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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.

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.

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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, Snydman, & 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, Roberton, & 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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Kavita Vedhara (lead author and guarantor for this manuscript) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1

PRISMA summary of search procedure

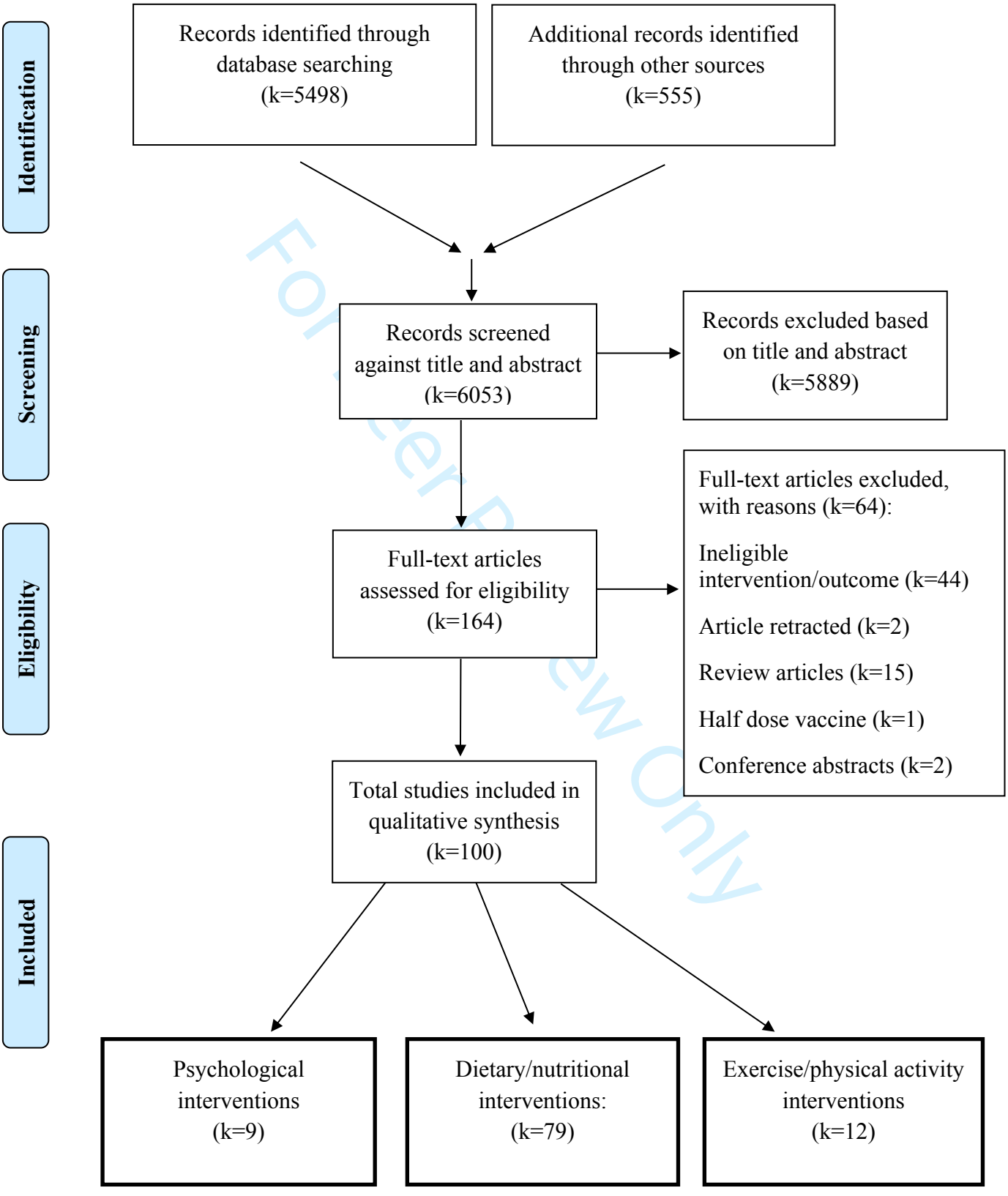


Table 1

Risk of Bias Assessments for all Included Studies

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ahmed	2009	H	H	?	?	L	L	H
Ahmed	2010	?	?	L	?	L	L	L
Akatsu	2013	L	?	L	?	L	L	L
Akatsu	2016	?	H	H	?	H	L	L
Albert	2003	L	?	L	?	L	L	L
Bahl	1999	L	?	L	L	L	L	L
Bahl	2002	L	?	L	?	L	L	L
Benn	1997	L	L	L	L	L	L	L
Benn	2002	L	L	L	L	H	L	?
Bhaskaram	1989	?	?	?	?	H	L	L
Bhaskaram	1997	?	?	?	?	?	?	L
Boge	2009	L	L	L	?	L	L	L
Bosch	2012	?	?	L	?	L	L	?
Braga	2015	?	?	L	L	?	L	L
Broome	2004	?	?	L	L	L	L	L
Brown	1980	L	?	?	?	H	L	L
Bunout	2002	L	?	L	?	H	L	L
Bunout	2004	H	H	H	H	L	L	L
Campbell	2010	H	?	H	?	?	?	L

Chandra	1985	?	?	?	?	L	L	L
Cherian	2003	?	?	L	?	H	L	L
Davidson	2011	L	L	L	L	L	L	L
Davidson	2003	?	?	H	?	?	?	L
De Vrese	2005	?	?	L	?	L	L	?
Duchateau	1981	?	?	?	?	?	L	L
Edwards	2006	?	?	H	?	?	?	?
Edwards	2007	H	?	H	?	?	?	L
Edwards	2008	?	?	H	?	?	?	L
Edwards	2012	?	L	H	L	?	?	L
Fang	2000	H	?	?	?	L	L	?
French	2009	L	?	L	?	L	L	?
Gibson	2012	L	?	?	L	L	L	L
Girodon	1999	L	?	L	L	H	L	L
Habib	2015	L	?	L	L	L	L	L
Harman	1986	?	?	?	?	?	L	L
Hawkes	2006	L	L	H	?	H	L	L
Hayney	2014	L	L	H	L	L	?	L
Heine	2011	?	?	L	?	?	L	H
Hsu	1995	?	?	H	?	?	?	L
Huang	1999	?	?	H	?	?	?	L
Isolauri	1995	?	?	?	?	?	L	?
Ivory	2017	L	L	L	L	L	L	L
Jespersen	2015	L	?	L	L	L	L	H
Karlsen	2003	?	H	?	?	?	L	?
Kelley	1998	n/a	n/a	n/a	n/a	n/a	L	n/a

Kelley	2000	?	?	?	?	L	L	L
Kohut	2004	?	?	H	?	?	?	L
Kohut	2005	?	?	H	?	?	?	L
Kriesel	1999	?	L	L	?	L	L	L
Kukkonen	2006	L	L	L	?	H	L	L
Kutukculer	2000	?	?	?	?	H	L	L
Langkamp-Henken	2004	?	?	?	?	H	?	L
Langkamp-Henken	2006	?	L	L	?	H	L	L
Link-Amster	1994	?	?	?	?	?	L	?
Loft	2012	L	?	H	?	?	?	L
Long	2012	?	?	H	?	?	?	L
Long	2013	?	?	H	?	?	?	L
Maruyama	2016	L	L	L	L	L	L	H
Meydani	1997	L	L	L	L	L	L	L
Namba	2010	?	?	L	?	H	L	H
Negishi	2013	?	?	L	?	H	L	H
Newton	2007	H	H	H	L	L	L	L
Olivares	2007	?	?	?	?	?	L	?
Osendarp	2006	L	?	L	?	H	L	L
Osendarp	2007	L	?	L	L	H	L	L
Paineau	2008	?	?	L	?	L	L	H
Petrie	1995	?	?	H	?	?	?	L
Prinicipi	2013	?	?	H	H	L	L	L
Provinciali	1998	?	?	?	?	?	L	L
Przemska	2016	L	?	L	?	L	L	H

Qadri	2004	?	L	L	?	L	L	L
Rahman	1998	?	L	L	?	?	L	H
Rahman	1999	?	?	L	?	?	L	L
Ramarque	1993	?	?	?	?	L	L	L
Ranadive	2014	?	?	H	?	?	?	L
Rizzardini	2012	L	?	L	?	L	L	L
Roman	2013	?	?	?	?	L	L	L
Scaglione	1996	?	?	L	?	L	L	H
Semba	1992	?	L	L	?	L	L	L
Semba	1995	L	?	L	?	?	?	L
Semba	1997	L	?	L	?	H	L	L
Semba	1999	L	?	L	?	H	L	L
Soh	2010	L	L	L	L	L	L	L
Stam	2011	?	?	L	?	H	L	?
Stetler	2006	?	?	H	?	?	?	L
Timby	2015	?	?	L	?	H	L	?
Turk	1998	?	?	L	?	L	L	L
Turnlund	2004	H	?	?	?	L	L	H
Udani	2010	?	?	L	L	L	L	L
Udani	2013	L	?	L	?	L	L	?
Van Puyenbroeck	2012	?	?	L	L	H	L	L
Vedhara	2003	H	H	H	?	L	?	H
Vidal	2012	L	L	L	L	L	L	L
West	2008	?	?	L	L	L	L	L
Whitham	2003	H	H	H	?	?	?	?

Woods	2009	?	?	H	L	?	?	L
Wouters-Wesseling	2002	?	?	?	?	L	L	L
Yalcin	2011	L	?	?	L	L	L	L
Yang	2008	H	H	H	?	L	?	L
Youngster	2011	L	?	L	L	L	L	L

Table 2 *Summary of Dietary Studies*

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Ahmed (2009) Quasi-experimental **Intervention code A**	Infants	Zinc	Cholera	✓
Ahmed (RVF) (2010) RCT **Intervention code A**	Infants	Zinc	Cholera	✓
Akatsu (RVF) (2013) RCT **Intervention code B**	Older adults	Probiotic	Influenza	✓
Akatsu (RVF) (2016) RCT **Intervention code B**	Older adults	Prebiotics	Influenza	✓
Albert (RVF) (2003) RCT **Intervention code A**	Children	Vitamin A and/or zinc	Cholera	✓
Bahl (RVF) (1999) RCT **Intervention code A**	Infants	Vitamin A	Measles	**X**
Bahl (RVF) (2002) RCT **Intervention code A**	Mothers and infants	Vitamin A	Polio, diptheria, pertussis, tetanus	✓
Benn (1997) RCT **Intervention code A**	Infants	Vitamins A and E	Measles and/or poliomyelitis	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Benn (2002) RCT **Intervention code A**	Children	Vitamin A	Measles	✓ .
Bhaskaram (RVF) (1989) Quasi-experimental **Intervention code A**	Children	Vitamin A	Diphtheria, Tetanus	✓
Bhaskaram (1997) Quasi-experimental **Intervention code A**	Infants	Vitamin A	Measles	✓
Boge (RVF) (2009) RCT **Intervention code B**	Older adults	Probiotic	Influenza	✓
Bosch (RVF) (2012) RCT **Intervention code B**	Older adults	Probiotic	Influenza	✓
Braga (RVF) (2015) RCT **Intervention code A**	Adult patients	Zinc	Pneumococcal	**X negative**
Broome (2004) Quasi-experimental **Intervention code A**	Adults	Selenium	Poliomyelitis	**X**
Brown (1980) Matched pairs **Intervention code A**	Children	Vitamin A	Tetanus	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Bunout (2002) RCT **Intervention code B**	Older adults	Prebiotic	Influenza and Pneumococcal vaccines	**X**
Bunout (2004) Quasi-experimental **Intervention code C**	Older adults	Nutritional supplement	Influenza and pneumococcal	**X**
Chandra (RVF) (1985) RCT **Intervention code E**	Older adults	Nutritional advice and oral dietary & medicinal supplements .	Influenza	✓
Cherian (2003) RCT **Intervention code A**	Infants	Vitamin A	Measles	**X**
Davidson (2011) RCT **Intervention code B**	Adults	Probiotic	Influenza	✓
De Vrese (2005) RCT **Intervention code B**	Adults	Probiotic	Polio	✓
Duchateau (1981) RCT **Intervention code A**	Older adults	Zinc	Tetanus	✓
Fang (2000) RCT **Intervention code B**	Adults	Probiotic	Salmonella	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
French (2009) RCT **Intervention code B**	Adults	Probiotics	Influenza	✓
Gibson (2012) RCT **Intervention code E**	Older adults	≥5 portions of fruit and vegetables	Tetanus, Pneumococcal	✓
Girodon (RVF) (1999) RCT **Intervention code A**	Older adults	Trace elements, vitamins or trace elements and vitamins combined	Influenza	✓
Habib (2015) RCT **Intervention code A**	Infants	Zinc	Polio virus	**X**
Harman (RVF) (1986) RCT **Intervention code A**	Adults and older adults	Vitamin E	Influenza	**X**
Hawkes (2006) RCT **Intervention code C**	Infants	NT (nucleotide) formula	Diphtheria, tetanus, pertussis; hepatitis B; haemophilus influenza type b	✓
Heine (2011) RCT **Intervention code A**	Adults	Vitamin D	Tetanus, diphtheria	✓
Isolauri (1995) RCT **Intervention code B**	Infants	Lactobacillus	Rotavirus	✓
Ivory (2017) RCT **Intervention code A**	Adults	Selenium	Influenza	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Jespersen (2015) RCT **Intervention code B**	Adults	Probiotics	Influenza	**X**
Karlsen (2003) RCT **Intervention code A**	Adults	Zinc	Cholera	✓
Kelley (1998) Quasi-experimental **Intervention code D**	Adults	Arachidonic acid	Influenza	✓
Kelley (2000) RCT **Intervention code D**	Adults	Dietary conjugated linoleic acid	Influenza	**X**
Kriesel (1999) RCT **Intervention code A**	Adults	Calcitriol	Influenza	**X**
Kukkonen (2006) RCT **Intervention code B**	Mothers and infants	Probiotics	Diphtheria, tetanus, whole cell pertussis; Haemophilus influenza type b	✓
Kutukculer (2000) RCT **Intervention code A**	Infants	Vitamin A, vitamin E or both	Diphtheria, pertussis, tetanus	✓
Langkamp-Henken (2004) RCT **Intervention code C**	Older adults	Antioxidant nutritional formula	Influenza	✓

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Langkamp-Henken (RVF) (2006) RCT **Intervention code C**	Older adults	Nutrition mediated immune formula.	Influenza	✓
Link-Amster (1994) RCT **Intervention code B**	Adults	Fermented milk	Salmonella	✓
Maruyama (RVF) (2016) RCT **Intervention code B**	Older adults	Lactobacillus	Influenza	✓
Meydani (1997) RCT **Intervention code A**	Older adults	Vitamin E	Hepatitis B; tetanus and diphtheria; pneumococcal	✓
Namba (RVF) (2010) RCT **Intervention code B**	Older adults	Bifidobacterium longum	Influenza	**X**
Negishi (RVF) (2013) RCT **Intervention code E**	Older adults	Mekabu fucoidan	Influenza	✓
Newton (RVF) (2007) RCT **Intervention code A**	Infants	Vitamin A	Diphtheria, polio, tetanus; Haemophilus influenza b; hepatitis B vaccine	✓
Olivares (2007) RCT **Intervention code B**	Adults	Lactobacillus	Influenza	✓

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Osendarp (RVF) (2006) RCT **Intervention code A**	Mothers and infants	Zinc	Bacillus Calmette-Guerin; diphtheria, tetanus, pertussis; haemophilus influenza type-b; polio	**X**
Osendarp (RVF) (2007) RCT **Intervention code A**	Infants	Zinc	Pneumococcal	✓
Paineau (2008) RCT **Intervention code B**	Adults	Probiotic	Cholera	✓
Prinicipi (2013) RCT **Intervention code A**	Children	Vitamin D	Influenza	**X**
Provinciali (RVF) (1998) RCT **Intervention code A**	Older adults	Zinc or Zinc plus arginine	Influenza	**X**
Przemska-Kosicka (2016) RCT **Intervention code B**	Adults and older adults	Probiotic	Influenza	**X**
Qadri (RVF) (2004) RCT **Intervention code A**	Children	Vitamin A; zinc or vitamin A and zinc	Cholera	**X negative**
Rahman (RVF) (1998) RCT **Intervention code A**	Infants	Vitamin A	Diphtheria, Pertussis, Tetanus; polio	**X**
Rahman et al. (RVF) (1999) RCT **Intervention code A**	Infants	Vitamin A	Diphtheria, pertussis, tetanus	✓

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Remarque (1993) RCT **Intervention code A**	Older adults	Zinc	Influenza	**X**
Rizzardini (2012) RCT **Intervention code B**	Adults	Probiotics	Influenza	✓
Roman (2013) RCT **Intervention code E**	Adults	Active hexose correlated compound	Influenza	✓
Scaglione (1996) RCT **Intervention code E**	Adults	Ginsana G 115	Influenza	✓
Semba (1992) RCT **Intervention code A**	Children	Vitamin A	Tetanus	✓
Semba (RVF) (1995) RCT **Intervention code A**	Infants	Vitamin A	Measles	**X negative**
Semba (RVF) (1997) RCT **Intervention code A**	Infants	Vitamin A	Measles	**X**
Semba (RVF) (1999) RCT **Intervention code A**	Infants	Vitamin A	Polio	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Soh (2010) RCT **Intervention code B**	Infants	Probiotics	**Vaccine schedule A:** Hepatitis B administered at ages 0 and 1 month, and Hexavalent diphtheria-tetanus-acellular pertussis at 6-months **Vaccine schedule B:** Hepatitis B administered at ages 0, 1, and 6-months	✓
Stam (2011) RCT **Intervention code B**	Infants	Prebiotic formula	Diphtheria, tetanus, pertussis; polio; Haemophilus influenza b; pneumococcal	**X**
Timby (2015) RCT **Itervention code C**	Infants	Formula supplemented with bovine milk fat globule membranes	Pneumococcal	**X negative**
Turk (RVF) (1998) RCT **Intervention code A**	Healthy adults and patients undergoing haemodialysis	Zinc	Influenza	**X**
Turnlund (2004) Quasi experimental **Intervention code A**	Adults	Copper	Influenza	**X negative**
Udani (2010) RCT **Intervention code E**	Adults	Arabinogalactan extracted from Larch	Pneumococcal	✓
Udani (2013) RCT **Intervention code E**	Adults	Arabinogalactan extracted from Larch	Tetanus; influenza	✓
Van Puyenbroeck (RVF) (2012) RCT **Intervention code B**	Older	Probiotic	Influenza	**X**

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Vidal (2012) RCT **Intervention code E**	Older adults	Wolfberry	Influenza	✓
West (2008) RCT **Intervention code B**	Infants	Lactobacillus	Diphtheria, tetanus toxoid, acellular pertussis; polio; haemophilus influenza b	**X**
Wouters-Wesseling (RVF) (2002) RCT **Intervention code C**	Older adults	Nutritional supplement containing vitamins, minerals antioxidants	Influenza	✓
Yalcin. (RVF) (2011) RCT **Intervention code A**	Children with congenital or acquired cardiac disease	Zinc	Influenza	**X**
Youngster (RVF) (2011) RCT **Intervention code B**	Infants admitted to a paediatric ward with acute illness	Probiotics	Mumps, measles, rubella; varicella	✓

RVF= risk of vaccine failure; intervention codes (A= vitamin and/or mineral; B= probiotic; C=nutritional formulae; D= fatty acid; E=other

Table 3 *Summary of Exercise Studies*

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Campbell (2010) RCT	Adult	Acute eccentric exercise	Influenza	**X**
Edwards (2006) RCT	Adults	Exercise stress four-step cycle ergometer test Mental stress mental arithmetic task	Influenza	✓
Edwards (2007) RCT	Adults	Acute eccentric exercise	Influenza	✓
Edwards (2008) RCT	Adults	Exercise stress: four-step cycle ergometer test Mental stress: mental arithmetic task	Meningococcal A+C	✓
Edwards (2012) RCT	Adults	Elastic resistance band exercise	Pneumococcal	**X**
Kohut (2004) RCT	Older adults	Aerobic exercise	Influenza	✓
Kohut (2005) RCT	Older adults	Aerobic exercise .	Influenza	✓
Long (2012) RCT	Adults	45 mins brisk walking	Pneumococcal	**X**
Long (2013) RCT	Adult women	Lifestyle consultation, pedometer and prompting	Pneumococcal	**X**
Ranadive (2014) RCT	Older adults	Aerobic exercise	Influenza	**X**
Whitham (2003) Non-randomized	Adult males	Increasing exercise	Influenza	✓
Woods (2009) RCT	Older adults	Increasing cardio exercise	Influenza	✓

Table 4 *Summary of Psychological Intervention Studies*

First author (year of publication); trial design	Participants	Intervention	Vaccine	Evidence of improved antibody response
Davidson (2003) RCT	Adults	Mindfulness	Influenza	✓
Hayney (2014) RCT	Adults	Mindfulness	Influenza	**X**
Hsu (1995) RCT	Infants	Massage	Diphtheria, tetanus, pertussis	✓
Huang (1999) RCT	Infants	Massage	Diphtheria, tetanus pertussis	**X**
Loft (2012) RCT	Adults	Massage	Hepatitis B	**X negative**
Petrie (1995) RCT	Adults	Expressive writing	Hepatitis B	✓
Stetler (2006) RCT	Adults	Expressive writing	Influenza	✓
Vedhara (2003) Matched control design	Older adults	Cognitive-behavioural stress management	Influenza	✓
Yang (2008) Waiting-list control design	Older adults	Taiji/Qigong meditation	Influenza	✓

Table 5: Intervention categorisations from the most detailed (Categorisation 1) to the least detailed (Categorisation 3)

Intervention Categorisation 1	Intervention Categorisation 2	Intervention Categorisation 3
Control	Control	Control
Placebo	Placebo	Placebo
Vitamin A	Vitamins / Minerals	Dietary
Zinc	Vitamins / Minerals	Dietary
Vitamin A + Zinc	Vitamins / Minerals	Dietary
Vitamin E	Vitamins / Minerals	Dietary
Zinc + Arginine (amino acid)	Vitamins / Minerals	Dietary
Vitamin and Trace element supplements	Vitamins / Minerals	Dietary
vitamin D	Vitamins / Minerals	Dietary
Nutritional formula	Nutritional formula	Dietary
Probiotic	Probiotic	Dietary
Fatty Acid	Fatty Acid	Dietary
Fruit + Vegetables	Other Dietary	Dietary
AHCC (mushroom extract)	Other Dietary	Dietary
wolfberry	Other Dietary	Dietary
Other Dietary	Other Dietary	Dietary
Aerobic Exercise	Physical Activity	Physical Activity
Flexibility/Balance training	Physical Activity	Physical Activity
Body Massage	Psychosocial	Psychosocial
disclosure	Psychosocial	Psychosocial
mindfulness	Psychosocial	Psychosocial

Table 6

Posterior mean and 95% credible intervals for the relative effects of each intervention compared with placebo for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for seroprotection. Also presented the estimated between antigen sd, between study sd, posterior mean residual deviance, number of datapoints and studies.

Posterior mean (95% CrI) Relative to Placebo	Standardised Mean Difference in Antibody Titre	Log-odds ratio for seroconversion (excluding Rizzardini 2012)	Log-odds ratio for sero-protection
Control	-0.2734(-1.18, 0.5956)	-0.782 (-2.190, 0.675)	-0.239 (-1.117, 0.628)
Vitamins & minerals	-0.1456(-0.6833, 0.3896)	0.081 (-0.201, 0.372)	-0.065 (-0.470, 0.309)
Nutritional formula	0.9947(-0.08597, 2.083)	0.304 (-0.393, 1.083)	1.373 (-0.157, 2.994)
Probiotics	0.6456(0.05935, 1.233)	0.281 (-0.141, 0.715)	0.014 (-0.511, 0.523)
Fatty Acids	-0.2399(-2.397, 1.89)		
Other Dietary	0.2044(-0.7533, 1.168)	0.098 (-0.938, 1.119)	0.699 (-0.305, 1.659)
Physical Activity	-0.2914(-1.55, 0.9472)	-0.725 (-2.391, 0.930)	0.133 (-0.991, 1.305)
Psychosocial	-0.581(-1.903, 0.7392)	-1.018 (-2.675, 0.641)	-0.328 (-1.743, 1.136)
Between study sd	1.03 (0.82, 1.30)	0.38 (0.15, 0.64)	0.52 (0.28, 0.87)
Between antigen sd	0.29 (0.22, 0.37)	0.08 (0.00, 0.23)	0.05 (0.00, 0.16)
Residual deviance	343.1	108.2	115.7
No. datapoints	325	115	126
No. studies	48	25	23

Table 7

Posterior mean and 95% credible intervals for the relative effects of each intervention compared with placebo separately for those at low and high risk of vaccine failure for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for sero-protection.

Posterior mean (95% CrI) Relative to Placebo	SMD in Antibody Titre, low risk of vaccine failure	SMD in Antibody Titre, high risk of vaccine failure	Log OR for seroconversion, low risk of vaccine failure	Log OR for seroconversion, high risk of vaccine failure	Log OR for sero-protection, low risk of vaccine failure	Log OR for sero-protection, high risk of vaccine failure
Control	0.155 (-1.613, 1.885)	-0.412 (-1.524, 0.703)		-2.678 (-6.333, -0.097)	0.381 (-2.260, 4.587)	-0.168 (-1.59, 1.265)
Vitamins & minerals	-0.104 (-1.017, 0.812)	-0.211 (-0.917, 0.486)	0.336 (-0.146, 0.869)	-0.021 (-0.347, 0.294)	0.003 (-0.668, 0.690)	-0.099 (-0.719, 0.484)
Nutritional formula	0.035 (-2.078, 2.137)	1.303 (0.005, 2.615)		0.138 (-0.561, 0.866)	1.286 (-0.368, 2.96)	
Probiotics	1.005 (0.245, 1.761)	0.122 (-0.809, 1.045)	-0.044 (-0.566, 0.502)	0.769 (0.101, 1.441)	-0.137 (-0.843, 0.556)	0.376 (-0.646, 1.387)
Fatty Acids	-0.242 (-2.401, 1.924)					-
Other Dietary	0.290 (-0.731, 1.311)			0.409 (-0.686, 1.509)	1.454 (-1.689, 5.956)	0.527 (-0.889, 1.905)
Physical Activity	0.120 (-1.839, 2.050)				0.719 (-2.027, 4.996)	
Psychosocial	-0.285(-2.003, 1.422)				0.225 (-2.726, 4.588)	

FIGURE 2a-2c

Network plots for (a) antibody titre (b) seroconversion and (c) seroprotection. Nodes indicate interventions and lines indicate there is an RCT directly comparing those interventions.

Figure 2a

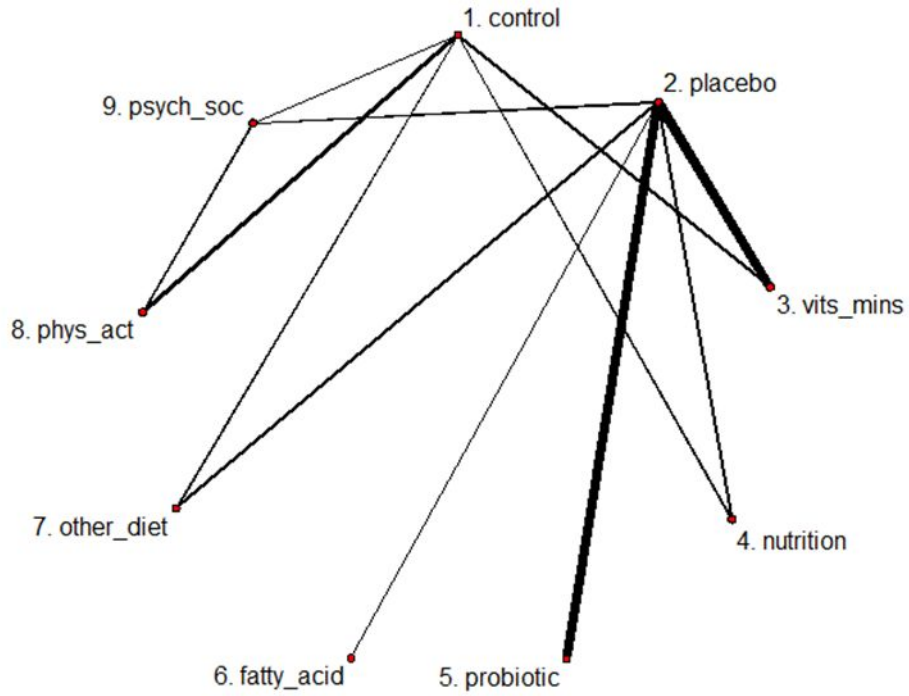


Figure 2b

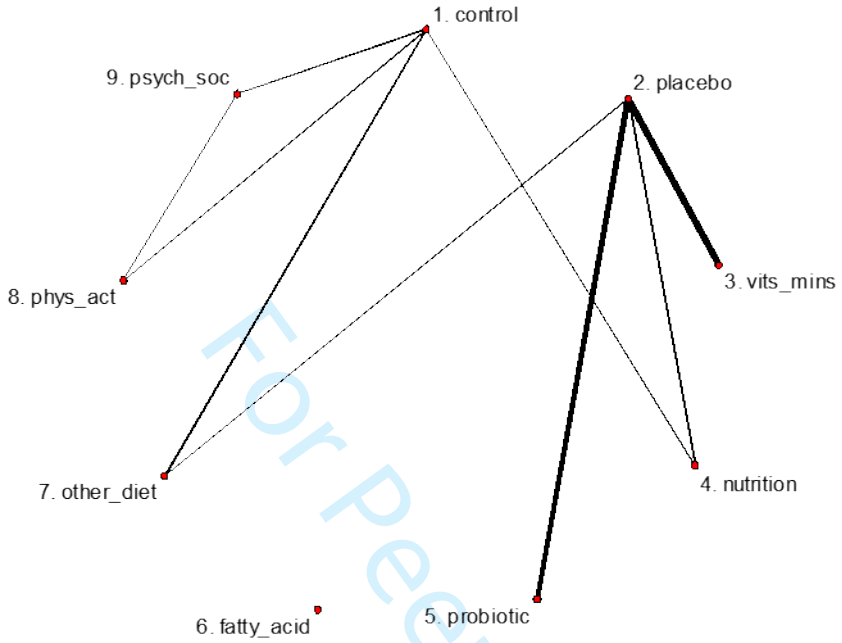
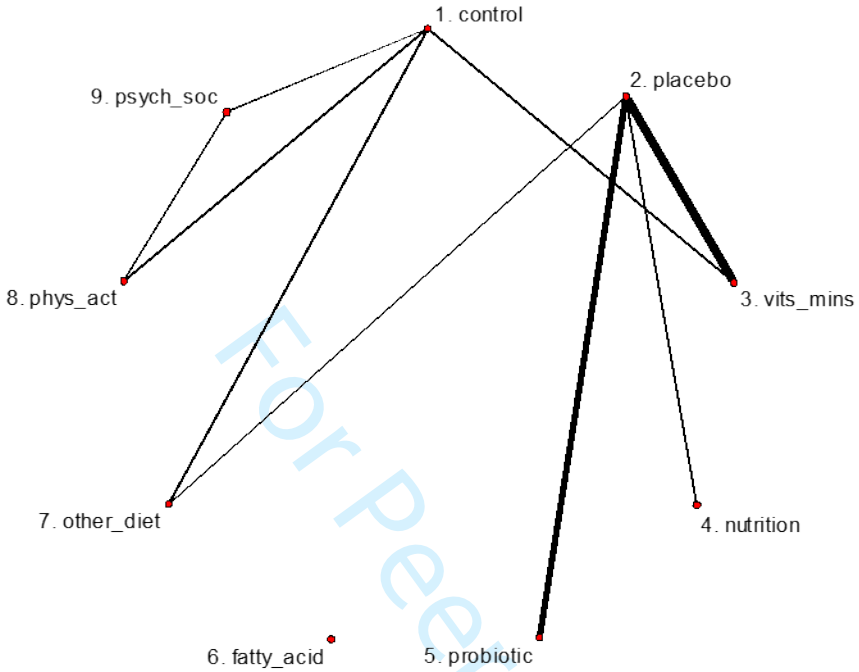


Figure 2c



Appendix 1

Network Meta-Analysis Model

All measures (not already reported on a log-scale) were converted to a log-scale assuming a Normal distribution on the log-scale, using the relation:

$$\mu = \log\left(\frac{m^2}{\sqrt{m^2+s^2}}\right) \quad \text{and} \quad \sigma = \sqrt{\log\left(1+\frac{s^2}{m^2}\right)}$$

where μ and σ are the mean and standard deviation on the log-scale and m and s the mean and standard deviation on a natural scale.

The NMA model follows that given in (15), however is extended to a hierarchical model to allow for the repeated measures in studies reporting results for more than one antigen.

Let $y_{i,s,k}$ be the mean change from baseline (where reported) or mean at follow-up (otherwise), for, antigen i, study s, and arm k, with corresponding standard error, $se_{i,s,k}$. A Normal likelihood is assumed:

$$y_{i,s,k} \sim N\left(mean_{i,s,k}, se^2_{i,s,k}\right)$$

with mean $mean_{i,s,k} = \theta_{i,s,k} s_{i,s,pooled}$ where $\theta_{i,s,k}$ is the standardised mean and $s_{i,s,pooled}$ the pooled standard deviation across arm for each antigen i, study s. We put the model on the standardised mean scale

$$\theta_{i,s,k} = \begin{cases} \mu_{i,s} & k = 1 \\ \mu_{i,s} + \eta_{i,s,k} & k = 2,3,\ldots \end{cases}$$

where $\mu_{i,s}$ is a nuisance parameter representing the arm 1 standardised mean, and $\eta_{i,sk}$ the standardised mean difference for arm k relative to arm 1 for antigen i, study s. There is a

hierarchical model over antigen-types within study, reflecting the belief that the different antigens are "similar" but not identical in their relative effectiveness:

$$\eta_{i,s,k} \sim N\left(\delta_{s,k}, \sigma^2_{antigen}\right)$$

where $\delta_{s,k}$ is the standardised mean difference, pooled across antigens, for study s, arm k relative to arm 1, and $\sigma_{antigen}$ the between antigen standard deviation.

There is a random effects model for the study-level standardised mean differences:

$$\delta_{s,k} \sim N\left(d_{\text{int}(k)} - d_{\text{int}(1)}, \sigma^2_{study}\right)$$

where $\text{int}(k)$ indicated the intervention number on arm k of study s, d_{int} is the pooled standardised mean difference for intervention int relative to the intervention 1, and σ_{study} is the between study standard deviation in standardised mean difference.

Flat Normal(0,10000) priors are given to the intervention effects d_{int}, Uniform(0,5) prior given for the standard deviation parameters, $\sigma_{antigen}$ and σ_{study} .

Supplementary Network Meta-Analysis Results

Table S1 *Model fit statistics for network meta-analysis (NMA) models fitted for the different intervention categorisations (Table X) and each outcome type, (a) antibody titre, (b) seroconversion (c) seroprotection.*

Model	No. Data-points	Posterior mean residual deviance	DIC	Between antigen sd	Between study sd
(a) ANTIBODY TITRES					
Categorisation 1 (Table X)	325	342.3	107.8	0.29 (0.22, 0.37)	1.18 (0.91, 1.52)
Categorisation 2 (Table X)	325	343.1	108.4	0.29 (0.22, 0.37)	1.03 (0.82, 1.30)
Categorisation 3 (Table X)	325	342.7	108.3	0.29 (0.22, 0.37)	1.05 (0.84, 1.32)
(b) SERO-CONVERSION					
Categorisation 1 (Table X)	127	131.5	713.3	0.16 (0.01, 0.36)	0.78 (0.54, 1.14)
Categorisation 2 (Table X)	127	132.2	711.3	0.13 (0.00, 0.34)	0.73 (0.51, 1.02)
Categorisation 3 (Table X)	127	130.6	710.3	0.15 (0.01, 0.36)	0.76 (0.55, 1.04)
(c) SERO-PROTECTION					
Categorisation 1 (Table X)	126	114.9	721.9	0.06 (0.00, 0.16)	0.59 (0.31, 0.90)
Categorisation 2 (Table X)	126	115.7	720.2	0.05 (0.00, 0.16)	0.52 (0.28, 0.87)
Categorisation 3 (Table X)	126	115.8	721.0	0.06 (0.00, 0.18)	0.57 (0.31, 0.90)

Table S2 ***Categorisation 1:*** *Posterior mean and 95% credible intervals for the relative effects of each intervention compared with placebo using Categorisation 1 for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for seroprotection. Also presented the estimated between antigen sd, and between study sd.*

Posterior mean (95% CrI) Relative to Placebo	Standardised Mean Difference in Antibody Titre	Log-odds ratio for seroconversion	Log-odds ratio for sero-protection
Control	-0.5131(-1.729, 0.7112)	-2.848(-6.663, 0.4671)	-0.04102(-1.419, 1.189)
Vitamin A	-0.02991(-0.9158, 0.8572)	0.06882(-0.4944, 0.6291)	0.08028(-0.4894, 0.6514)
Zinc	-0.3132(-1.2, 0.5756)	-0.0001051(-1.115, 1.114)	-0.02563(-1.288, 1.216)
Vitamin A + Zinc	-0.1481(-2.147, 1.842)	0.1343(-0.9744, 1.25)	-0.6278(-197.2, 199)
Vitamin E	-0.4416(-1.979, 1.109)	0.9634(-0.8337, 2.802)	0.5362(-2.527, 3.782)
Zinc + Arginine (amino acid)	-0.2542(-2.485, 2.013)	-2.396(-200.2, 194.1)	0.546(-197.6, 198.8)
Vitamin and Trace element supplements	0.1578(-196.5, 196.9)	-3.175(-199.2, 194.3)	-0.6639(-1.83, 0.4559)
vitamin D	-0.00403(-2.367, 2.36)	-0.2104(-1.87, 1.431)	-0.0249(-1.374, 1.331)
Nutritional formula	0.9565(-0.2842, 2.208)	0.1764(-1.129, 1.483)	1.252(-0.3149, 2.939)
Probiotic	0.6547(-0.001121, 1.317)	0.8486(0.2253, 1.456)	-0.007142(-0.5721, 0.5572)
Fatty Acid	-0.2566(-2.705, 2.167)	-3.537(-199, 193.8)	-0.4165(-198.3, 197.7)
Fruit + Vegetables	-0.14(-2.841, 2.551)	-3.122(-197.1, 193.1)	1.829(-0.295, 4.001)
AHCC (mushroom extract)	-0.02059(-192.9, 196.2)	-2.526(-6.78, 1.319)	-0.4462(-3.099, 1.969)
wolfberry	-0.2752(-2.724, 2.15)	-1.783(-197.4, 195.6)	-0.2088(-197.6, 196.1)
Other Dietary	0.3893(-0.9941, 1.767)	0.4251(-1.338, 2.186)	0.5487(-0.8214, 1.923)
Aerobic Exercise	-0.5527(-2.171, 1.072)	-2.799(-6.9, 0.9668)	0.3494(-1.204, 1.81)
Flexibility/Balance training	-0.6732(-3.522, 2.18)	-2.405(-197.3, 193.8)	0.1939(-196.1, 196.3)
Body Massage	-1.191(-3.919, 1.585)	-2.739(-198.3, 193.2)	-0.5195(-198.1, 194.5)
disclosure	-0.06403(-2.453, 2.327)	-2.549(-198.3, 193.9)	-0.009367(-194.8, 196.8)
mindfulness	-0.9717(-3.429, 1.512)	-3.076(-7.101, 0.6447)	-0.09356(-1.928, 1.508)
Between study sd	1.18 (0.91, 1.52)	0.78 (0.54, 1.14)	0.59 (0.31, 0.90)
Between antigen sd	0.29 (0.22, 0.37)	0.16 (0.01, 0.36)	0.06 (0.00, 0.16)

Table S3 ***Categorisation 2****: Posterior mean and 95% credible intervals for the relative effects of each intervention compared with placebo using Categorisation 2 for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for seroprotection. Also presented the estimated between antigen sd, between study sd, posterior mean residual deviance, number of datapoints and studies. Note these results include all studies in the NMA (including Rizzardini (2012) for the seroconversion outcome).*

Posterior mean (95% CrI) Relative to Placebo	Standardised Mean Difference in Antibody Titre	Log-odds ratio for seroconversion	Log-odds ratio for sero-protection
Control	-0.2734(-1.18, 0.5956)	-0.8307(-2.671, 1.002)	-0.239 (-1.117, 0.628)
Vitamins & minerals	-0.1456(-0.6833, 0.3896)	0.1078(-0.3508, 0.5655)	-0.065 (-0.470, 0.309)
Nutritional formula	0.9947(-0.08597, 2.083)	0.4236(-0.7255, 1.607)	1.373 (-0.157, 2.994)
Probiotics	0.6456(0.05935, 1.233)	0.8443(0.2683, 1.414)	0.014 (-0.511, 0.523)
Fatty Acids	-0.2399(-2.397, 1.89)	-1.019(-194.2, 192.2)	
Other Dietary	0.2044(-0.7533, 1.168)	0.03911(-1.457, 1.523)	0.699 (-0.305, 1.659)
Physical Activity	-0.2914(-1.55, 0.9472)	-0.7602(-3.204, 1.654)	0.133 (-0.991, 1.305)
Psychosocial	-0.581(-1.903, 0.7392)	-1.047(-3.472, 1.36)	-0.328 (-1.743, 1.136)
Between study sd	1.03 (0.82, 1.30)	0.73 (0.51, 1.02)	0.52 (0.28, 0.87)
Between antigen sd	0.29 (0.22, 0.37)	0.13 (0.00, 0.34)	0.05 (0.00, 0.16)

Table S4 *Model fit statistics for each model fitted for each outcome type, (a) antibody titre, (b) seroconversion (c) seroprotection. Intervention categorisation 2 (see Table X) is used in all cases.*

Model	No. Data-points	Posterior mean residual deviance	DIC	Between antigen sd	Between study sd	Regression Coefficient
(a) ANTIBODY TITRES						
All data NMA Model	325	343.1	108.4	0.29 (0.22, 0.37)	1.03 (0.82, 1.30)	
Unrelated Mean Effect Model	325	342.8	108.1	0.29 (0.22, 0.37)	1.03 (0.80, 1.32)	
Subgroups: vaccine type	325	342.6	108.0	0.29 (0.22, 0.37)	1.12 (0.87, 1.45)	
Subgroups: risk of failure	325	343.1	108.3	0.29 (0.22, 0.37)	1.05 (0.82, 1.33)	
Subgroups: age group	325	342.9	107.9	0.29 (0.22, 0.36)	1.16 (0.89, 1.50)	
Meta-regression: follow-up time	325	342.5	107.7	0.29 (0.22, 0.37)	0.99 (0.78, 1.25)	0.027 (0.003, 0.051)
Meta-regression: 1/√n	325	342.5	107.6	0.29 (0.22, 0.37)	1.01 (0.80, 1.28)	-4.12 (-8.84, 0.58)
Excluding high ROB studies	295	313.8	72.0	0.29 (0.21, 0.37)	1.12 (0.88, 1.43)	
(b) SERO-CONVERSION						
All data NMA Model	127	132.2	711.3	0.13 (0.00, 0.34)	0.73 (0.51, 1.02)	
Unrelated Mean Effect Model	127	131.4	710.8	0.15 (0.00, 0.35)	0.72 (0.50, 1.01)	
Subgroups: Vaccine Type	127	130.9	711.4	0.15 (0.01, 0.35)	0.77 (0.53, 1.09)	
Subgroups: risk of failure	127	131.4	712.2	0.15 (0.00, 0.35)	0.74 (0.51, 1.05)	
Subgroups: age group	127	131.5	712.2	0.14 (0.00, 0.35)	0.68 (0.45, 0.99)	
Meta-regression: follow-up time	127	131.2	711.4	0.15 (0.00, 0.36)	0.74 (0.52, 1.04)	-0.003 (-0.030, 0.024)
Meta-regression: 1/√n	127	132.3	712.9	0.14 (0.00, 0.35)	0.73 (0.51, 1.04)	-1.56 (-8.77, 5.79)
Excluding high ROB studies	116	122.5	656.4	0.17 (0.01, 0.39)	0.77 (0.53, 1.11)	
Excluding Rizzardini (2012)	115	108.2	629.2	0.08 (0.00, 0.23)	0.38 (0.15, 0.64)	
Subgroups: risk of failure, excluding Rizzardini (2012)	115	106.4	627.9	0.07 (0.00, 0.22)	0.35 (0.13, 0.59)	

(c) SERO-PROTECTION						
All data NMA Model	126	115.7	720.2	0.05 (0.00, 0.16)	0.52 (0.28, 0.87)	
Unrelated Mean Effect Model	126	115.6	722.0	0.06 (0.00, 0.18)	0.59 (0.29, 1.01)	
Subgroups: Vaccine Type	126	113.8	719.7	0.05 (0.00, 0.16)	0.58 (0.31, 0.99)	
Subgroups: risk of failure	126	116.0	722.7	0.06 (0.00, 0.18)	0.60 (0.29, 1.02)	
Subgroups: age group	126	114.2	720.8	0.06 (0.00, 0.16)	0.63 (0.33, 1.05)	
Meta-regression: follow-up time	126	115.2	720.1	0.06 (0.00, 0.18)	0.55 (0.27, 0.90)	0.003 (-0.013, 0.020)
Meta-regression: 1/√n	126	114.9	719.6	0.05 (0.00, 0.16)	0.56 (0.30, 0.90)	0.19 (-5.81, 5.94)
Excluding high ROB studies	116	108.0	655.5	0.06 (0.00, 0.17)	0.55 (0.30, 0.88)	

Table S5 *Posterior mean and 95% credible intervals for the direct and NMA estimates of each pair of interventions where direct estimates are available, for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for seroprotection.*

COMPARISON	Direct Estimate	NMA Estimate
(a) ANTIBODY TITRES SMD (95%CrI)		
Vitamins & minerals vs Control	0.08986 (-0.8726, 1.065)	-0.14 (-0.9678, 0.6916)
Vitamins & minerals vs Placebo	0.07285 (-0.4853, 0.6271)	0.1489 (-0.3849, 0.6827)
Nutritional formula vs Control	-3.255 (-5.488, -1.025)	-1.284 (-2.556, -0.008108)
Nutritional formula vs Placebo	-0.4239 (-1.62, 0.7948)	-0.9953 (-2.107, 0.09824)
Probiotics vs Placebo	-0.6473 (-1.224, -0.06225)	-0.6445 (-1.239, -0.06379)
Fatty Acids vs Placebo	0.2359 (-1.887, 2.343)	0.2413 (-1.906, 2.419)
Other Dietary vs Control	-0.3703 (-2.483, 1.73)	-0.4851 (-1.674, 0.6991)
Other Dietary vs Placebo	-0.2259 (-1.286, 0.8421)	-0.1963 (-1.17, 0.771)
Physical Activity vs Control	0.06358 (-0.984, 1.102)	0.01713 (-0.9063, 0.9337)
Psychosocial vs Control	0.5347 (-0.965, 2.039)	0.2999 (-0.9175, 1.526)
Psychosocial vs Placebo	0.04989 (-2.062, 2.148)	0.5887 (-0.7462, 1.939)
Psychosocial vs Physical Activity	0.516 (-1.454, 2.459)	0.2828 (-1.11, 1.67)
(b) SERO-CONVERSION Log-OR (95% CrI)		
Vitamins & minerals vs Placebo	-0.1071 (-0.5596, 0.3338)	-0.1078 (-0.5654, 0.3509)
Nutritional formula vs Control	-2.615 (-5.634, -0.07995)	-1.254 (-3.15, 0.6038)
Nutritional formula vs Placebo	-0.1704 (-1.37, 1.019)	-0.4236 (-1.606, 0.7258)
Probiotics vs Placebo	-0.8474 (-1.424, -0.2612)	-0.8443 (-1.413, -0.2683)
Other Dietary vs Control	-0.3623 (-2.286, 1.543)	-0.8698 (-2.515, 0.7467)
Other Dietary vs Placebo	-0.3749 (-2.015, 1.243)	-0.03911 (-1.523, 1.457)
Psychosocial vs Control	0.2034 (-1.331, 1.72)	0.2162 (-1.324, 1.756)
Psychosocial vs Physical Activity	0.2784 (-1.266, 1.819)	0.2868 (-1.262, 1.852)
(c) SEROPROTECTION		

Log-OR (95% CrI)		
Vitamins & minerals vs Control	-0.06405 (-1.187, 0.9978)	-0.1742 (-0.9787, 0.6469)
Vitamins & minerals vs Placebo	0.05218 (-0.3778, 0.5092)	0.06496 (-0.3091, 0.47)
Nutritional formula vs Placebo	-1.303 (-3.028, 0.2925)	-1.373 (-2.993, 0.1572)
Probiotics vs Placebo	-0.01428 (-0.5732, 0.557)	-0.01355 (-0.5232, 0.5111)
Other Dietary vs Control	-1.029 (-2.32, 0.3431)	-0.9376 (-1.849, 0.01765)
Other Dietary vs Placebo	-0.4842 (-1.842, 0.8766)	-0.6985 (-1.659, 0.3053)
Physical Activity vs Control	-0.42 (-1.548, 0.6692)	-0.3723 (-1.163, 0.3822)
Psychosocial vs Control	0.1744 (-1.199, 1.502)	0.08899 (-1.062, 1.189)
Psychosocial vs Physical Activity	0.5043 (-0.8382, 1.853)	0.4613 (-0.6923, 1.599)

Table S6 *Posterior mean and 95% credible intervals for the relative effects of each intervention (categorisation 2) compared with placebo by vaccine type for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for sero-protection.*

Posterior mean (95% CrI) Relative to Placebo	Influenza	Pneumococcal	Measles / MMR + Varicella	Other
(d) ANTIBODY TITRES SMD (95%CrI)				
Control	-0.5512 (-2.007, 0.8775)			-0.07353 (-2.514, 2.346)
Vitamins & minerals	-0.4541 (-1.793, 0.8808)	-0.2422 (-1.535, 1.055)	0.1233 (-1.201, 1.435)	-0.09345 (-1.008, 0.8296)
Nutritional formula	1.265 (-0.1473, 2.688)			0.0337 (-2.213, 2.3)
Probiotics	0.1827 (-0.6683, 1.029)			1.228 (0.2911, 2.163)
Fatty Acids	-0.2321 (-2.547, 2.108)			
Other Dietary	0.2245 (-1.411, 1.871)	0.2358 (-1.387, 1.84)		0.2997 (-3.067, 3.636)
Physical Activity	-0.3026 (-2.158, 1.53)			
Psychosocial	-0.5186 (-2.229, 1.195)			-0.7346 (-4.135, 2.666)
(e) SERO-CONVERSION Log-OR (95% CrI)				
Control	-0.9365 (-2.899, 0.973)			
Vitamins & minerals	-0.1938 (-1.789, 1.419)		0.0366 (-0.7089, 0.781)	0.2207 (-0.4488, 0.9072)
Nutritional formula	0.422 (-0.7685, 1.643)			
Probiotics	0.9621 (0.2834, 1.647)			0.4623 (-0.7664, 1.702)
Fatty Acids	-1.243 (-196.5, 196.5)			
Other Dietary	-0.0177 (-1.573, 1.524)			
Physical Activity	-0.8842 (-3.415, 1.64)			
Psychosocial	-1.161 (-3.676, 1.327)			
(f) SEROPROTECTION				

Log-OR (95% CrI)				
Control	0.9207 (-1.406, 3.234)			0.1104 (-1.222, 1.478)
Vitamins & minerals	-0.3923 (-1.248, 0.4517)	-0.02439 (-1.252, 1.228)	-0.0007331 (-0.7475, 0.7715)	0.1502 (-0.669, 0.9615)
Nutritional formula	1.333 (-0.3151, 2.957)			
Probiotics	-0.1035 (-0.7341, 0.489)		0.6081 (-0.7725, 1.976)	
Fatty Acids				
Other Dietary	0.5497 (-0.783, 1.924)			1.903 (-0.09841, 3.894)
Physical Activity	1.298 (-1.208, 3.759)			
Psychosocial	0.8091 (-1.875, 3.441)			

Table S7 *Posterior mean and 95% credible intervals for the relative effects of each intervention (categorisation 2) compared with placebo by age group for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for sero-protection. Haemodialysis patients were not included in these results.*

Posterior mean (95% CrI) Relative to Placebo	Infants	Children	Adults	Older Adults
(a) ANTIBODY TITRES SMD (95%CrI)				
Control	0.01169 (-2.549, 2.551)		0.127 (-1.55, 1.817)	-1.187 (-3.099, 0.6845)
Vitamins & minerals	0.02431 (-1.008, 1.048)	0.04581 (-1.062, 1.158)	-0.2437 (-1.69, 1.208)	-0.9382 (-2.636, 0.7351)
Nutritional formula	0.03772 (-2.298, 2.377)			1.077 (-0.4336, 2.589)
Probiotics	1.23 (0.2721, 2.199)		0.1865 (-2.162, 2.558)	0.1808 (-0.7634, 1.131)
Fatty Acids			-0.2476 (-2.633, 2.135)	
Other Dietary	-0.2198 (-2.545, 2.094)		0.6419 (-0.8392, 2.131)	-0.2794 (-2.703, 2.127)
Physical Activity			0.1832 (-2.667, 3.049)	-1.247 (-3.48, 0.9762)
Psychosocial			-0.2879 (-2.168, 1.566)	-1.661 (-4.491, 1.175)
(b) SERO-CONVERSION Log-OR (95% CrI)				
Control				-2.586 (-5.781, 0.3199)
Vitamins & minerals	0.002538 (-0.5959, 0.6012)	0.0997 (-0.5756, 0.7831)		0.9853 (-0.6518, 2.705)
Nutritional formula				0.1858 (-0.9782, 1.363)
Probiotics	0.4772 (-0.7179, 1.699)		1.688 (0.8117, 2.562)	0.2749 (-0.608, 1.16)
Fatty Acids				
Other Dietary				0.4628 (-1.114, 2.062)
Physical Activity				-2.532 (-6.017, 0.7357)
Psychosocial				-2.823 (-6.35, 0.4247)
(c) SEROPROTECTION Log-OR (95% CrI)				

Control	-0.02967 (-1.314, 1.319)			
Vitamins & minerals	0.03644 (-0.6124, 0.6864)	0.06951 (-0.7467, 0.904)		-0.6657 (-1.885, 0.5018)
Nutritional formula				1.28 (-0.3693, 2.975)
Probiotics	0.6814 (-0.7362, 2.146)		-0.1011 (-0.9425, 0.7212)	-0.1274 (-1.195, 0.9539)
Fatty Acids				
Other Dietary				0.5401 (-0.887, 1.974)
Physical Activity				
Psychosocial				

Table S8 *Posterior mean and 95% credible intervals for the relative effects of each intervention (Categorisation 2) compared with placebo excluding studies at high risk of bias (ROB), adjusting for small study effets, and adjusting for follow-up time (results for 52 weeks follow-up). Results presented for (a) SMD for antibody titre, (b) log-odds ratio for seroconversion, and (c) log-odds ratio for sero-protection.*

Posterior mean (95% CrI) Relative to Placebo	All Data NMA Model	Excluding High ROB Studies	Adjusting for Small Study Effects (Antibody titre results only)	Adjusting for follow-up time at 52 weeks follow-up (Antibody titre results only)
(a) ANTIBODY TITRES SMD (95%CrI)				
Control	-0.2734(-1.18, 0.5956)	-0.317 (-1.343, 0.7017)	-0.4135 (-1.288, 0.4643)	-0.4607 (-1.336, 0.404)
Vitamins & minerals	-0.1456(-0.6833, 0.3896)	-0.1396 (-0.7643, 0.4926)	0.4318 (-0.4072, 1.283)	0.6934 (-0.2235, 1.621)
Nutritional formula	0.9947(-0.08597, 2.083)	1.007 (-0.1587, 2.192)	1.628 (0.3391, 2.941)	2.098 (0.6576, 3.569)
Probiotics	0.6456(0.05935, 1.233)	0.6278 (-0.02741, 1.287)	1.497 (0.3796, 2.626)	1.5 (0.5523, 2.459)
Fatty Acids	-0.2399(-2.397, 1.89)		0.5423 (-1.74, 2.818)	0.8949 (-1.419, 3.185)
Other Dietary	0.2044(-0.7533, 1.168)	0.1975 (-0.8518, 1.249)	1.001 (-0.3209, 2.324)	1.341 (-0.03635, 2.727)
Physical Activity	-0.2914(-1.55, 0.9472)	-0.3295 (-1.746, 1.077)	0.5338 (-1.028, 2.085)	0.6761 (-0.8068, 2.167)
Psychosocial	-0.581(-1.903, 0.7392)	-0.6079 (-2.068, 0.8506)	0.001382 (-1.453, 1.467)	0.4168 (-1.134, 1.983)
(b) SERO-CONVERSION Log-OR (95% CrI)				
Control	-0.8307(-2.671, 1.002)	-0.937 (-2.949, 0.9693)		
Vitamins & minerals	0.1078(-0.3508, 0.5655)	0.06901 (-0.4591, 0.6017)		
Nutritional formula	0.4236(-0.7255, 1.607)	0.4677 (-0.7507, 1.713)		
Probiotics	0.8443(0.2683, 1.414)	0.8444 (0.2396, 1.447)		
Fatty Acids	-1.019(-194.2, 192.2)			
Other Dietary	0.03911(-1.457, 1.523)	-0.02526 (-1.648, 1.58)		
Physical Activity	-0.7602(-3.204, 1.654)	-0.8738 (-3.477, 1.641)		
Psychosocial	-1.047(-3.472, 1.36)	-1.164 (-3.777, 1.343)		

(c) SERO-PROTECTION Log-OR (95% CrI)				
Control	-0.239 (-1.117, 0.628)	-0.3487 (-1.768, 1.161)		
Vitamins & minerals	-0.065 (-0.470, 0.309)	-0.06437 (-0.5031, 0.3583)		
Nutritional formula	1.373 (-0.157, 2.994)	1.305 (-0.252, 2.951)		
Probiotics	0.014 (-0.511, 0.523)	0.01707 (-0.5257, 0.549)		
Fatty Acids				
Other Dietary	0.699 (-0.305, 1.659)	0.6666 (-0.4482, 1.826)		
Physical Activity	0.133 (-0.991, 1.305)	-0.0001899 (-1.642, 1.765)		
Psychosocial	-0.328 (-1.743, 1.136)	-0.5026 (-2.381, 1.369)		

Table 2

Summary of Dietary Studies

First Author (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
Ahmed (2009) Bangladesh Non-RCT Quasi-experimental design **Intervention code A**	Infants 6-9 months old group: n= 176; male n=87, female n= 89. Mean age 7.5months 10-18months old group: n=164; males n= 67, female n= 97, mean age 14 months vaccine mixed with bicarbonate buffer (DUK-SF) group n= 98 or mixed with water (DUK-W) group n=32 or mixed with no fluid (DUK-Only) group n= 44 Withholding breastfeeding group (DUK-SF/BF) n= 66 Zinc supplementation group DUK-SF/Zn n= 70	Each study group was split into two age groups; 6-9 month and 10-18month Zinc supplementation: - 20mg zinc acetate syrup daily for 42 days starting 3 weeks before 1st vaccine dose and finished 1 week after 2nd dose Breastfeeding:- this was withheld 3hrs prior to vaccine Timing: 2 doses of vaccine given at 2 week intervals Adherence:. verified weekly by home visits – compliance over 90% Mediating mechanisms: not reported	Cholera Vibriocidal antibody levels Antibody specific IgA and IgG (CT, LPS) Enzyme-Linked Immunosorbent assay (ELISA) Baseline, 7 days post 1st dose, 7 days post 2nd dose	DUK-Sf/Zn older children showed significant amplification of vibriocidal responses after 2 doses LPS-IgA significantly higher magnitude in DUK-SF/Zn group

First Author (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
Ahmed (RVF) (2010) Bangladesh RCT **Intervention code A**	Infants from urban slum area (malnutrition likely) Age range: 10-18 months n=25 male, 33 female Intervention: n=18 (zinc + vaccine) n=20 (zinc only); Control: n=20 (vaccine only)	Intervention: 20mg zinc daily for 42 days. Control: no treatment First dose of vaccine administered 3 weeks after commencing intervention/control treatments; second dose of vaccine administered 2 weeks later (1 week before the end of the intervention/control treatments) Adherence: verified by weekly home visits, but data not reported Mediating mechanisms: zinc levels increased significantly in both groups receiving zinc supplementation over treatment period	Cholera Vibrocidal antibody levels Antibody specific IgA and IgG (CTB, LPS) Enzyme-Linked Immunosorbent assay (ELISA) Zinc + vaccine group: study entry, pre-first vaccine dose, 7 days, 14 days, 21 days Zinc only group: study entry, 21 days post first vaccine dose. Vaccine only group: pre-first vaccine dose, 7 days, 14 days, 21 days	Compared with the control group, zinc resulted in significantly greater vibrocidal antibody levels

First Author (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
Akatsu (RVF) (2013) Japan RCT **Intervention code B**	Elderly patients fed by enteral tube feeding aged 65yrs or over (institutionalized) Main illness was Alzheimer disease or cerebral vascular problem Intervention group n=23; mean age 82.5 yrs, 7 male, 16 female, BMI 17.4 Control group n=22; mean age 81 yrs, 6 male, 16 female, BMI 17.6	Intervention group:- Given Probiotic Bifidobacterium longum 2g (BB536) twice daily for 12 weeks Control group:- given 2g placebo powder (consisting mainly dextrin) twice daily for 12 weeks Timing:- vaccine given at week 4 Adherence:- No reported adherence to probiotic documented but delivered by nursing staff Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody titers via hemagglutination inhibition assay Total IgG, IgA, IgM, IgE in serum via Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures:0, 4, 6, 8, 12, 16 weeks	Increase of serum IgA in intervention group compared to placebo at week 4 and 16 but not statistically significant At week 6, number of patients with antibody titer ≥20 for one influenza strain was significantly higher in the intervention group compared to placebo IgG and IgA increased sooner in the intervention group (week 4 or 6) compared to placebo (week 12)

First Author (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
Akatsu (RVF) (2016) Japan RCT **Intervention code B**	Elderly, fed by enteral tube feeding (institutionalized) Intervention group (F) n=15; mean age 77.8, 3 male, 9 female, BMI 17.6 Control group (C) n=15; mean age 84.5, all female, BM1 17.4	Intervention group – standard Fibren enteral formula containing prebiotics (lactic acid fermented milk products, galacto-oligosaccharide, bifidogenic growth stimulator) for 10 weeks Control group – different standard enteral formula (Meibalance) without prebiotics Standard formulas almost identical – Fibren contained less vitamin K, biotin, manganese, and iodine Vaccine given at week 4 Adherence- Adherence to probiotic not documented, but presumed high given unblinded study Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody titres, titre ≥40 = seroprotective antibody Haemagglutination inhibition assay Timing of immune measures: 4, 6, 10 weeks	Significantly higher seroprotective rates in the intervention group for one strain compared to the control group at week 10. Antibody titres in control group decreased and at week 10 they were not significantly higher than week 4. Whereas, all antibody titres in intervention group were significantly higher than those at week 4.

First Author (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
Albert (RVF) (2003) Bangladesh RCT **Intervention code A**	Children with vitamin A deficiency (immunosuppressed) Age range 2-5 years Intervention: n=61 (vitamin A and placebo); (A) n=63 (Zinc and placebo); (Z) n=62 (vitamin A and zinc) (AZ) Control: n= 63 (P)	Intervention: 200,000 IU vitamin A and or 20 mg zinc received daily for 42 days. Control: placebo syrup First dose of vaccine administered 3 weeks after commencing intervention/control treatments; second dose of vaccine administered 2 weeks later (1 week before the end of the intervention/control treatments) Adherence: weekly measurement of amount of syrup consumed. However, data not reported. Mediating mechanisms: All 4 groups (including control) showed a significant increase in vitamin A levels between the first and last assessments; only the groups supplemented with zinc showed a significant increase in zinc levels	Cholera Vibriocidal antibody levels and seroresponder rates (≥ 4 fold increase in titre from baseline) Assay method not documented 0 weeks (pre-vaccine), 1 week after first dose of vaccine, and 1 week after second dose of vaccine	Proportion with ≥4 fold increase in antibody titer significantly greater in vitamin A and zinc intervention group compared to control Proportion with ≥4 fold increase in antibody titer significantly greater in zinc supplemented groups compared to non-zinc groups

First Author (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
Bahl (RVF) (1999) India RCT **Intervention code A**	Infants from urban slum area (malnutrition likely) 9 months of age 321 males, 297 females Intervention: n=309 Control: n=309	Intervention: Single dose of 30 mg vitamin A (retinol palmitate) Control: placebo Vaccination received at the same time as intervention/control treatment Adherence: single dose intervention so not applicable Mediating mechanisms: not reported	Measles IgG antibody titres and seroresponder rates (4-fold increase in titre). Enzyme-Linked Immunosorbent assay (ELISA) 0 (pre-vaccine) and 12 weeks post-vaccine	No significant differences between groups in IgG antibody titres or seroresponder rates

First Author (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
Bahl (RVF) (2002) India RCT **Intervention code A**	Mothers and their infants in a slum area (malnutrition likely) Intervention: n=194 Control: n=205 215 males, 184 females Mean age: 0.78 months (intervention); 0.77 months (control).	Intervention: mothers received 60 mg retinol equivalent (RE) vitamin A 18-28 days after delivery; infants received 7.5 mg RE vitamin A at 6, 10, and 14 weeks of age Placebo: Soybean oil Adherence: single dose intervention so not applicable Vaccinations administered within 20 minutes of receiving intervention/control treatment at 6, 10 and 14 weeks of age Mediating mechanisms: not reported	Polio & Diptheria, pertussis, tetanus vaccines Antibody titres to polio vaccine; seroresponding rate (titre ≥ 4) Neutralization assay and standard assay developed by the analysis and control department of the Statens Serum Institut, Copenhagen 0 (pre-vaccine) and 12-weeks post-vaccine	Intervention group exhibited significantly higher titres to poliovirus type 1compared with the control group

First Author (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
Benn (1997) Guinea-Bissau RCT **Intervention code A**	Infants from urban area Group 1; 79 males, 71 females; mean age 193 days Groups2&3; 155 males, 157 females; mean age 293 days Intervention: Group 1: n=78 Groups 2&3: n=149 Control: Group 1: n=72 Groups 2&3: n=163	Intervention: 100,000 IU vitamin A and 40IU vitamin E given at: 6 & 9 months (group 1) 6& 9 months (group 2) 9 months (group 3) Control: placebo 40IU vitamin E in vegetable oil Adherence: intervention given at the same time as the vaccine so adherence not applicable Vaccinations administered at same time as intervention/control treatment Mediating mechanisms: not reported	Measles only at 6 and 9 months (GROUP 1) Or Poliomyelitis at 6 months and Measles at 9 months (GROUP 2) Or Measles only at 9 months (GROUP 3) HI antibody titres and seroresponder rates (titres > 128mIU) Haemagglutination inhibition assay Immune measures: pre-vaccine and 18-months of age	HI antibody titres and seroresponder rates did not differ significantly between intervention and control groups

First Author (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
Benn (2002) Guinea-Bissau Follow up study of RCT **Intervention code A**	Age range 6.8 – 8.2 yrs old Group 1:- placebo n= 49; male 21, female 28 Vitamin A n= 42; male 20, female 22 Group 2 & 3:- placebo n= 79;41 male, 38 female Vitamin A n= 74; 37 male, 37 female	Follow up study at age 6-8yrs Group 1:-2 doses measles vaccine at 6 + 9 months and Vitamin A Group 2 & 3 – one vaccine at 9 months All children randomised to placebo or Vitamin A supplementation 100 000 IU Group 2 & 3 further split into subgroups of either 2 doses of Vitamin A/placebo at 6 + 9 months or 1 dose Vitamin A/placebo at 9 months Adherence: intervention given at the same time as the vaccine so adherence not applicable Mediating mechanisms: not reported	Measles vaccine Geometric mean titres (GMTs) of measles antibodies (titres ≥125IU considered protective) Assay method not documented Timing of immune measures: 4.5 -6.5 yrs post measles vaccine	There was a significant difference in the protective antibody concentrations of Vitamin A supplemented children vs control. Vitamin A supplemented children had higher protective antibody levels.

First Author (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
Bhaskaram (RVF) (1989) India Non-RCT Quasi-experimental design **Intervention code A**	Children aged 1-6yrs (vitamin A deficient group i.e. low retinol group immunosuppressed) **Total number in study** n= 123; male n=55, female n= 68 - Oral Vitamin A 100,000 IU group n= 49; mean age 5.1yrs - Oral Vitamin A 200,000 IU group n= 48; mean age 5.3yrs - Low retinol level group n= 59; mean age 5yrs Normal retinol level group n= 64; mean age 5.4yrs **Children who agreed to have vaccine:** **Intervention groups:** - Oral Vitamin A 100,000 IU group n=26 - Oral Vitamin A 200,000 IU group n=23 Number in low or normal retinol group not reported **Control group** n=26; Low retinol group n=13, normal retinol group n=7	Intervention groups – one off dose of either given 100 000 IU Vitamin A orally or 200 000 IU Control group – no oral vitamin A **Timing:** not clear when vaccine given **Adherence:** single dose intervention so adherence not applicable Mediating mechanisms: not reported	IM Diphtheria and Tetanus (D&T) toxoid Mean antibodies titers to D&T Haemagglutination inhibition assay Timing of immune measures: Baseline, 4 weeks	In the intervention groups antibody titres to diphtheria and tetanus were significantly higher than the control group at 4 weeks. Increase in antibodies to Diphtheria & Tetanus similar in children who received 100 000 or 200 000 IU.

First Author (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
Bhaskaram (1997) India Non RCT Quasi-experimental desgin, used systematic sampling, pre-post intervention study **Intervention code A**	Infants recruited from routine immunisation clinic Intervention=50 Control: n=50 Mean age: 9 months	Intervention: single dose of 100,000 IU vitamin A Control: groundnut oil Adherence: single dose intervention so adherence not applicable Vaccination administered at the same time as intervention/control treatment Mediating mechanisms: not reported	Measles vaccine HI antibody titres and indices of seroresponding (titres > 1:8; 2 fold rise from baseline) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine) and 4 weeks post-vaccination	Significantly higher proportion of infants in the intervention group achieved titres > 1:8

First Author (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
Boge (RVF) (2009) France RCT **Intervention code B**	Institutionalized older adults PILOT STUDY: 15 males,56 females Intervention group n=44; mean age 82.4yrs Control group n=42; mean age 85yrs CONFIRMATORY STUDY: 74 males, 148 females Intervention group n=113; mean age 85 yrs Control group n=109; mean age 84.3yrs	Intervention: Actimel (sweet fermented dairy drink containing a probiotic strain) consumed daily for 7 weeks (pilot study) or 13 weeks (confirmatory study) Control: non-fermented control dairy product Adherence: reported as 97% and 98.5% for intervention and control groups respectively (pilot study) and 96.3% for both groups (confirmatory study). Vaccination administered 4 weeks after commencing intervention/control treatment Mediating mechanisms: not reported	Influenza vaccine Geometric mean antibody titres (GMT) and seroresponder rates (≥40 in HI test; 4 fold increase in titre) Hemagglutination inhibition assay Timing of immune measures: Pilot study: 0 weeks (pre-vaccine), 3 weeks, 3 months and 5 months post-vaccine confirmatory study: 0 weeks (pre-vaccine), 3, 6, 9 weeks and 5 months post-vaccine	Pilot study: trends towards higher antibody levels and seroresponder rates in intervention group compared with control group Confirmatory study: antibody titres significantly higher in intervention group, compared with controls up to 9 weeks post vaccine A significantly higher proportion were seroprotected against 1 strain in the probiotic group compared to control (data not shown but this is in a smaller sample because a higher proportion were seroprotected at baseline so were not included in the analysis)

First Author (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
Bosch (RVF) (2012) Spain RCT **Intervention code B**	Institutionalized 65-85yrs old Group A n= 19 Group B n= 14 Group C n= 15	Both intervention groups started taking probiotic 3-4 months after vaccination, daily, for a period of 3 months Group A:- received $5*10^9$ cfu/day of L.plantarum CECT 7315/7316 in 20g powered skim milk Group B:- received $5*10^8$ cfu/day of L.plantarum CECT 7315/7316 Group C:- control group, no probiotic, 20g powered skim milk only Adherence: not reported. Mediating mechanisms: not reported	Influenza vaccine Influenza-specific IgA, IgG and IgM Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (before starting probiotic not prior to vaccine), 3 months (post completion of probiotic course)	Significant increase in influenza-specific IgG in Group A Significant increase in Influenza specific IgA in groups A & B but not group C Increased influenza specific IgM in Group A but not statistically significant

First Author (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
Braga (RVF) (2015) Brazil RCT **Intervention code A**	Patients undergoing post-operative chemotherapy for colorectal adenocarcinoma and healthy controls (immunosuppressed) Chemo group; mean age 63, male 9, female 16, BMI 24.8 Control group; mean age 61, male 17, female 15, BMI 29.1 Chemo-Zn n= 10 Chemo-placebo n=15 Control-Zn n=21 Control-placebo n=11	70mg zinc sulfate capsules daily or identical placebo for 16 weeks Timing – vaccine given 2 days after start of Zinc (Zn)/placebo Adherence – not reported Mediating mechanisms: not reported	Pneumococcal vaccine Seroconversation, pneumococcal specific antibody titre Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: baseline, 4 and 16 weeks	No significant difference in seroconversation rates between intervention and control groups Antibody titer significantly higher for one strain in the placebo group compared to the intervention group

First Author (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
Broome (2004) UK Non- RCT Quasi-experimental design, sequentially allocated intervention study **Intervention code A**	Adults with low selenium levels. Intervention groups: 50 µg selenium/day n=22; mean age: 33.9 100 µg selenium/day n=22; mean age 31.7 years Control n=22; mean age 32.3 years	Intervention: 50 or 100 µg selenium daily for 15 weeks. Control: placebo Adherence: no measure of adherence reported, Vaccination administered after 6 weeks of intervention/control and continued for a further 3 weeks. Mediating mechanism: both intervention groups displayed significant increases in selenium concentrations within 6 weeks of commencing supplementation, while no significant change observed in the control group.	Poliomyelitis vaccine Poliovirus specific antibody titres Enzyme-linked immunosorbent assay Timing of immune measures: 0 (pre-vaccine), 7, 14, 21, days post-vaccine	No significant between group differences in antibody titres.

First Author (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
Brown (1980) Bangladesh Non-RCT Matched pairs design Coin toss for intervention/control out of that pair **Intervention code A**	Total=95 Children aged between 1-6yrs From rural Bangladeshi villages Vitamin A group n= 46; mean age 39.7 months Control group n= 49; mean age 38.5 months	Vitamin A group – children given IM 200,000 IU vitamin A palmitate Intervention: 200 UI Vitamin A, given post initial vaccine Control group –no Vitamin A 3 doses vaccine given to all subjects – 1st day after baseline measures taken, 2nd when reviewed at 4weeks, 3rd when reviewed at 8 weeks Adherence: single dose intervention given at same time as first vaccine so adherence not applicable Mediating mechanisms: not reported	IM tetanus toxoid Tetanus antitoxin Geometric mean levels Mouse protection assay Timing of immune measures: Baseline, 4weeks, 8weeks	After 8 weeks and 2nd dose of vaccine, no significant difference between geometric mean antitoxin in both groups

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Bunout (2002) Chile RCT **Intervention code B**	Healthy free living elderly subjects ≥70yrs Intervention group n= 20; mean age 76.2, BMI 28 Control group n= 23; mean age 75.2, BMI 26	Intervention group:- given prebiotic mixture 6g/day of 70% raftilose and 30% raftiline mixture (2x3g sachets) daily for 28 weeks Control group:- Given placebo 6g of malto-dextrin powder (2x3g sachets) daily for 28 weeks Both groups:- instructed to mix placebo/intervention sachets with government nutritional supplement, 1.6MJ, 15g protein, 50% of daily vitamin reference values per day. Timing:- vaccine given week 2 of study Adherence: adherence to prebiotic not reported. Mediating mechanisms: not reported	Influenza and Pneumococcal vaccine Specific influenza and pneumococcal antibodies titers Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: week 0, 2, 8	There were no significant differences in antibody responses between groups

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Bunout (2004) Chile Non- RCT Quasi- experimental design, patients in one clinic formed the intervention group and another clinic formed the control group **Intervention code C**	Healthy older adults of low socio-economic status. Intervention group n=30; 26 female, 4 male, mean age 74.3yrs Control group n=30; 29 female, 1 male, mean age 74.5yrs	Intervention: nutritional supplement providing 480 kcal, 31.4 g proteins, 12.4 g fat, 62 g carbohydrates, 120 IU vitamin E, 0.24 mg thiamin, 0.4 mg riboflavin, 2 mg pyridoxine, 400µg folic acid, 3.8 µg vitamin B12, 6 g fructo-oligosaccharides and 109 cfu of *Lactobacillus paracasei*. Supplement received daily for 1 year. Control: not specified Adherence: assessed by counting number of unused sachets at monthly follow-ups. Mean adherence reported as 92.4% Vaccination administered 4 months after commencing intervention/control supplement. Mediating mechanisms: not reported	Influenza and pneumococcal vaccine Specific influenza and pneumococcal antibody titres, seroresponding rates to pneumococcal vaccine (2 fold increase in titre to at least 30% of the serotypes tested) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 4 months (pre-vaccines) and 6 months (2 months post-vaccines)	No significant differences between groups in antibody titres to either vaccine or serosresponding rates

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Chandra (RVF) (1985) Canada RCT **Intervention code E**	Older adults who met criteria for poor nutritional status (immunosuppressed) Age range 70-84 years Intervention: n=15 Control: n=15	Intervention: 4 weeks of nutritional advice and oral dietary & medicinal supplements in accordance with each participant's documented malnutrition. Controls: no treatment Adherence: no measures reported. Vaccination administered on the first day of the intervention Mediating mechanisms: intervention group showed a significant improvement in nutritional status after 4 weeks.	Influenza vaccine Influenza specific antibody titres (HI) and seroresponder rates (≥ four-fold increase in titre) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine) and 4 weeks post-vaccine	Significantly higher antibody titres and seroresponder rates in intervention group compared with controls.

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Cherian (2003) India RCT **Intervention code A**	Infants attending routine immunisation clinic Mean age: 9.8 months 105 males, 93 females Intervention: n=198 Control: n=197	Intervention: single dose 100,000 IU vitamin A Control: placebo Adherence: single dose intervention so adherence not applicable Vaccination administered at the same time as intervention/control treatment Mediating mechanisms: not reported	Measles Antibody titres, indices of seroresponding (≥ 8 in infants with no detectable antibody at baseline; 4 fold increase at 4 weeks post-vaccine in infants with detectable antibody at baseline; titre > 120 at 6 months post-vaccine) Geometric mean titer (GMT) Plaque reduction neutralization (PRN) assay Timing of immune measures: Pre-vaccination, 1 and 6-month follow-up	No significant between group differences in antibody levels or indices of seroresponding

First Author (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
Davidson (2011) USA RCT **Intervention code B**	Healthy adults during 2007-2008 season Intervention group n=21; mean age 33.5, female 12, male 9 Control group n=21; mean age 33.1, 14 female, 7 male	Intervention group:- given an oral probiotic Lactobacillus (LGG) twice daily for 28days. Gelatin capsule with $1x10^{10}$ LGG organisms, 295mg Inulin. Control group:- given matching placebo twice daily for 28 days. Gelatin capsule with 355mg Inulin Timing:- received vaccine then started LGG or placebo Adherence: not reported. Mediating mechanisms: not reported	Influenza vaccine Influenza specific HI antibody titres, GMT titires, seroprotection (Titers ≥1:40), Seroconversion (increase from <1:40 to ≥1:40 or ≥4-fold rise in HI antibody titers) Haemagglutination inhibition assay Timing immune measures: Baseline, day 28, day 56	A significant increase in protective titers for one strain in the LGG compared to placebo group 28 days post vaccine. Although, this increase did not remain statistically significant at 56 days.

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De Vrese (2005) Germany RCT **Intervention code B**	Healthy males aged between 20-30yrs Mainly university students GG group: n= 21 CRL431 group n= 21 Control group n= 22	Both groups had probiotic (GG or CRL431) or placebo for 5 weeks Intervention group (GG):- given chemically acidified clotted milk with 10^{10} Lactobacillus rhamnosus GG Intervention group (CRL431):- given chemically acidified clotted milk with 10^{10} Lactobacillus acidophilus CRL431 Control group:- given chemically acidified clotted milk only as placebo Timing:- vaccine given on day 8 Adherence: not reported Mediating mechanisms: not reported	Polio vaccine Poliovirus neutralizing antibody titres (NT), serum poliovirus-specific IgA and IgG titers Neutralization test and Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 4 weeks before vaccine, immediately before vaccine, 2, 4, 7 weeks post vaccine	Significant increase in IgA specific antibody for particular strain in LGG group compared to controls Significantly increased IgM in CRL431 group compared to controls and LGG group, Significantly higher IgM in LGG group than controls

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Duchateau (1981) Belgium RCT **Intervention code A**	Older adults 15 males, 15 females Intervention: n=15; mean age: 81 yrs Control: n=15; mean age 79.6yrs	Intervention: 440mg zinc sulfate daily for 1 month Control: not described Adherence: not reported Vaccination administered at the end of the treatment period Mediating mechanisms: not reported	Tetanus vaccine Tetanus specific IgG antibody titres Solid-phase radioassay Timing of immune measures: 0 (pre-vaccine), 3 weeks post vaccine	Antibody titres (data not shown) significantly greater in the intervention group compared with control group.

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Fang (2000) Finland RCT **Intervention code B**	Healthy adults Females 15, males 15 Aged from 20-50yrs LGG group n= 10 L group n= 10 P group n=9	All groups took probiotic/placebo for 7days Intervention LGG group:- oral lyophilised Lactobacillus GG $4x10^{10}$ units (cfu) per day Intervention L group:- Lactococcus lactis $3.4x10^{10}$ cfu per day Control P group:- given placebo ethyl cellulose Timing:- all subjects received vaccine on days 1, 3, 5 Adherence: not reported Mediating mechanisms: not reported	Salmonella typhi vaccine Specific salmonella antibodies IgA, IgG, IgM, as geometric mean titers (GMT) Elispot assay Timing of immune measures: 1 day before vaccine given (day 0) and 7 days after 1st vaccine dose (day 8)	Trend towards increase in IgA specific antibody in LGG group compared to L group and P group, however this is not statistically significant.

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French (2009) Australia RCT **Intervention code B**	Healthy adults Probiotic group n=22; average age 31, 53% female Control group n=26; average age 32, 64% female	Both groups started probiotic/placebo 2 weeks before vaccine and continued it for 4 weeks post Intervention: hard gelatine capsules with Lactobacillus fermentum strain VRI 003 (PCC) $1x10^9$ cfu with microcrystalline cellulose, Control group: placebo hard gelatine capsules with microcrystalline cellulose only Timing: vaccine given at 14 days Adherence: not reported Mediating mechanisms: not reported	Influenza vaccine HI influenza specific antibody titres, seroconversation Haemagglutination inhibition assay Timing of immune measures: Day 14 just prior to vaccine, 4 weeks post vaccine	Significantly increased median serum HI titres to one strain compared to placebo Mean HI titres for 2 strains were also slightly increased compared to placebo 94.5% seroconverters in the probiotic group compared to 72% in the placebo group

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Gibson (2012) Northern Ireland RCT **Intervention code E**	Healthy free-living older adults with low fruit and vegetable in-take (≤ 2 portions a day) Intervention group n=41; mean age 70.9yrs, male 21, female 20. Control group n=39; mean age 71.1yrs, male 7, female 32	Intervention: ≥5 portions of fruit and vegetables for 16 weeks Control: ≤ 2 portions per day for 16 weeks Adherence: weekly telephone calls and formally assessed at 6, 12 & 16 weeks (self-reported diet history). However, no data on adherence reported. Vaccinations administered 12 weeks after start of intervention Mediating mechanisms: fasting blood samples taken at 6, 12 and 16 weeks showed higher micronutrient levels in the intervention compared to the control group	Tetanus and Pneumococcal vaccine IgG antibody titres and seroresponder rates (4 fold increase in titre – pneumococcal only) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 0 (pre vaccine) and 16 weeks	No significant between groups differences in antibody titres to tetanus. Significantly higher antibody titres and seroresponder rates to pneumococcal vaccine in the intervention group compared to control

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Girodon (RVF) (1999) France RCT **Intervention code A**	Older adults' resident in nursing homes ((institutionalized) Mean age 83.9 years 185 males, 540 females Intervention: Group 1: n=182 Group 2: n=180 Group 3: n=181 Control: n=182 Representative subsample of these groups (n=140) received the vaccine and participated in the immune assessment	Intervention: Group 1: Trace elements (20mg zinc sulfate and 100µg selenium sulphide) Group 2: Vitamins (120mg ascorbic acid, 6mg beta carotene, 15 mg α-tocopherol) Group 3: Trace elements & vitamins. All taken daily for 2 years Control: placebo Adherence: monitored by nursing staff administering pills; 6 monthly count of any remaining pills; No data reported but presumed high adherence rate. Vaccine administered after 15-17 months of supplementation Mediating mechanisms: blood micronutrient levels. showed all 3 treatment groups showed a significant increase in serum micronutrients.	Influenza vaccine HI antibody titres and seroresponder rates (HI titre ≥ 80) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine), 28,90,180,270 days post-vaccine	Antibody titres were higher in groups that received trace elements or a combination of trace elements and vitamins at 28- and 90-days post-vaccine compared to the control group. However, the vitamin group had significantly lower antibody levels on days 28 and 90 post vaccine compared to the control group Seroresponder rates significantly higher in the trace elements and trace elements & vitamin groups on days 28 and 90 post-vaccine, compared to other groups.

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Habib (2015) Pakistan RCT **Intervention code A**	Newborns 0-14 days old Control group n=202; median age 9 days. Intervention group n=202; median age 8 days	Intervention -10mg zinc daily for 18 weeks Control – placebo daily for 18 weeks Timing - vaccine given at birth, 6 weeks, 10 weeks, 14 weeks Adherence: not reported Mediating mechanisms: not reported	Oral poliovirus vaccine Seroconversion, antibody titires, Seropositive = reciprocal titer ≥ 8. Seroconversation ≥ 4 fold rise over expected decline in maternal antibody Assay method not clearly documented Timing of immune measures: baseline, 18 weeks	no significant difference in antibody response between control and intervention groups

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Harman (RVF) (1986) USA RCT **Intervention code A**	Adults and older adults in a chronic care facility Age range: 24-104 years Intervention: 200mg n=26 400mg n=25 Control: n=52	Intervention: 200mg or 400 mg Vitamin E per day for 6 months. Control: no treatment Adherence: not reported. Vaccination administered one month after commencing intervention treatment. Mediating mechanisms: not reported	Influenza vaccine influenza specific antibody (HI) titres Haemagglutination inhibition assay Timing of immune measures: One month and two days pre-vaccine; 1, 2 & 3-months post vaccine	No significant between group differences in antibody titres.

First Author (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
Hawkes (2006) Australia RCT **Intervention code C**	Healthy infants recruited from postnatal ward Control formula group n=102; male 53, female 49 Formula fortified with NT group n= 98; male 51, female 47 Breastfed group n= 125	NT (nucleotide) All infants had either type of milk as the only source of milk for 7 months Control formula group:- standard whey adapted cows milk protein based S26 in powder for with NT 10mg/l NT formula group:- same whey-adapted formula with NT 33.5mg/l Breastfed group:- no formula milk, just breastfed Timing: DTPa=hep B given at 2, 4, 6 months of age. Hib given at 2 and 4 months of age Adherence: adherence to intervention via daily diary, visits/telephone, 90% (NT & formula groups), breastfed group decreased to 59% by end of study Mediating mechanisms: not reported	Diphtheria, tetanus, pertussis (DTPa), hepatitis B (hep B), Haemophilus influenza type b vaccines (Hib) Diphtheria toxoid, tetanus toxoid, Hib specific antibodies Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 7 months old 33+/- 7 days after 3rd DTPa-hepB and 99+/- 13days after 2nd Hib vaccine	Significant increase in antibody response to tetanus toxoid IgG in NT group compared to control Breastfed infants had a significantly lower IgG antibody to Hib than both formula fed groups Trend to show NT group had higher antibody titre to diphtheria than control, but not statistically significant

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Heine (2011) Germany RCT **Intervention code A**	Adults from a dermatology clinic Vitamin D group n=20; 7 male, 13 female; median age 30 (IQ range 26-34.5) Placebo group n=12; 3 male, 9 female: median 28.5 (IQ range 26-32.7)	Placebo (neutral oil, same volume) Intervention: vitamin D (2000 IU D3 oil) Placebo: neutral oil Given vitamin D or placebo daily for 10 weeks All participants also had a daily supplement containing 1200mg of Calcium. Vaccine given after 9 weeks supplementation Adherence – checked the amount of study medication consumed at the end of the 10-week period. However, no data reported. Mediating mechanisms: Significant increase in vitamin d levels in the intervention group after 10 weeks compared to baseline	Tetanus/diphtheria toxoid vaccine Specific titers of IgG, IgA and IgE antibodies Enzyme immunoassay Timing of immune measures: baseline, 4 and 16 weeks	Specific IgG titers significantly increased in vitamin D group No significant increase IgA or IgE.

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Isolauri (1995) Finland RCT **Intervention code B**	Healthy infants, delivered at term with no neonatal issues 2-5-month-old mean age 4.1 months LGG group n= 29 Control group N=29	Both groups had 30mls soy milk with 5ml 7.5% sodium bicarbonate, then LGG/placebo then vaccine, continued to take LGG/placebo for 5 days at home having 2 doses daily LGG group: lactobacillus casei GG (LGG) 0.1g dry powder with $5x10^{10}$ cfu and microcrystalline cellulose. Control group:- placebo containing microcrystalline cellulose Adherence:- not reported Mediating mechanisms: not reported	oral rotavirus vaccine Rotavirus specific antibodies, IgA, IgM, IgG, seroconversion Enzyme-Linked Immunosorbent assay (ELISA) plaque assay Timing of immune measures: baseline, day 8 post vaccine	Significant increase in mean number of IgM antibody in LGG group compared to placebo from baseline to 8 days post vaccine Trend of higher IgA antibodies post vaccination in LGG group compared to control group but not statistically significant Trend of higher mean IgG levels post vaccine in LGG group but not statistically significant.

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Ivory (2017) UK RCT **Intervention code A**	Healthy adults 50-64yrs old All had Selenium plasma levels <110ng/ml (suboptimal) Group 1; daily capsules 0 µg Selenium n=20; mean age 55.8, 10 male, 10 female, BMI mean 25 Group 2; daily capsules 50 µg Selenium n=18; age 56.5, 9 men, 9 female, BMI 26.1 Group 3; daily capsules 100 µg Selenium n=21; age 58.4, 11 men 10 female, BMI 26.3 Group 4; daily capsules 200 µg Selenium n=23; age 56.1, 11 men, 12 female, BMI 25.9 Group 5; onion containing meals <1 µg/day Selenium n=17; age 58.2, 6 men, 11 female, BMI 26.6 Group 6; onion containing meals 50 µg/day Selenium n=18; age 57.7, men 6, female 12, BMI 26.	Intervention: different amounts of selenium Placebo: no selenium Intervention/Placebo given for 12 weeks Vaccine given at 10 weeks Adherence: not reported Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody titers (IgG and salivary IgA) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Week 0 (baseline), w10 (pre-vaccine), w11 (1w post), w12 (2w post)	No significant change in antibody response between groups

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Jespersen (2015) Germany and Denmark RCT **Intervention code B**	Healthy adults Aged 18-60yrs BMI 19-30 kg/m^2 L.casei group n=548; mean age 31.6, 240, female 308, BMI 23.7 Control group n=551; mean age 31.3, men 213, female 338, BMI 23.8	All subjects had probiotic or placebo once daily for 42 days, 3 weeks before and 3 weeks post vaccine L. casei 431 group: acidified milk drink 100ml with L.casei 431 1 x 10^9 cfu's Control group: placebo of acidified milk drink 100ml but no probiotic Timing:- had vaccine 3 weeks into study, day 21 Adherence: 99.9% for both groups- measured by counting number of returned unopened bottles Mediating mechanisms: not reported	Influenza vaccine HI influenza specific antibodies, seroprotection and seroconversion rates, mean titers Haemagglutination inhibition assay (serum antibodies) Enzyme-Linked Immunosorbent assay (ELISA) (salivary antibodies) Timing of immune measures: -21, 0, 21 (days)	No significant effect of L casei 431 on antibody titres or response

First Author (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
Karlsen (2003) Norway RCT **Intervention code A**	Medical students from the University of Bergen Aged 20-29yrs Zinc intervention group n= 15 Control group (no zinc) n= 15	Zinc group:- took one effervescent tablet containing 45mg elemental zinc and 200mg zinc sulfate 3 times a day for 2 periods of 9 days, each period starting 2 days before each vaccine dose Control group:- no zinc Timing: Vaccine was given 2 days into the 9 day period. Two vaccines given with a 17 day interval Adherence:- not reported Mediating mechanisms: not reported	Cholera vaccine Cholera specific serum antibody titres, vibriocidal antibody titers, Anti-CTB IgA and IgG Fecal IgA antibody titer (anti-CTB IgA) Modified microplate Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (3 days before vaccine and day before zinc started in intervention group), Day 10, 17 and 30.	Rise in serum anti-CTB IgA and IgG titers from Day 0 to Day 30 were significantly lower in zinc group compared to controls Higher rise in vibriocidal antibody titers from day 0 to day 17 and from day 0 to day 30 in zinc group compared to control but **not** statically significant Significant rise in fecal anti-CTB IgA from day 0 to day 30 in zinc group compared to control

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Kelley (1998) USA Non-RCT Quasi-experimental, cross over design **Intervention code D**	Adult males Intervention n=6; mean age 31.2 years Control n=4; mean age 32.2 years	Intervention: basal diet for 15 days, supplemented with 1.5g of arachidonic acid per day for 50 days (day 16-65) Control: basal diet; with diets crossed-over between groups on days 66-115 Adherence: participants were resident at study site for duration of study and consumed only those foods prepared by staff. Vaccination administered on day 92 of study Mediating mechanisms: not reported	Influenza vaccine HI specific antibody titre and seroresponder rates (achieving titres ≥40 or 160) Haemagglutination inhibition assay Timing of immune measures: Day 92 (pre-vaccine) & Day 115 (post-vaccine)	No significant between group differences in antibody titres or seroresponder rates.

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Kelley (2000) USA RCT **Intervention code D**	Adult females Intervention n=10; mean age 27 years Control n=7; mean age 29.3 years	Intervention: basal diet and placebo for 30 days; followed by 3.9g Tonalin (dietary conjugated linoleic acid) daily for 63 days Control: basal diet and placebo for 93 days Adherence: participants were resident at study site for duration of study and consumed only those foods prepared by staff. Vaccination administered on day 65 of study, 35 days after commencing intervention/control treatment. Mediating mechanisms: not reported	Influenza vaccine HI specific antibody titers Haemagglutination inhibition assay Timing of immune measures: Antibodies measured on days 65 (pre-vaccine) and 92 (post-vaccine)	No significant between group differences HI antibody titres.

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Kriesel (1999) USA RCT **Intervention code A**	Medical students Age 18-49yrs Calcitriol group n=87; 48 male, 39 female; mean age 32, white 78 Placebo n=88; 44 male, 44 female; age 32, white 83	Intervention group – 1ml (1 μg) IM calcitriol Placebo group – saline instead Given straight after IM vaccine into adjacent site more than 1cm away Adherence – single dose intervention so adherence not applicable Mediating mechanisms: not reported	Influenza vaccine HI influenza specific antibody titres Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine) and 4 weeks post-vaccine	No significant difference in titres between both groups

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Kukkonen (2006) Finland RCT **Intervention code B**	Mothers and ~~their unborn babies~~infants at risk of atopy Intervention (Probiotic group) n= 47; 26 male, 21 female Control (placebo) group n= 40; 23 male, 17 female	Mothers given either probiotic/placebo twice daily 4 weeks before delivery, infants continued probiotic/placebo once daily for 6 months postnatally Intervention group:- mothers had one capsule with Lactobacillus rhamnosus GG $5x10^9$ cfu, L. rhamnosus $5x10^9$ cfu, Bifidobacterium breve $2x10^8$cfu,Propionibacterium freudenreichiissp. shermanii $2x10^9$ cfu. Infants received 1 opened capsule with same probiotics and 20drops of sugar syrup with 0.8g galacto-oligosaccharides Control group: mothers took capsules with microcrystalline cellulose only. Infants received sugar syrup with no galacto-oligosaccharides Timing: infants given vaccine DTwP at 3, 4, 5 months old and ~~Hib~~ _____given at 4 months old. Adherence:- assessed by questionnaires and interviews at visits but data not reported Mediating mechanisms: not reported	Diphtheria, tetanus, whole cell pertussis (DTwP) and Haemophilus influenza type b (Hib) 7 infants vaccinated with old Hib vaccine and 54 with new one Diphtheria, tetanus, Hib specific IgG antibodies, geometric mean antibodies (GMT), seroprotection Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 6 months old	Significantly higher proportion of participants in the probiotic group had protective Hib IgG antibody concentrations (≥1µg/ml), compared to the control group, (50% probiotic group vs 21% control group).. Hib IgG antibodies tended to be higher in probiotic group but not statistically significant No significant difference between diphtheria or tetanus IgG antibodies between 2 groups

First Author (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
Kutukculer (2000) Turkey RCT **Intervention code A**	Infants aged between 2 months to 16-18months All had normal levels of vitamin A and E at baseline Group 1 n= 24 Group 2 n= 21 Group 3 n= 21 Group 4 n= 23	Group 1:- 30,000 IU oral Vitamin A for 3 days just after each 3 doses of primary vaccination Group 2:- 150mg oral Vitamin E for one day post each vaccine Group 3:- Vitamins A and E together in same doses as above groups Group 4:- no vitamin after vaccine doses Timing:- Vaccine doses given to all subjects at 2 months of age, 2nd at 3 months of age and 3rd at 4 months of age Adherence: Subjects with low compliance to intervention were excluded. However, no data reported. Mediating mechanisms: not reported	Diphtheria-pertussis-tetanus (DPT) vaccine, given in 3 doses Tetanus toxoid specific IgG (antitoxins), geometric mean titres Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (2months of age), 5 months of age (1 month after 3rd dose), 16-18 months of age (before DPT booster dose)	No significant difference in serum tetanus antitoxin levels between 4 groups After 1st 3 doses of vaccine, at 5 months of age, Vitamin A and Vitamin A&E groups (Group 1 and Group 3) showed much better serum antitoxin levels than control group but this was not statistically significant

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Langkamp-Henken (2004) USA RCT **Intervention code C**	Older adults in assisted living and independent living facilities Intervention group n=16; mean age: 83.7 years, 7 male, 9 female Control group n=18; 82.3 years, 6 male, 12 female (control)	Intervention: 8oz of nutritional formula containing antioxidants, zinc, selenium, fermentable oligosaccharides, and structured triacylglycerol, taken daily for 183 days. Control: placebo Adherence: reported as good – measured via adherence self - reported on daily forms. However, no data reported Vaccination administered 15 days (+/-2) after commencing intervention/control treatment Meditating mechanisms: intervention participants had an increase in serum α-tocopherol levels and a higher α-tocopherol/lipid ratio.	Influenza vaccine Influenza specific antibody titre (HI), seroresponder rates (4 fold increase in antibody & (≥ 40HI units) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine), 57 and 183 days post-vaccine	Antibody titres and rates of seroprotection did not differ between groups at any time point Significantly higher seroresponse for one strain in the intervention group compared to control on day 57. Trend towards higher mean titres in the intervention compared to control group on day 57

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Langkamp-Henken (RVF) (2006) USA RCT **Intervention code C**	Older adults resident in nursing homes (institutionalized) 29 males, 63 females Intervention n=76; mean age 81.4 years Control n=72; mean age 85.4 years	Intervention: 240 ml per day for 10 weeks of a nutrition mediated immune formula. Control: commercially available nutritional formula Adherence: daily intake of formula recorded by study coordinators. Adherent participants defined as those with mean daily intake ≥ 180ml and who completed at least 60 of the 70 study days. 52/76 adherent in intervention group and 40/72 adherent in the control group Vaccine administered after 4 weeks of consuming intervention/control formula and continued for a further 6 weeks. Mediating mechanisms: not reported serum α-tocopherol and β-carotene significantly increased in the intervention group	Influenza vaccine Influenza specific antibody (HI) titres, measures of seroresponding (≥ 4-fold increase in antibody; >180 antibody to H1N1 or ≥ 40 antibody to H3N2), Haemagglutination inhibition assay Timing of immune measures: 0 weeks (pre-vaccine), 4 weeks (vaccination) and 10 weeks (6 weeks post-vaccine)	In adherent participants only the % of seroresponders to one strain by 10 weeks was significantly greater in the intervention group compared with the control group All other between group comparisons in antibody titres, seroresponder rates were not significant

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Link-Amster (1994) Switzerland RCT **Intervention code B**	PRELIM STUDY: healthy male volunteers Group 1 n= 5 Group 2 n= 5 MAIN STUDY: healthy adult volunteers, 14 female, 16 male, aged 19-59, mean age 37.3 Group A n= 16 Group B n= 14	**Prelim study** groups:- **Group 1,** Intervention 3x125g fermented milk per day for 3 weeks. **Group 2** (control) no fermented milk. Vaccine given to both groups day8, 10, 12. Blood taken baseline, 14, 24 and 42 days post vaccine. **Main study** All subjects excluded fresh fermented products from diet from day 21 (t -21) to day 8 (t-8) before vaccine **Intervention group A:-** from day 7 (t-7) before vaccine to day 13 post vaccine (+13) subjects had 3x125g fermented milk per day for 3 weeks **Control group B:-** carried on exclusion diet, no fermented milk given for same time frame as group A Timing:- vaccine given on t 0, +2 and +4 days Adherence:- not reported Mediating mechanisms: not reported	Salmonella vaccine Vaccine specific IgA, IgM, IgG antibody titers and total serum IgG and IgA and salivary IgA Enzyme-Linked Immunosorbent assay (ELISA) and radial immunodiffusion Timing of immune measures: t-10 (10days pre vaccine), days +9 (saliva only), +14, +24 (blood only) post vaccine	Significant rise in IgA titre in intervention group compared to control group Total serum IgA in group A significantly increased between t -10 to t+14. No significant changes in serum IgG or salivary IgA No significant difference between groups in prelim study

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Maruyama (RVF) (2016) Japan RCT **Intervention code B**	Nursing home residents ≥65yrs (institutionalized) Intervention group n=22; mean age 89, 3 male, 18 female, BMI 21.7 Placebo group n=23; mean age 85.3, male 5, female 16, BMI 22.2	Jelly containing Lactobacillus paracasei (intervention group) or jelly containing no lactobacilli (placebo group) daily for 6 weeks Timing – vaccine given 3 weeks into study Adherence: 98.8% in intervention group and 98.5% in placebo group. How this has been measured is not reported. Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibodies (HI) titres Haemagglutination inhibition assay Timing of immune measures: baseline, 6 weeks	No significant difference in antibody response between both groups over whole cohort In ≥85yrs sub group (n=16) – antibody titres significantly increased in 2 strains in the intervention group compared to control group (n=11).

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Meydani (1997) USA RCT **Intervention code A**	Free living older adults 34 males, 44 females Mean age: 69.9 – 72.4 years (intervention groups); 70.4-70.8 (control) Intervention groups: 60mg n=20; 200mg n=20; 800mg n=19 Control: n=19	Intervention: daily supplement of 60, 200, or 800 mg of vitamin E for 235 days Control: placebo Adherence: measured by counting pills from returned pill packages. Six participants considered non-adherent (2 in placebo group, 2 in 60mg group, 1 in 200mg group and 1 in 800mg group). This data was excluded from the analysis. A further 10 participants missed 1-4 days' worth of supplements. This data was included in the analysis. Vaccinations administered on day 156 of intervention/control treatment, with hepatitis boosters given on days 186 and 216. Meditating mechanisms: significant increase in vitamin E levels in the intervention groups	Hepatitis B, tetanus and diphtheria, and pneumococcal IgG antibody titres and seroresponder rates to hepatitis B (titres ≥ 8IU/ml) after third vaccine. Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 0 (pre-vaccine), 1 month post-vaccine (day 186) &days 216 & 246	Antibody titres to hepatitis B significantly increased over time in participants receiving 200mg or 800mg daily; compared with no significant change in the placebo and 60mg per day groups. No significant differences in seroresponder rates. However, analyses in participants in the upper tertile of vitamin E levels showed significantly higher antibody titres and seroresponder rates to hepatitis B. No significant between group differences in antibody responses to diphtheria, pneumococcal and tetanus

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Namba (RVF) (2010) Japan RCT **Intervention code B**	Elderly subjects, mean age 86.7yrs from healthcare facility in Japan (institutionalized) Intervention group n=13; 2 males, 11 females, mean age 86.2 Control group n=14; 1 male, 13 female, mean age 87.3	Both groups had test food with $1x10^{11}$ cfu Bifidobacterium longum BB536 daily for 5 weeks. Then bloods taken, from week 6 started next phase P2 below Intervention group:- continued BB536 once daily for further 14 weeks Control group:- continued placebo once daily for further 14 weeks. Contained 2g dextrin. Timing:- vaccine given at week 3 Adherence:- intervention given as part of the food supplied by the healthcare facility so adherence not applicable. Mediating mechanisms: not reported	Influenza vaccine Specific influenza antibody titers IgG, IgM, IgA Assay method not documented Timing of immune measures: week 5, 10, 15, 20	No significant differences in antibody response between placebo and intervention group at any time point during the study Proportion of subjects who contracted influenza was significantly lower in intervention group compared to placebo

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Negishi (RVF) (2013) Japan RCT **Intervention code E**	Elderly Japanese nursing home residents, >60yrs (institutionalized) MF Group n= 27; mean age 86.6yrs, 32 female, 3 male Control group n= 30; mean age 87.34yrs, 32 female, 3 male	MF group:- Mekabu fucoidan (MF) 300mg/day and 300mg indigestible dextrin granules daily for 20 weeks Control group:- dextrin granules daily for 20 weeks Timing:- vaccine given at week 4 Adherence: checked and recorded by nurses but results not reported Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibodies, HI titres, seroconversion, seroprotection Haemagglutination inhibition assay Timing of immune measures: Baseline (before vaccination, 4 weeks before study diet intake) 5, 20 weeks post vaccine	Higher antibody titres in MF group for all strains compared to placebo but not statistically significant Specific antibody titres against one strain significantly increased in MF group compared to placebo at 5 weeks and 20 weeks Proportion of seroprotection and seroconversaion higher in MF group compared to placebo for all strains

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Newton (RVF) (2007) Ghana RCT **Intervention code A**	Infants from area with a high prevalence of vitamin A deficiency (likely malnutrition and immunosuppressed) Vitamin A group n=460; male 48%, female 52%, mean age at 6 week blood test 49.3 days old, at 18 week test 146.3 days old Control group n=428; male 47.6%, female 52.4%, mean age at 6 week blood test 50.1 days old, at 18 week test 147.5 days old	Vitamin A (intervention) group:- 15mg retinol equivalent Vitamin A at the time of vaccination so 3 doses in total Control group:- no Vitamin A given at vaccination Adherence: intervention given at the same time as the vaccine so adherence not applicable. Timing:- Vaccine given at 6, 10, 14 weeks old Mediating mechanisms: not reported	Diphtheria, polio, tetanus, Haemophilus influenza b, hepatitis B vaccine some components of vaccine given orally and some via injection Anti-Hib and anti-hep B antibodies Enzyme-Linked Immunosorbent assay (ELISA) Seroprotection rates and geometric mean antibody concentration (GMC) Timing of immune measures: 6 weeks of age (straight after 1st vaccine dose) 18 weeks of age (4 weeks post 3rd dose of vaccine)	Vitamin A significantly increased hep B antibodies at 18 weeks compared to controls Vitamin A did not affect immune response to Haemophilus influenza type b, in GMC levels or antibodies No significant difference between groups and GMC levels

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Olivares (2007) Spain RCT **Intervention code B**	Healthy adult volunteers 31 male, 19 female, mean age 33yrs Intervention group n= 25 Control group n= 25	Subjects started taking one of the below 2 weeks before vaccination until 2 weeks post vaccination Intervention group:- oral daily dose Lactobacillus fermentum $1x10^{10}$ cfu's per day in 200mg methycellulose Control group:- oral daily dose of placebo (200mg methylcellulose) Adherence:- not reported Mediating mechanisms: not reported	Influenza vaccine Total and influenza specific IgA, IgG, IgM Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline, day 0, day 14 (just before vaccination), day 28	Significant increase in specific IgA antibody in the intervention group compared to control, 2 weeks post vaccine Significant decrease in IgG antibody response in placebo group 2 weeks post vaccine Significant increase in total IgM compared to control Incidence of influenza like illness lower in probiotic group 5 months post vaccination

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Osendarp (RVF) (2006) Bangladesh RCT **Intervention code A**	Infants and their mothers from areas of Dhaka city slums (likely malnutrition) Intervention group infants n= 96 Control group n= 107	Intervention group: mothers given 30mg elemental zinc daily from 12-16 weeks gestation to delivery Control group: mothers given cellulose from 12-16 weeks gestation to delivery Timing: Vaccinations given to infants. All infants received BCG vaccine within 72hrs of birth but sub-cohort received DTP-Hib as well starting at 9 weeks of age, 3 doses given at monthly intervals Adherence: 86% - checked by counting remaining pills left in packs during unannounced home visits. Mediating mechanisms: not reported	Bacillus Calmette-Guerin (BCG) vaccine and (Diphtheria, tetanus, pertussis, haemophilus influenza type-b (DTP-Hib) vaccine and polio (TOPV) vaccine Antibodies to H.influenzae b, geometric mean titres (GMT) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (pre-vaccine) at 4 weeks of age, post vaccine at 24weeks of age	No significant difference in antibodies post vaccine course between Zinc group and control

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Osendarp (RVF) (2007) Bangladesh RCT **Intervention code A**	Infants from an area with a high prevalence of zinc deficiency (likely malnutrition) Intervention group n= 121 Control group n= 120 Mean age 0.88 months, 39.6% male, 60.4% female	Intervention group:- 5ml sucrose liquid with 5mg elemental zinc (zinc acetate) daily from 4 weeks to 33 weeks of age Control group:- 5ml sucrose liquid daily from 4 weeks old to 33 weeks old Adherence: 85% - checked weekly by measuring liquid levels at routine visit but also added in unannounced spot check visits. Timing:- BCG, DTP-Hib, TOPV at 9, 13, 18 weeks old. PNC given to all infants ≤4months + 15days old, 3 doses in total, 4 weeks apart Mediating mechanisms: not reported	7-valent pneumococcal conjugate vaccine (PNC) Pneumococcal specific IgG antibodies, Geometric mean antibody titres (GMT) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (before vaccine at 4weeks old), After 2nd dose at 24weeks old, 1 month post 3rd dose at 29 weeks old	Significantly higher antibody titres for zinc compared to control in one (9V serotype) Pneumococcal specific IgG antibody. This was after 3 doses of PNC at 29 weeks of age.

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Paineau (2008) France RCT **Intervention code B**	Healthy volunteers, aged 18-62yrs Bifidobacterium lactis Bi-07 n=9; mean age 35.3, BMI 23.8, male 3, female 6 Bifidobacterium lactis BI-04 n=9; mean age 38yrs, BMI 23.4, 3 male, 6 female Lactobacillus acidophilus La-14 n=9; mean age 34.5yrs, BMI 22.5, male 5, female 4 Lactobacillus acidophilus NCFM n=9; mean age 40.6yrs, BMI 24.3 male 5, female 4 Lactobacillus plantarum Lp-115 n=9; mean age 35, BMI 21.8, male 5, female 4 Lactobacillus paracasei Lpc-37 n=9; mean age 44.5yrs, BMI 23.9, male 2, female 7 Lactobacillus salivarius Ls-33 n=9; mean age 35.5yrs, BMI 21.9, male 3, female 6 Placebo n=20; mean age 34.5yrs, male 5, female 15, BMI 22.6	Subjects either placebo/probiotic over 3 weeks **7** Intervention groups as 7 probiotic strains, all part of Lactobacillus or Bifidobacterium genera tested. Given 2 capsules per day total $2x10^{10}$ cfu. Control group:- maltodextrin Timing:- vaccine given at day 7 and day 14 Adherence: Assessed via questionnaires and diary with 83% adhering to diet and medication advice for whole study period. Mediating mechanisms: not reported	Cholera vaccine Serum – cholera specific IgA, IgG, IgM Saliva- cholera specific IgA Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Blood and saliva Day 0, Day 21, Day 28	Between day 0 – 21 IgG significantly increased in Bifidobacterium lactis B1-04 and Lactobacillus acidophilus La-14 compared to control.

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Prinicipi (2013) Italy RCT **Intervention code A**	Children with a history of recurrent otitis media Total n=116; mean age 3yrs, 61 male (52.6%), 55 female Vitamin D group n=59; mean age 3.3yrs Placebo group n=57; mean age 2.9yrs Baseline vitamin D similar in both groups <20ng/ml n=23, 20-29.9ng/ml n=60, >30ng/ml n=33	Intervention – daily vitamin D 1000 IU Placebo – further details not given Given for 4 months Vaccine given at start and then 1 month after Adherence – checked via diaries and amount of medication at monthly checks. However, data not reported. Mediating mechanisms: not reported	Influenza vaccine HI titres, seroconversion, seroprotection, median GMT (geometric mean titre) Haemagglutination inhibition assay Timing of immune measures: baseline, 4 months (end of treatment)	No significant difference between antibody responses in both groups, (even when different seroconversation/seroprotection levels were applied) nor by baseline level of vitamin D

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Provinciali (RVF) (1998) Italy RCT **Intervention code A**	Older adults resident in community nursing home (institutionalized) Mean age 82 years 3 studies done over 3 seasons Study 1 Intervention n=27 (zinc sulphate) control n=36 Study 2 Intervention n=100 (zinc sulphate) control n=123 Study 3 Intervention: n=33 (zinc sulphate) n=34 (zinc sulphate plus arginine) Control: n=31	Intervention: 400 mg/day zinc for 60 days or 400mg/day zinc plus 4g/day arginine for 60 days. Control: no treatment Adherence: not reported. Vaccination administered after 15 days of treatment. Mediating mechanism: zinc concentrations increased significantly after first 15 days of treatment in intervention groups, but did not change significantly thereafter.	Influenza vaccine HI antibody titres and seroresponder rates Haemagglutination inhibition assay Timing of immune measures: -15, 0, and 45 days post-vaccine	No significant differences between groups in antibody titre or seroresponder rates across all studies

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Przemska-Kosicka (2016) UK RCT **Intervention code B**	OLDER COHORT: 60-85yrs; mean age 69, 18 male, 45 female Placebo n=33 Intervention n=29 YOUNGER COHORT: (18-35yrs); mean age 26; 23 mal, 39 female Placebo n=31 Intervention n=31	Probiotic with prebiotic (B.longum + GI-OS) Placebo – maltodextrin Taken daily for 8 weeks Adherence: checked by counting returned sachets. However, data not reported. Vaccine given at 4 weeks Mediating mechanisms: faecal samples showed an increased trend of B.longum in the gut for both younger and older adults.	Influenza vaccine Total antibody (HI) titres,(Haemagglutination inhibition assay), vaccine specific IgA, IgM, IgG [Enzyme-Linked Immunosorbent assay (ELISA)], seroprotection, Timing of immune measures: Baseline, 4 weeks 6 weeks, 8 weeks	In the younger cohort, there was a reduction in antibody titres to one strain in the intervention group compared to placebo. In older adults, there was a reduced seroconversion and IgG response to one strain in the intervention group compared to placebo. However, there were no significant differences in antibody response between intervention and control groups, in both older and younger adults.

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Qadri (RVF) (2004) Bangladesh RCT **Intervention code A**	2-5 yrs old children with vitamin A deficiency (immunosuppressed) Group A n= 61 Group Z n= 63 Group AZ n= 62 Group P n= 63	Group A:- Vitamin A and placebo syrup Group Z:- Zinc and placebo syrup Group AZ:- both Vitamin A and zinc Group P:- both placebo syrups Vitamin A single dose 200,000 IU given day 15 (week 3) 5ml Zinc acetate equivalent to 20mg elemental zinc given daily from day 0 for 42 days Timing:- 2 doses of vaccine given to all children with 2 week interval between doses 1st dose given day 22, 2nd dose day 36 Adherence:- 97% adherent to intervention Mediating mechanisms: not reported	Cholera Specific IgA and IgG antibodies (CT-IgA, CT-IgG) Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (day 0 week 1), Day 29 (week 5), Day 42 (week 7)	After 1st dose, median CT-IgA titre in AZ group significantly lower than group A and P After 1st dose median CT-IgG titre in AZ group significantly lower than group A After 2nd dose, median CT-IgA titres in Z and AZ groups significantly lower than P group Responders significantly lower in group A vs group Z for CT-IgA post 2nd dose

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Rahman (RVF) (1998) Bangladesh RCT **Intervention code A**	Infants from urban slum area (likely malnutrition) Aged 6-17weeks Vitamin A group n= 34 Placebo group n= 23	Vitamin A group:- 50,000 IU Vitamin A orally Placebo group:- no vitamin A, placebo given instead Timings:- 3 doses of vaccine given in total, 1st followed by 2nd 4weeks after and 3rd 8 weeks after Vitamin A or placebo given in clinic each time vaccine given Adherence: intervention same time as vaccine so assumed to be 100% But no data reported. Mediating mechanisms: not reported	DPT (Diphtheria, Pertussis, Tetanus) and OPV (oral polio vaccine) Serum antibody titre for polio geometric mean titre (GMT) (seroconversation if titres at least 1:16 in previously seronegative infant or 4-fold rise) Assay method not documented Timing of immune measures: Baseline and 1 month post 3rd dose of vaccine	No significant difference in seroconversion to polio between infants in Vitamin A or placebo group

First Author (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
Rahman et al. (RVF) (1999) Bangladesh RCT **Intervention code A**	Infants from urban slum area (likely malnutrition) Intervention: n=33; mean age 75.3 days 15 male, 18 female, control: n=23; mean age 75.4 days, 12 male, 11 female	Intervention: 15mg (50,000 IU) vitamin A received monthly over 3 months Control: placebo Adherence: intervention/placebo received at study site at the time of each of 3 vaccinations so assumed to be 100%. But no data reported. Vaccines administered immediately after each dose of the intervention/placebo Mediating mechanisms: not reported	Diphtheria, pertussis, and tetanus IgG antibody titres Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: Baseline (pre-vaccine), 1 month post third dose of vaccine	IgG antibody concentration for diphtheria was significantly greater in intervention group compared with controls; between group comparisons for pertussis and tetanus not significant.

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Remarque (1993) Netherlands RCT **Intervention code A**	Ambulatory older adults Zinc group n=43; mean age 80.5yrs, 27 female, 16 male Control group n=41; mean age 80yrs, 27 female, 14 male	Zinc group: 220mg zinc sulfate twice daily for 28days, starting 7 days before vaccination Control group:- lactose containing placebo given twice daily for 28 days, starting 7 days before vaccine Timing:- vaccination given on day 7 Adherence: not reported Mediating mechanisms: not reported	Influenza vaccine Specific HI antibody titer levels Hemagglutination inhibition assay Timing of immune measures: Baseline, immediately prior to vaccination, 21 days post vaccine	No significant difference in antibody levels between groups

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Rizzardini (2012) Italy RCT **Intervention code B**	Healthy adults Mean age:33.2 years 93 males, 118 females Intervention: n=109 Control: 102	Intervention: Group 1: Probiotic strain BB-12 capsule taken once daily for 6 weeks; Group 2: Probiotic strain L. casei 431 acidified dairy drink taken once daily for 6 weeks Control: Group 1: placebo capsule Group 2: Placebo acidified dairy drink Adherence: Self-reported adherence ranged from 98.5% to 99.6% Vaccination administered 2 weeks after starting intervention/control treatment Mediating mechanisms: not reported	Influenza vaccine Influenza specific serum IgG antibody titres and seroresponding rate (≥ 2-fold increase in titre from baseline). Influenza specific salivary IgA, IgG and IgM Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 0 (pre-vaccine) and 4 weeks post-vaccine	Significantly higher antibody titres, seroresponding and vaccine specific salivary IgA rates in both intervention groups compared with control groups

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Roman (2013) USA RCT **Intervention code E**	Healthy adults Intervention n=14; mean age 60.8years, 9 male, 5 female Control n=15; mean age 57.8 years, 7 male, 8 female	Intervention: 3g per day of active hexose correlated compound (AHCC), for 3 weeks. Control: no treatment Adherence: not reported Vaccination administered on first day of intervention treatment Mediating mechanisms: not reported	Influenza vaccine HI specific antibody titres and indices of seroresponding rates (titres ≥40 & 4 fold rise in titre) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine) and 21 days post-vaccine	Significant increase in antibody titres for one strain in intervention group compared to control No significant between group differences in indices of seroresponding.

First Author (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
Scaglione (1996) Italy RCT **Intervention code E**	Adults volunteers attending private practices in Milan Intervention group n=114; mean age 48yrs, male 66, female 48 Control group n=113; mean age 48.5yrs, 66 male, 47 female	Both groups had daily oral doses (2 capsules) for 12 weeks Intervention group:- 100mg standardised ginseng extract Ginsana G 115 Control group:- placebo capsules Timing:- vaccine given at week 4 Adherence: data not reported Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody titres Haemagglutination inhibition assay Timing of immune measures: 0, 4, 8, 12 weeks	Antibody titres significantly higher by week 8 in intervention group compared to control and remained significantly higher at 12 weeks Frequency cold common/influenza significantly higher in placebo group compared to control

First Author (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
Semba (1992) Indonesia RCT **Intervention code A**	Pre-school children in West Java, Indonesia Aged 3-6yrs Clinically normal + vitamin A (Group 1) n= 59; mean age 58.2 months, 43 male, 16 female Clinically normal + placebo (Group 2) n= 59; mean age 58.7 months, 42 male, 17 female Mild xerophthalmia + vitamin A (Group 3) n= 58; mean age 60.3, 41 male, 17 female Mild xerophthalmia + placebo (Group 4) n= 60; mean age 58.3, 43 male, 17 female	Vitamin A group:- oral 60,000µg retinol equivalent solution given just after baseline bloods taken Placebo group:- given placebo oral solution, no vitamin A given just after baseline blood taken Timing:- vaccines given 2 weeks after baseline bloods and dose of Vitamin A/placebo Adherence:- single dose intervention given straight after baseline bloods so adherence not applicable. Mediating mechanisms: not reported	Tetanus specific IgG levels Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: baseline, 3 weeks post vaccine	Clinically normal and xerophthalmic children receiving vitamin A had a significantly greater IgG response to tetanus than both groups of children receiving placebo Primary antibody response – vitamin A supplemented groups had a significant 2.5 times greater IgG response than placebo Secondary antibody response- vitamin A supplemented groups had a significant 2.1 times greater IgG response than placebo

First Author (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
Semba (RVF) (1995) Indonesia RCT **Intervention code A**	Infants in area with high prevalence of vitamin A deficiency (immunosuppressed) Mean age: 6 months Intervention: n=169 Control: n=167	Intervention: single dose of 100,000 vitamin A Control: placebo Adherence: assumed to be 100% as intervention administered at same time as vaccine, Vaccination administered at same time as intervention/placebo treatment, with booster dose given 6 months later Mediating mechanisms: not reported	Measles Antibody titres; seroresponding rates (4-fold rise in titre) Geometric mean titres (GMT) Plaque reduction neutralisation (PRN) assay Timing of immune measures: 0 (pre-vaccine), 1 and 6 months post-vaccination	Antibody titres significantly lower in intervention group at 1 and 6 months post-vaccine

First Author (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
Semba (RVF) (1997) Indonesia RCT **Intervention code A**	Infants in area with high prevalence of vitamin A deficiency (immunosuppressed) Vitamin A Group 1 n= 132; mean age 9.9 months;72 male, 60 female Vitamin A group 2 n= 132; mean age 9.9 months; 74 male, 58 female Placebo n= 130; mean age 10 months; 66 male, 64 female	Vitamin A Group 1:- Vitamin A dose at 6, 10, 14 weeks 50 000 IU and 100 000 IU at 9 months Vitamin A Group2:- Vitamin A dose at 6,10, 14 weeks 25 000 IU and 100 000 IU at 9 months Placebo group:- received identical looking placebo capsule at 6,10,14 weeks and 9 months Timing:- vaccine given at 9 months, Vitamin A or placebo given at same time Adherence:- not reported Mediating mechanisms: not reported	Measles vaccine Measles specific antibody titres Geometric mean titres (GMT), seroconversion (titres ≥1:120) Plaque reduction neutralisation (PRN) assay Timing of immune measures: baseline, 1 month and 6 months post vaccination	Seroconversion rates similar in vitamin A and placebo treatment groups No significant differences in GMT levels to measles at 1 or 6 months post vaccine between the 3 groups

First Author (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
Semba (RVF) (1999) Indonesia RCT **Intervention code A**	Infants in area with high prevalence of vitamin A deficiency (immunosuppressed) aged between 6 weeks and 9 months Vitamin A 7.5mg RE group n= 156; mean age 53.1 days, 88 male, 68 female Vitamin A 15mg RE n= 155; mean age 52.7 days, 86 male, 69 female Placebo group n= 156; mean age 53.8 days, 82 male, 74 female	Either given Vitamin A 7.5mg retinol equivalent (RE), or 15mg RE, or placebo at 6, 10, 14 weeks of age alongside vaccines Timing: Vaccines given at 6, 10 and 14 weeks old. Placebo or Vitamin A given 10-30mins after TOPV vaccine Adherence: intervention given at the same time as the vaccine so adherence not applicable. Mediating mechanisms: Vitamin A (retinol) levels significantly increased in intervention groups	oral polio vaccine polio specific antibody titers (seroconversation titres ≥2 at 9 months minus expected titre of materal antibody, seroprotection ≥8 at 9 months) microvirus neutralization assay timing of immune measures: Baseline (6 weeks old), 14 weeks old, 9 months old	No significant difference in mean antibody titers or seroconversation to polio among groups No significant differences in protective titer levels among groups

First Author (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
Soh (2010) Singapore RCT **Intervention code B**	Infants with allergic disease in a first degree relative Mean age: 6 months Vaccine schedule A: Intervention: n=29, control n=28. Vaccine schedule B: Intervention: n=77, control = 68	Intervention: 2.8×108 CFU of probiotic bacteria per day from 12 hours after delivery for 6 months. Control: commercially available formula Adherence:89% intervention group, 85% placebo group. Mediating mechanisms: not reported	**Vaccine schedule A:** Monovalent Hepatitis B administered at ages 0 and 1 month, and then with Hexavalent diphtheria-tetanus-acellular pertussis (DTPa) just at 6-months **Vaccine schedule B:** Monovalent Hepatitis B administered at ages 0, 1, and 6-months Hepatitis specific IgG antibody titres & seroresponding rate Assay method not clearly documented Timing of immune measures: baseline and 12 months	Seroresponding rates did not differ between intervention and control groups for either vaccine schedule. Intervention was associated with significantly higher antibody titres, compared with controls, for participants who received vaccine schedule A,

First Author (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
Stam (2011) Netherlands RCT **Intervention code B**	Children in first year of life, recruited before 8 weeks of age Prebiotics group n= 80 Control group n= 84	All infants fed control/prebiotic formula for 12 months Prebiotics group:- standard non-hyrolyzed cow's milk-based formula with mixture of scGOS, IcFOS, ratio 9:1 and pAOS added. Total OS 8g/l with 6.8g/l neutral and 1.2g/l AOS Control group:- standard non-hydrolyzed cow's milk-based formula with no prebiotic Timing:- 2, 3, 4, 11 months of age Adherence: data not reported. Mediating mechanisms: not reported	Diphtheria, tetanus, pertussis, polio, Haemophilus influenza b (Hib) and pneumococcal vaccine Some also had hepatitis B at same time Hib and tetanus specific IgG antibodies and seroprotection (tetanus >0.1IU/ml and Hib >1.0 µg/ml) Enzyme immunoassay used Timing of immune measures: 6 and 12 months of age	No significant effect of prebiotic supplementation on vaccine specific antibody levels

First Author (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
Timby (2015) Sweden RCT **Intervention code C**	Infants aged <2months – 6 months old 160 formula fed 80 breast fed controls Intervention group (EF) n= 80 Control group (SF) n= 80 Breast fed controls (BFR) n=80	Infants fed control formula or intervention formula from <2 months old to 6 months old Control formula – unsupplemented standard formula Intervention formula- standard formula altered and supplemented by bovine MFGM (milk fat globule membranes) Timing – vaccine given at 3+5 months of age Adherence – not clearly reported. Mediating mechanisms: not reported	Pneumococcal vaccine Pneumococcal specific IgG antibodies levels Timing of immune measures: 6 months of age Fluorescent bead-based multiplex immunoassay	EF group had significantly lower IgG levels compared to the SF group for 3 serotypes. However, the vaccine used during the study changed 3 times, and the components of each vaccine were different. Only one serotype was consistently used in all 3 vaccines.

First Author (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
Turk (RVF) (1998) Turkey RCT **Intervention code A**	Healthy adults and patients undergoing haemodialysis (immunosuppressed) Group 1: haemodialysis patients + zinc n= 13; 8 female, 5 male, mean age 37yrs Group 2: haemodialysis patients +placebo n= 13; 8 female, 5 male 46yrs Group 3: healthy subjects n=11; 6 male, 5 female 38.7yrs	Intervention (group 1): 120mg zinc after each dialysis session (2/3 times per week Duration of intervention not specified. Placebo (group 2): not specified Group 3 – not reported Adherence: no data reported Unclear when vaccination was administered in relation to intervention Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody titres No assay method documented Timing of immune measures: 0 (pre-vaccine) & 1 month post-vaccine.	Baseline antibodies not reported. Comparison between groups 1 and 2 indicated no significant difference in antibody titres.

First Author (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
Turnlund (2004) USA Non- RCT Quasi experimental Pair matched controls **Intervention code A**	Male adult subjects Mean age 38. Intervention group n=9 Control group n=10	Intervention group:- confined to research unit for 18 days, average 1.6mg copper per day. Then 129 days in free living, supplemented own diet with 7mg copper per day. Then research unit again for 18days same as 1st period but copper intake 7.8mg per day. 1g ascorbic acid (Vitamin C) given day 14 of each live in period. Subjects walked 3miles per day to maintain physical fitness Control group:- no copper supplements just their normal diet Timing:- vaccine given after week 12 of supplementation, 2 weeks before end of high copper intake period Adherence:- reports monitoring this during the free living period but no methods or data reported. Mediating mechanisms: urine and stool samples analysed for copper levels. No significant increase reported between different study periods.	Influenza vaccine Influenza specific antibody titer Haemagglutination inhibition assay Timing of immune outcomes: Baseline, 14 days post vaccine	Antibody titers lower for all 3 strains in the intervention group compared to control group. However, this was only significant for one strain.

First Author (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
Udani (2010) USA RCT **Intervention code E**	Healthy adults 18-65yrs BMI 18-30 Intervention group n=21; mean age 33.52, 9 male, 12 female Control group n=24; mean age 38.25, 16 male, 8 female	Both groups started at Day 0 and took placebo/intervention daily dose 4.5g for 72 days Intervention:- had Arabinogalactan extracted from Larch (ResistAid) Control:- had placebo agent (maltodextrin) Timing:- vaccine given on day 30 Adherence: there were 4 visits during the study period – adherence was assessed at each one via a diary, interview, and the packets (containing intervention/placebo) returned. However, data not reported. Mediating mechanisms: not reported	Pneumococcal vaccine Pneumococcal specific IgG antibodies and salivary IgA Assay for serum antibodies not documented Immune-array assay with a minimum sensitivity of 1µg/ml was used for salivary IgA Timing of immune measures: Day 0, 51, 72	Significantly greater IgG antibody response in intervention group compared to control in specific IgG antibodies at Day 51 and Day 72 Significant change scores from baseline in intervention group compared to placebo for specific antibodies at Day 51 and Day 72

First Author (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
Udani (2013) USA RCT **Intervention code E**	Healthy adults 18-61yrs, BMI 18-30 kg/m^2 Intervention group 1.5 n=27 Intervention group 4.5 n= 25 Control group n=23	All subjects had intervention/placebo for 60 days Intervention group 1.5:- given 1.5g/day ResistAid (Arabinogalactan extracted from Larch) Intervention group 4.5:- given 4.5g/day ResistAid (Arabinogalactan extracted from Larch) Control group:- placebo, maltodextrin, no ResistAid, Timing:- vaccine given at day 30 Adherence: there were 4 visits during the study period – adherence was assessed at each one via a diary, interviews, and the packets (containing intervention/placebo) returned. However, data not reported. Mediating mechanisms: not reported	Tetanus and influenza vaccines Specific tetanus (IgG) and influenza (A, B, IgG, IgM) antibodies Tetanus - measured by enzyme immunoassay Influenza - antibody enzyme-linked immunosorbent assay Timing of immune measures: Baseline, days 45, 60	Significant increase in tetanus IgG levels day 60 in 1.5g/day group compared to placebo.

First Author (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
Van Puyenbroeck (RVF) (2012) Belgium RCT **Intervention code B**	Older adults resident in nursing homes (institutionalized) Intervention n=375; mean age: 83.95 years, 99 male, 276 female Control n=362; 84.17 years, 85 male, 277 female	Intervention: 330 ml per day of milk product containing the probiotic *lactobacillus casei* Shirota; taken for 176 days. Control: placebo Adherence: self-report and nursing staff reports of consumption. However, findings not reported Vaccination administered on day 21 of intervention/control treatment Mediating mechanisms: not reported	Influenza vaccine HI specific antibody titres and seroresponding rates (titres ≥40) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-intervention & pre-vaccine), 50 (4 weeks post-vaccine) and 176 days (41 weeks post-vaccine)	No significant between group differences in antibody titres or seroresponding rates

First Author (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
Vidal (2012) China RCT **Intervention code E**	Healthy community dwelling older Chinese adults Intervention n=75; mean age: 67 years, 39 male, 36 female Control n=75; mean age 66 years, 39 female, 36 male	Intervention:530 mg/gram wolfberry fruit daily for 92 days Control: placebo Adherence: monitored by study personnel, but no description provided as to how monitoring was undertaken or levels of adherence achieved. Vaccination administered on day 30 of intervention/control treatment Mediating mechanisms: not reported	Influenza vaccine IgG and IGM antibody titres and seroresponding rates Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 0 (pre-treatment/pre-vaccine),30 (day of vaccination), days 60 and 90 (days 30 and 60 post vaccine)	Significantly higher IgG antibody titres at days 30 and 60 post-vaccine in intervention group compared with control group. No significant between group differences in any outcomes relating to IgM levels. Significantly higher seroresponding rates in the intervention, compared to control by day 60.

First Author (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
West (2008) Sweden RCT **Intervention code B**	Infants Mean gestational age at delivery: 40.2 weeks (intervention); 39.9 weeks (control) Intervention: n=84 Control: n=87	Intervention: One serving per day of cereal supplemented with 1 x 10^8 CFU lactobacillus paracasei (LF19) for 9 months from 4-13months Control: Cereal without LF19 Adherence: measured by a daily diary completed by parents which showed no difference between mean in-take of cereals between groups. Vaccine doses administered at 3 months (pre-intervention/control treatment) at 5.5 and 12 months (during intervention/control treatment) of age Mediating mechanisms: not reported	Diphtheria, tetanus toxoid and acellular pertussis (DTaP), polio and haemophilus influenza b (Hib) vaccines Hib, tetanus and diphtheria IgG specific antibody titres Hib and tetanus antibodies - Enzyme immunoassay Diphtheria antibodies – Vero cell neutralization test Timing of immune measures: 5.5 months (2.5 months after vaccination), 6.5, 12, and 13-months of age	No significant between group differences in antibody titres to vaccine antigens.

First Author (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
Wouters-Wesseling (RVF) (2002) Netherlands RCT **Intervention code C**	Older adults resident in nursing homes (institutionalized) Mean age: 84 years 42% male;58% female Intervention: n=10 Control: n= 9	Intervention: nutritional supplement containing 30-160% of United States recommended daily allowance of vitamins and minerals with enhanced levels of antioxidants and 250kcal energy taken twice daily for 7 months. Control: placebo Adherence: reported adequate compliance to supplement. However, no data reported Vaccination administered after 6 months of commencing intervention/control treatment. Mediating mechanisms: not reported	Influenza vaccine Influenza specific antibody (HI) titres; seroresponder rates (4 fold increase in titre & titre ≥ 40) Haemagglutination inhibition assay Timing of immune measures: 0 (pre-vaccine) and 1 month post-vaccine	Significant increase in antibody titres for all 3 strains in the intervention group compared to a significant increase in only one strain in the control group. No significant differences in seroresponder rates. Although the intervention group had greater responder rates to one viral strain compared to control.

First Author (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
Yalcin. (RVF) (2011) Turkey RCT **Intervention code A**	Children with congenital or acquired cardiac disease (immunosuppressed) Total n=44; 18 males, 26 female Intervention: n=23; Mean age: 13.8 years Control: n=21; mean age 13.3 years	Intervention (ZV): 30 mg zinc daily for 28 days Control (V): no treatment Adherence: pill count. Participants who received < 6 pills a week were considered non-adherent and excluded. Vaccination administered on first day of treatment Mediating mechanisms: not reported	Influenza vaccine IgA and IgG antibody geometric titres (GMT), seropositivity Enzyme-Linked Immunosorbent assay (ELISA) Timing of immune measures: 0 (pre-vaccine) and 28 days	No significant differences reported in seropositivity rates or GMT levels between ZV and V group

First Author (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
Youngster (RVF) (2011) Israel RCT **Intervention code B**	Infants admitted to a paediatric ward with acute illness (immunosuppressed) Intervention: n=25 Control: n=22 Mean age at study entry: 9.8 months (intervention group), 9.5 months (control group)	Intervention: probiotic powder containing 3×10^9 CFUs each of lactobacillus acidophilus, Bifi dobacterium bifi dum, Bifi dobacterium longum and Bifi dobacterium Infantis. Given once a day for 5 months from age 10 months onwards Control: placebo Adherence: twice weekly calls to encourage adherence; intervention/placebo supply replenished monthly and empty sachets collected However, data not reported. Vaccination administered 2 months after commencing intervention/control treatment Mediating mechanisms: not reported	Mumps, measles, rubella, and varicella vaccine Seroresponder rates (>40 IU/ml rubella, >150 mIU/ml varicella, >200mIU/ml measles & 40mIU/ml mumps). Automated semi quantitative enzyme linked fluorescent assay Timing of immune measures: 0 (12mths of age/pre-vaccine) and 3-months post-vaccination	No significant differences found between intervention and control groups in seroresponder rates for individual vaccine components; although intervention group had significantly higher seroresponder rates when antibodies to all vaccine components were combined.

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; IgA= Immunoglobulin serotype A, IgE= Immunoglobulin serotype E, CTB= , LPS= Lipopolysaccharide, CT= Cholera toxin,, CFU= colony-forming unit, CTB= Cholera toxin B subunit, CT = Cholera toxin, LPS-IgA= Lipopolysaccharide Immunoglobulin serotype A, anti-Hib= anti Haemophilus influenza type B, anti-CTB IgA = anti Cholera toxin B subunit Immunoglobulin serotype A, anti-CTB-IgG= anti Cholera toxin B subunit Immunoglobulin serotype G, anti-HB= anti-hepatitis B; RVF= risk of vaccine failure.; intervention codes (A= vitamin and/or mineral; B= probiotic ; C=nutritional formulae; D= fatty acid; E=other).

Table 3

Summary of Exercise Studies

First author (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
Campbell (2010) UK RCT (pseudorandomized maintaining even sex distribution between groups)	Intervention: n=116 Control: n=39 Healthy adults Mean age 20 years 76 male, 80 female	Intervention: acute eccentric exercise (dumbbell lifts in repeating pattern for 25 mins) either immediately before vaccination (n=38), 6 hours before vaccination (n=39) or 48 hours before vaccination (n=39) Control: Quiet rest for 25 minutes prior to vaccination Mediating mechanisms: Each of the exercise groups had a significantly greater percentage increase in upper arm and forearm circumference immediately post intervention compared to controls.	Vaccine: Influenza Haemaglutination inhibition assay Baseline and 28 days post vaccination Change in antibody titres to each of the three viral strains in the vaccine as geometric mean, change in log-transformed antibody titres for each strain by group compared to baseline	All three viral strains elicited strong antibody responses but eccentric exercise in the intervention groups did not augment any antibody response compared to the control group.

First author (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
Edwards (2006) UK RCT	Intervention: n=40 Control: n=20 Healthy adults Mean age 22 years 31 male, 29 female	Intervention: Exercise stress group performed a four-step cycle ergometer test at increasing workloads for 45 mins prior to vaccination (n=20). Mental stress group performed a mental arithmetic task for 45mins prior to vaccination (n=20) Control: Rest for 45 mins prior to vaccination Mediating mechanisms: There was a substantial increase in serum cortisol levels in the exercise stress group which was not seen in the mental stress or control groups post-intervention. There were substantial increases in heart rate in the two intervention groups post intervention that were not seen in the control group. IL-6 levels did not change significantly in the control group immediately before	Vaccine: Influenza Haemaglutination inhibition assay Baseline, 4 weeks and 20 weeks post vaccination Change in antibody titres to each of the three viral strains in the vaccine as geometric mean, change in log-transformed antibody titres for each strain by group compared to baseline	For one of the vaccine strains (A/Panama) females in both the exercise and mental stress groups exhibited significantly higher antibody responses at 4 weeks and higher responses at 20 weeks that were not significant. There were no significant differences in the other strains nor to any of the strains in males

First author (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
		and post intervention. IL-6 levels in females were increased at 60 mins recovery in both the exercise and mental stress groups. In males an increase in IL-6 was only seen in the exercise group.		
Edwards (2007) UK RCT	Intervention: n=40 Control: n=20 Healthy adults Mean age 20 years 29 male, 31 female	Intervention: acute eccentric exercise (dumbbell lifts in repeating pattern for 25 mins) 6 hours prior to vaccination Control: rest period for 25 mins 6 hours prior to vaccination Mediating mechanisms: Mean upper arm circumference was higher in men in the exercise group post intervention but not in women. Both men and women reported greater arm pain in the exercise post intervention than in the control group.	Vaccine: Influenza Haemaglutination inhibition assay Baseline, 6 weeks, 8 weeks and 20 weeks post vaccination Change in antibody titres to each of the three viral strains in the vaccine as geometric mean, change in log-transformed antibody titres for each strain by group compared to baseline	Females exhibited higher antibody titres for all three strains in the exercise compared to control groups. Males exhibited lower antibody titres for all three strains in the exercise compared to the control groups.

First author (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
Edwards (2008) UK RCT	Intervention: n=40 Control: n=20 Healthy adults Mean age 22 years 29 male, 31female	Intervention: Exercise stress group performed a four-step cycle ergometer test at increasing workloads for 45 mins prior to vaccination (n=20). Mental stress group performed a mental arithmetic task for 45mins prior to vaccination (n=20) Control: Rest for 45 mins prior to vaccination Mediating mechanisms: not reported	Vaccine: Meningococcal A+C Microsphere-based multiplexed assay of serum IgG antibody concentrations to both types Baseline, 4 weeks and 20 weeks post vaccination Serum antibody concentrations for each type by group compared to baseline	Meningococcal type A IgG antibody concentrations were greater in males in both intervention groups at four weeks but there no differences at 20 weeks. There were no significant differences in women. There were no significant differences in meningococcal type C IgG antibody concentrations between control and intervention groups.

First author (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
Edwards (2012) USA RCT	Intervention: n=66 Control: n=68 Healthy adults Mean age 22 years 58 male, 75 female	Intervention: elastic resistance band exercise for 15 mins prior to vaccination Control: 20 mins quiet rest prior to vaccination Mediating mechanisms: IL-6 was significantly greater in the exercise group than the control group post intervention but GM-CSF levels did not differ. Neither were significant predictors of antibody response. Upper arm and forearm increases in circumference and arm pain were greater in the exercise group compared to the controls post intervention.	Vaccine: Pneumococcal 12 pneumococcal IgG antibody concentrations were measured with Luminex assay each corresponding to a pneumococcal subtype present in the vaccine Baseline and 28 days post vaccination Change in antibody concentration to the pneumococcal strains in the vaccine that were measured as geometric mean, change in log-transformed antibody concentrations to the pneumococcal strains in the vaccine that were measured compared to baseline	No significant differences in antibody outcome.

First author (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
Kohut (2004) USA RCT	Intervention: n=14 Control: n=13 Older adults Mean age 72 years The data from males and females was combined as there was no effect of gender on any of the immune parameters measured	Intervention: Supervised aerobic exercise class three times per week for 10 months from 4 weeks post vaccination Control: Continue current exercise program (low intensity or no exercise) Adherence: not reported Mediating mechanisms: Subjects in the exercise group significantly improved their 6-minute walk distance and total walk distance.	Vaccine: Influenza Haemaglutination inhibition assay Baseline, 1 week, 4 weeks and 3 months post vaccination Geometric mean for serum antibody titre calculated as log-transformed reciprocal HI titre. Change from baseline calculated as log of the mean fold increase (MFI)	The exercise group had significantly higher antibody titres to 2 of the 3 viral strains in the vaccine

First author (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
Kohut (2005) USA RCT	Intervention: n=14 Control: n=13 Older adults Mean age 72 years 13 male, 14 female	Intervention: Supervised aerobic exercise class three times per week for 10 months from 4 weeks post vaccination Control: Continue current exercise program (low intensity or no exercise) Adherence: not reported Mediating mechanisms: Subjects in the exercise group significantly improved their 6-minute walk distance and total walk distance. The intervention had positive effects on 2 aspects of psychosocial functioning – depression and sense of coherence as determined by psychometric testing pre and post intervention.	Vaccine: Influenza Haemaglutination inhibition assay Baseline, 1 week, 4 weeks and 3 months post vaccination Geometric mean for serum antibody titre calculated as log-transformed reciprocal HI titre. Change from baseline calculated as log of the mean fold increase (MFI)	After controlling for the effect observed in the psychosocial measures, the antibody response remained significantly higher in the exercise group. The authors conclude that the increases in antibody response were not mediated by the psychosocial factors.

First author (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
Long (2012) UK RCT	Intervention: n=61 Control: n=61 2 age cohorts, in younger cohort mean age 21 years, in older cohort mean age 58 years Equal numbers of male and female in each group	Intervention: 45 mins brisk walking maintaining heart rate at or above 55% of maximum prior to vaccination Control: 45 mins quiet rest prior to vaccination Mediating mechanisms: Actual percentage of maximum heart rate achieved during the intervention showed a trend towards significantly predicting follow up titres of one of the influenza strains in the vaccine	Vaccine: Pneumococcal 12 pneumococcal IgG antibody concentrations were measured with Luminex assay each corresponding to a pneumococcal subtype present in the pneumococcal vaccine Baseline and 4 weeks post vaccination Log transformed antibody titres for each strain with titre for each strain entered together as the dependent variable in the analysis. Participants were also classified according to whether they had responded to the vaccine as defined by reaching a predefined titre for 8 out of 12 strains	No significant effect on antibody response in either age cohort

First author (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
Long (2013) UK RCT	Intervention: n=44 Control: n=45 Sedentary women Mean age 47 years	Intervention: 16 week exercise programme including lifestyle consultation, pedometer and prompting with vaccination in week 12 Control: advisory leaflet and vaccination after week 12 Adherence: Significant increase in 1-week step counts in the intervention group compared to the control group Mediating mechanisms: Minutes of moderate physical activity per week predicted antibody response at 4 weeks post vaccination with more activity associated with a higher response	Vaccine: pneumococcal 12 pneumococcal IgG antibody concentrations were measured with Luminex assay each corresponding to a pneumococcal subtype present in the pneumococcal vaccine Baseline, 4 weeks and 6 months Log transformed antibody titres for each strain with titre for each strain entered together as the dependent variable in the analysis. Participants were also classified according to whether they had responded to the vaccine as defined by reaching a predefined titre for 8 out of 12 strains	No significant effect on antibody response was detected

First author (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
Ranadive (2014) USA RCT	Intervention: n=28 Control: n=27 Healthy older adults Mean age 67 years	Intervention: 40 minute moderate intensity aerobic exercise at 55-65% of maximum heart rate immediately prior to vaccination Control: no activity prior to vaccination Mediating mechanisms: there was significant correlation between change in IL-6 levels 24 hrs after vaccination and antibody titres 4 weeks post vaccination in the exercise group	Vaccine: Influenza Haemaglutination inhibition assay Baseline and 4 weeks post vaccination Geometric means for serum antibody titres to each of the three strains in the vaccine were calculated as log2 reciprocal titres. Seroprotection was defined as a titre >40	No significant effect on antibody response was detected.

First author (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
Whitham (2003) UK Trial of 2 exercise regimes – not randomized	21 participants but group allocation numbers not recorded Healthy male adults Mean age 23 years	Intervention: increased exercise intensity over 4 week period (heavy exercise group) Control: usual exercise intensity over 4 weeks (light exercise group) Adherence: Training impulse scores calculated from heart rate monitor recording and exercise diary were significantly higher in the intervention group than in the control group. Mediating mechanisms: not reported	Vaccine: Influenza ELISA assay for antibody response to each of the three strains in the vaccine Baseline at week 3 of intervention prior to vaccination and then at 2 days, 4 days, 7 days, 10 days, 14 days and 12 months post vaccination Geometric means of the grouped and overall antibody responses	Greater antibody response at 12 months in the heavy exercise group.

First author (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
Woods (2009) USA RCT	Cardio intervention: n=74 Flex intervention: n=70 Older adults Mean age 70 years 54 male, 90 female	Cardio intervention: increasing cardio exercise regime over 10 months with 3 supervised sessions per week 45 to 60 mins Flex intervention: muscle stretching and balance exercises over 10 months at 2 supervised sessions per week approx. 75 mins Adherence: reported as 83% in the flex group and 82% in cardio group Mediating mechanisms: Cardio intervention resulted in a significant reduction in body weight and body fat and a significant increase in VO2 and maximal exercise capacity. Flex participants gained weight and fat during the intervention and did not increase VO2 or maximal exercise capacity.	Vaccine: Influenza Haemaglutination inhibition assay Baseline and at 3, 6 and 24 weeks post vaccination (which occurred in the fourth month of the intervention) Geometric means of serum antibody titres. Seroprotection was defined as a titre >40	Cardiovascular exercise resulted in a significant increase in seroprotection 24 weeks after vaccination. There was no increase in the flexibility training group.

Table 4

Summary of Psychological Intervention Studies

First author (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
Davidson (2003) USA RCT	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.

First author (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
Hayney (2014) USA RCT	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.

First author (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
Hsu (1995) Taiwan RCT	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: microagglutination assay 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. No significant between group differences in tetanus titres at any time point. Compared with controls, the intervention group exhibited higher pertussis agglutinin titres at 18 and 19 months, but no significant difference at 6 or 7 months.

First author (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
Huang (1999) Taiwan RCT	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.

First author (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
Loft (2012) New Zealand RCT	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.

First author (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
Petrie (1995) New Zealand RCT	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.

First author (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
Stetler (2006) Canada RCT	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.

First author (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
Vedhara (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.

First author (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
Yang (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.

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