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Exercise prior to influenza vaccination for limiting influenza incidence and its related complications in adults (Protocol)

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Exercise prior to influenza vaccination for limiting influenza incidence and its related complications in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of exercise prior to influenza vaccination to enhance influenza prevention in adults.

BACKGROUND

Description of the condition

Influenza is an infectious virus affecting both humans and animals; in humans symptoms present as fever, cough, sore throat, runny nose, headache, muscle and joint pain, and malaise (CDC 2009; WHO 2011). There are three types of influenza: A, B and C. Influenza A has three subtypes of hemagglutinins (H1, H2 and H3) and two subtypes of neuraminidases (N1 and N2). Influenza B and C are not subdivided. Influenza A has the ability to make periodic changes to its strain over time, making efficacious prevention by vaccination a challenge (Demicheli 2014). The epidemiological profile of influenza is influenced by multiple factors, including transmissibility of the virus and the susceptibility of the population (CDC 2009; Nair 2011). Annually, it is estimated to infect 5% to 10% of adults, with higher rates in winter seasons in countries with seasonal variation (WHO 2012).

The incidence of influenza varies according to age group, with greater risk observed in children under five years old and adults aged 65 years or over. Chronic medical conditions and pregnancy also predispose individuals to influenza-related illness and hospitalisation, which is why these groups of people are a priority target for influenza vaccination (CDC 2010; Molinari 2007).

Influenza is estimated to affect three to five million people worldwide annually, with an economic impact of USD 71 to 167 billion per year in the USA (Molinari 2007). Costs are predominantly due to medical care, loss of productivity and death (CDC 2010;

[WHO 2012](#)).

Description of the intervention

Exercise has a positive impact on health and is considered a core behavioural strategy for health promotion ([Booth 2012](#)). In this review, we will use the exercise concept "a planned and structured programme of motor actions to improve or maintain components of physical fitness" ([Carpersen 1985](#)). Exercise, just like the dosing of medicines, has important components such as frequency, time, type and intensity ([Lobelo 2014](#)). Different types of exercise provoke different physiological responses ([Burton 2004](#)).

How the intervention might work

Moderate exercise appears to enhance immune function ([Edwards 2007](#)), through the induction of a pro-inflammatory environment in skeletal muscle, particularly during the eccentric phase of muscle contraction ([Peake 2005](#)). Proposed benefits include increased leukocyte numbers, particularly monocytes and dendritic cells ([Tossige-Gomes 2014](#)), enabling enhanced cell migration to the site of antigen exposure ([Krüger 2008](#)). Immune transport is further aided by augmentation of lymph drainage resulting from muscle contraction ([Schillinger 2006](#)). In contrast, intense exercise may suppress the immune system, causing increased susceptibility to infection for the first 24 hours after exercise through a negative effect on neutrophil phagocytic function and a reduction in natural killer cell and lymphocyte numbers ([Kakanis 2010](#)). Moderate-intensity exercise prior to intramuscular vaccine administration may therefore improve the initial immune response to vaccination in comparison to preceding rest or vigorous muscle activity ([Pascoe 2014](#)).

Why it is important to do this review

Influenza vaccination is ingrained in public health agendas across several countries, despite evidence from Cochrane systematic reviews showing no impact on hospitalisation or complication rates ([Demicheli 2014](#); [Jefferson 2010](#); [Thomas 2013](#)). However, these reviews have demonstrated a moderate effect from vaccination on symptom reduction and reduction in the number of working days lost through ill health ([Demicheli 2014](#); [Jefferson 2010](#); [Thomas 2013](#)). If this review shows improvement of vaccination efficacy it could further reduce the number of sick days and symptoms caused by influenza. Knowledge gained from this review will build upon previous Cochrane reviews about influenza vaccination. The number of randomised controlled trials supporting exercise before influenza vaccination is growing ([Campbell 2010](#); [Edwards 2006](#); [Edwards 2007](#); [Edwards 2010](#); [Kohut 2002](#); [Kohut 2004](#); [Ranadive 2014](#); [Woods 2009](#)). However, it is necessary to synthesise the evidence, critically assess its quality and organise it into a

review. We will present the best available evidence so consumers, policy makers and professionals can make better informed decisions.

O B J E C T I V E S

To assess the efficacy and safety of exercise prior to influenza vaccination to enhance influenza prevention in adults.

M E T H O D S

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of exercise prior to influenza vaccination for the general adult population. We plan to include studies that use a cross-over or cluster-RCT design because they are valid and important additional sources of information.

Types of participants

Adults (aged 18 years or older) randomised to exercise or no exercise prior to receiving influenza vaccination.

Types of interventions

We will include studies that compare exercise prior to influenza vaccination with a group that did not exercise prior to influenza vaccination. Exercise intervention could be single or multiple bouts, resistance or aerobic exercise, specific muscle group or whole body exercise. Possible comparisons that might be included are:
1. exercise versus no exercise prior to influenza vaccination;
2. exercise (with influenza vaccination) versus exercise (with placebo vaccination).

Types of outcome measures

Primary outcomes
1. Incidence of influenza (as reported by primary studies).
2. Complications related to influenza illness.
3. Adverse effects of vaccination.

Secondary outcomes

1. Number of working days or days lost related to influenza illness.
2. Blood parameters (IgG, IgM, IL-6, etc.).
3. Exercise compliance rate of participants.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL, latest issue), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to latest issue), EMBASE (1974 to latest issue), CINAHL (1981 to latest issue), LILACS (Latin American and Caribbean Health Sciences) (1982 to latest issue), PEDro (the Physiotherapy Evidence Database) and SPORTDiscus (1985 to current date).
We will use the search strategies described in Appendix 1 and Appendix 2 to search MEDLINE and EMBASE. We will combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011). We will adapt the search strategy to search the other databases. We will not use any language or publication restrictions. In case of articles in other languages, we will use academic networks and Cochrane resources to translate the critical parts to enable screening of abstracts and, if necessary, critical parts of the full paper.

Searching other resources

We will search the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for completed and ongoing studies. We will check the reference lists of all primary studies and review articles for additional references. We will email experts in the field about other published and unpublished studies that may be eligible for inclusion.

Data collection and analysis

Selection of studies

Two review authors (AJG, DN or ET) will independently assess all studies identified from the database searches by screening titles and abstracts. We will separate potential studies for full-text reading. A third review author (CF) will resolve any disagreements. We will describe the reasons for including and excluding trials in the full review (Higgins 2011a).

Data extraction and management

Two review authors (AJG, HR) will independently extract data from the included studies using a standard data extraction form.

Assessment of risk of bias in included studies

Two review authors (AJG, HR) will independently assess the risk of bias for each included study using the 'Risk of bias' tool published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). One review author (CF) will resolve any disagreements by discussion. We will assess the risk of bias according to the following domains.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective reporting (reporting bias).
7. Other bias (other sources of bias related to particular trial design (cross-over and cluster-randomised) or specific circumstances such as adjustment of prognostic factors (e.g. baseline exercise habits, physical fitness).

We will classify the risk of bias as: low risk, high risk or unclear risk of bias (Higgins 2011b).

Measures of treatment effect

Types of measurements of treatment effect that may be used include the following.

1. Dichotomous data: we will use risk ratio (RR) for likely binary outcomes, e.g. complications related to influenza-related illness, adverse effects of vaccination and adherence to the group intervention.
2. Continuous data: we will combine the results using the mean difference (MD) for measures using the same scale or the standardised mean difference (SMD) where different scales have been used to evaluate the same outcome for the following outcomes: number of working days or days lost related to influenza-related illness; blood parameters (IgG, IgM, IL-6, etc.).
3. Rate: we will use rate ratio to compare rates between groups for the outcome number of influenza episodes.

Unit of analysis issues

We will consider the individual the unit of analysis. If cross-over RCTs are included, we will only include the phase before crossing over interventions. If cluster-RCTs are included, we will make necessary statistical adjustments for clustering participants.

Dealing with missing data

We will send two emails (one initial, one reminder) to the corresponding trial author to ask for any missing data or incompletely

reported study details. We will check for consistency between the randomised and analysed individuals to verify the intention-to-treat (ITT) analysis for each outcome.

Assessment of heterogeneity

We will assess the inconsistencies between studies using the I^2 statistic and describe the percentage of variability in effect. We will consider heterogeneity substantial if I^2 is over 50%. See below for subgroup analysis.

Assessment of reporting biases

If mismatches are identified between study protocols and reports, we will contact the trial authors to clarify the information. We plan to explore the impact of including such studies by conducting a sensitivity analysis. We will perform a funnel plot asymmetry test if 10 or more trials are included.

Data synthesis

We will present the data separately for RCTs, cross-over trials or cluster-RCTs. We will meta-analyse trials if the combination of data for the outcomes is possible. We will use a random-effects model, independently of the heterogeneity identified. Forest plot graphics produced by RevMan 2014 will illustrate meta-analyses. If the combination of data is not possible, we will present a narrative analysis of individual studies. We will create a 'Summary of findings' table using the outcomes proposed in this protocol and we will present the quality of the body of evidence considering the five GRADE assumptions (study limitations, consistency of effect, imprecision, indirectness and publication bias) contributing to the meta-analyses for the pre-specified outcomes.

Subgroup analysis and investigation of heterogeneity

We will consider the following individuals, settings and intervention characteristics.
Patient variables:
1. Age groups (adults and elderly).
2. Immunocompromised adults and healthy adults.
Exercise variables:
1. Type of exercise (resistance, endurance, stretching).
2. Frequency of exercise (number of sessions/week).
3. Intensity of exercise: light (1.6 to 2.9 metabolic equivalents (METs), moderate (3 to 5.9 METs), vigorous $\geq$ 6 METs) using the physical activity compendium.
4. Duration (duration of individual sessions).

Sensitivity analysis

We will pool included studies to verify whether the impact of risk of bias affects the overall effect of exercising prior to influenza vaccination. We will explore which studies increased heterogeneity.

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* Indicates the major publication for the study

APPENDICES

Appendix 1. MEDLINE (OVID)

1 exp INFLUENZA/
2 influenza.mp.
3 or/1-2
4 exp VACCINES/
5 exp VACCINATION/
6 (immuniz$ or immunis$).mp.
7 vaccin$.mp.
8 or/4-7
9 3 and 8
10 exp Influenza Vaccine/
11 (influenz$ adj (vaccin$ or immun$)).mp.
12 or/10-11
13 9 or 12
14 exp Exercise/
15 exp Exercise Movement Techniques/
16 exp Exercise Therapy/
17 Physical Fitness/
18 physical endurance/ or exercise tolerance/
19 Physical Exertion/
20 exp Sports/
21 Dancing/
22 (exercis* or sport* or fitness* or gym* or aerobic*).tw.
23 ((weight* or strength* or enduranc* or circuit*) adj5 (program* or train* or session*)).tw.
24 (physical* adj5 (fit* or activ* or movement* or train* or condition* or program*)).tw.
25 (activ* adj2 life*).tw.
26 (run* or walk* or jog* or sprint* or treadmill* or row* or swim* or bicycl* or cycl* or danc* or yoga or tai chi or tai ji or qigong or qi gong).tw.
27 or/14-26
28 13 and 27

Appendix 2. EMBASE search strategy

#23 #11 AND #22
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#21 run*:ab,ti OR walk*:ab,ti OR jog*:ab,ti OR sprint*:ab,ti OR treadmill*:ab,ti OR row*:ab,ti OR swim*:ab,ti OR bicycl*:ab,ti OR cycl*:ab,ti OR danc*:ab,ti OR yoga:ab,ti OR 'tai chi':ab,ti OR 'tai ji':ab,ti OR qigong:ab,ti OR 'qi gong':ab,ti AND [embase]/lim
#20 (activ* NEAR/2 life*):ab,ti AND [embase]/lim
#19 (physical* NEAR/5 (fit* OR activ* OR movement* OR train* OR condition* OR program*)):ab,ti AND [embase]/lim
#18 ((weight* OR strength* OR enduranc* OR circuit*) NEAR/5 (program* OR train* OR session*)):ab,ti AND [embase]/lim
#17 exercis*:ab,ti OR sport*:ab,ti OR fitness*:ab,ti OR gym*:ab,ti OR aerobic*:ab,ti AND [embase]/lim
#16 'sport'/exp AND [embase]/lim
#15 'training'/de OR 'endurance'/de OR 'exercise tolerance'/de OR 'physical capacity'/de AND [embase]/lim
#14 'physical activity'/exp OR 'physical activity, capacity and performance'/de AND [embase]/lim
#13 'kinesiotherapy'/exp AND [embase]/lim
#12 'exercise'/exp AND [embase]/lim
#11 #1 OR #10
#10 #5 AND #9
#9 #6 OR #7 OR #8
#8 immuniz*:ab,ti OR immunis*:ab,ti
#7 'immunization'/exp
#6 'vaccine'/exp OR 'vaccination'/de
#5 #2 OR #3 OR #4
#4 'influenza virus a'/exp OR 'influenza virus b'/de
#3 influenza*:ab,ti OR flu:ab,ti
#2 'influenza'/exp
#1 'influenza vaccine'/de

CONTRIBUTIONS OF AUTHORS

Antonio Jose Grande (AJG) co-ordinated retrieval of papers, and wrote the background and methods of the protocol.

David Nunan (DN) co-wrote the background and methods of the protocol.

Hamish Reid (HR) co-wrote the background and methods of the protocol.

Emma Thomas (ET) co-wrote the background and methods of the protocol.

Charlie Foster (CF) co-wrote the background and methods of the protocol.

DECLARATIONS OF INTEREST

Antonio Jose Grande: declares that there are no conflicts of interest.

David Nunan: declares that there are no conflicts of interest.

Hamish Reid: declares that there are no conflicts of interest.

Emma E Thomas: declares that there are no conflicts of interest.

Charles Foster: declares that there are no conflicts of interest.

SOURCES OF SUPPORT

Exercise prior to influenza vaccination for limiting influenza incidence and its related complications in adults (Protocol)

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