6-S8).

INSERT FIGURE 2A-2C AND TABLE 5-7 HERE

Discussion

The present review has synthesised evidence from 100 papers reporting 106 trials examining the effects of a broad range of non-pharmacological adjuvants on vaccine effectiveness, as measured by antibody responses. The results from the NMA found early evidence in support of dietary interventions: with probiotics and nutritional formulae associated with increased antibody titres, and in people at risk of vaccine failure there was some evidence that probiotics increased the odds of seroconversion. The NMA found no evidence of efficacy for physical activity and psychological interventions, however this may reflect the absence of reliable data in these areas due to the evidence being modest, heterogeneous, often characterised by small sample sizes and methodological limitations, some of which are considered below. The NMA also found no evidence that the effects of non-pharmacological interventions varied significantly between different vaccines or age ranges, although this too may be due to insufficient data. We acknowledge, however, that this review and our resultant conclusions are based on searches of the literature last updated in 2018. This is not unusual for reviews involving a large and complex literature, and NMA reviews in particular (Cipriani et al., 2018; Shields, Spahr, & Slavich, 2020), where a trade-off has to be made between the time involved in updating searches, screening and analyses, with the likelihood of identifying new studies which might significantly alter one's findings. In the case of the present review our experience is that this is not a rapidly changing field (e.g., searches undertaken between

2015 and 2017 yielded only 4 new trials suitable for inclusion)(Akatsu et al., 2016; Habib et al., 2015; Maruyama et al., 2016; Timby et al., 2015). Thus, we concluded that an update was not warranted, as it would be unlikely to change the nature of our conclusions or alter the issues we have highlighted as worthy of discussion. The first of these issues is that, while the NMA allowed us to make comparisons across a range of interventions, it is appropriate to acknowledge the presence of significant heterogeneity in both the approaches to intervention and characteristics of the target populations. In terms of interventions, we classified these into three broad categories (dietary/nutritional formulae, physical activity and psychological), but even within these categories there was significant heterogeneity, with trials evaluating a total of 61 different interventions which varied in duration from 1 minute to 2 years and with vaccinations variously administered pre, post and during the interventions. In the NMA we explored a more detailed categorisation of these interventions (See Table 5), but did not find evidence that the categorisation or definition of interventions was a key driver of heterogeneity.

In terms of populations, the trials reviewed here included groups across the lifespan (including studies where the intervention commenced in utero as a result of being offered to women during pregnancy), and studies on healthy volunteers as well as people characterised by other risk factors such as co-existing disease, nutritional deficiency and poverty. Despite extensive subgroup analyses, meta-regression, and sensitivity analyses we were unable to reduce this heterogeneity. It is perhaps not surprising then that this heterogeneity resulted in uncertainty in our pooled estimates which, in turn, necessitates that we encourage caution in the interpretation of findings. Indeed, the findings from all the interventions should be interpreted within the context of the populations in which they have been tested e.g., evidence of effectiveness (or lack of effectiveness) in an older population, should not be interpreted as evidence of effectiveness (or otherwise) in a younger population and vice versa.

Notwithstanding this heterogeneity, a number of observations can be made. For example, the evidence from our narrative synthesis showed that, over half of all trials ($k=58/106$) and RCTS ($k=50/94$) demonstrated an improvement in one or more antibody outcome and that relatively few trials ($k=6$) resulted in a significant impairment in the antibody response to vaccination. These results suggest that while the evidence on benefit is unclear, non-pharmacological interventions, thus far, carry with them little evidence of harm.

The NMA also found no evidence that the effectiveness of interventions was related to the type of vaccination or age of participants. Although this may be due to insufficient data, if this was upheld in future trials, it could suggest that non-pharmacological interventions could be deployed across a range of vaccines and populations. At a time when the scientific and medical community is rightly consumed with trying to identify an effective vaccine against Coronavirus 2019 (COVID-19)(Chen, Strych, Hotez, & Bottazzi, 2020), it is ever more important for us to determine the adjuvant potential of non-pharmacological interventions.

The narrative synthesis also illuminated two methodological issues which characterised many of the trials included in this review. First, we observed that in 46/106 of trials (46%) it was not possible to determine participant adherence to the intervention (i.e., establish if participants engaged with the treatments as prescribed); and in 76/107 of trials (72%) it was not possible to determine intervention fidelity (i.e., did the intervention have the desired effects on the target mechanisms or processes). The absence of such information means it is difficult to conclude whether a null effect is due to the genuine absence of an effect, or due to participants not engaging appropriately with the intervention or failings in the intervention itself or its delivery. We would suggest that future work would benefit from the inclusion of fidelity checks or process evaluations; and for interventions longer than single sessions, or not delivered under supervision, to include robust measures of intervention adherence.

The second issue relates to the assessment of outcomes. In the review we focused on only one feature of the immune response to vaccination: the antibody response. Although antibody levels are widely accepted to be the best surrogate marker of clinical effectiveness we observed considerable variability in the ways this outcome 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 (Nauta, Beyer, & Osterhaus, 2009; Richens et al., 2010). 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) (Briem & Safary, 1994; Horowitz, Ershler, McKinney, & Battiola, 1988; Milne & Waldon, 1992; Van Damme et al., 1994); 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). The choice of primary outcome may also be influenced by the nature of the vaccine itself (Siegrist, 2013). 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 advocated by the COMET initiative (Williamson & Altman, 2010). 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 and could help to achieve harmonisation in both the choice and timing of outcome assessment as indicated above. To that end, we strongly support the use of consensus methods (e.g., Delphi) to arrive at core outcome sets in this area. Although we recognise that the

inherently multidisciplinary nature of the field, and the need to reconcile potentially differing clinical, academic, patient and public views, may make this challenging. Finally, we also recommend greater uptake of pre-registration of trial designs and analysis plans as this would alleviate concerns regarding 'researcher degrees of freedom' (Simmons, Nelson, & Simonsohn, 2011) which can also lead to false-positive results. It is also worth noting that some features of vaccinations may themselves conspire to obscure the effects of non-pharmacological interventions on antibody responses. For example, influenza vaccine is seasonal with many people receiving the vaccination every year. While the viral strains present in the vaccines often vary, there has been a concern that the vaccine may become less effective over time (Iorio et al., 2007; Ramsay et al., 2019). Consistent with this, there is evidence from both observational and intervention studies that non-pharmacological influences on antibody levels are often most pronounced for the most novel viral strains (Vedhara et al., 2003; Vedhara et al., 1999). In addition, many vaccines contain pharmacological adjuvants designed to boost effectiveness (Shah, Hassett, & Brito, 2017). It remains theoretically possible, therefore, that these adjuvants result in a ceiling effect which would limit the scope for further improvements through non-pharmacological adjuvants.

In summary, considerable heterogeneity exists in the evidence pertaining to non-pharmacological vaccine adjuvants. However, we suggest that there is some early evidence that probiotics and nutritional formulae may be effective, while the evidence for other interventions is unclear. Methodological challenges exist in relation to the design of trials in this field. Large, well-designed trials with a consistent set of core outcomes and assessments of intervention adherence and fidelity are needed if we are to be able to determine with certainty the potential for non-pharmacological interventions to increase the effectiveness of vaccines.

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