



INSTITUTO DE SAÚDE
COLETIVA DA UFF

MEB Departamento de
Epidemiologia e
Bioestatística



Revisão Sistemática e Metanálise

2019

Revisão tradicional / Revisão sistemática

- Abrangente (vários enfoques)
 - Busca bibliográfica segundo critério do autor
 - Seleção dos artigos segundo critério do autor
 - Extração dos dados de forma não explicitada
 - Sumarização heterogênea
 - Análise não quantitativa
- **Focada (hipótese) aprofundada**
 - **Busca bibliográfica segundo critérios definidos**
 - **Seleção dos artigos segundo critérios de inclusão/exclusão e de qualidade**
 - **Extração dos dados de forma padronizada**
 - **Sumarização dos dados em forma de tabelas e gráficos**
 - **Análise (medida sumário)***

a) Pergunta bem formulada:

- **Hipótese**
- **Exposição e desfechos definidos?**
- **População definida?**

Revisão-sistemática: possibilidades

Estudos descritivos

- Prevalência ou incidência de desfechos relevantes

Estudos analíticos

- Fatores de risco
- Estudos de teste diagnóstico
- **Ensaio clínico randomizado**

Revisão Sistemática

Etapas

- **Artigo-exemplo:** *Norhayati et al., 2017. Influenza vaccines for preventing acute otitis media in infants and children. Cochrane Database Syst Rev. 2017;10:CD010089*
- **Hipótese:** Influenza vaccines might be an effective way of preventing the development of AOM.

b) Definir critérios de inclusão e de exclusão de estudos: estratégia **P I C O S**

- **P**articipantes: sexo, idade, características clínicas
- **I**ntervenção e **C**omparação: tratamento vs placebo ou padrão (ou exposição vs. não exposição)
- **O** desfecho (**O**utcome): morte, cura, melhora, prevenção
- **S**tipo de estudo (**S**tudy) Desenho: ensaios clínicos, estudos observacionais

Artigo-exemplo: critérios de inclusão/PICOS

Types of participants

Infants and children aged younger than six years old of either sex and of any ethnicity, with or without a history of recurrent AOM.

Types of interventions

Vaccination with any influenza vaccine, live or inactivated, and whole, split-virus, or subunit-type vaccines. Vaccines may be monovalent or polyvalent, single dose or multidose, and administered by any route of administration.

Comparison: placebo or no treatment.

Artigo-exemplo: critérios de inclusão/PICOS

Primary outcomes

1. Number of children having at least one episode of AOM during the follow-up period.
2. Number of episodes of AOM recorded during the follow-up period.

Types of studies

Randomised controlled trials comparing influenza vaccine with placebo or no treatment. We included blinded and open-label studies.

c) Identificação de estudos

Bases eletrônicas (através de palavras-chave):

Medline - medicina e saúde

Lilacs - saúde (América Latina e Caribe)

Embase, Scisearch – entre outros.

Cochrane - medicina baseada em evidência

Outras fontes:

Especialistas, congressos, simpósios

Busca manual de artigos (Referências bibliográficas de artigos)

Artigo-EXEMPLO: busca (fontes bibliográficas)

We searched:

- the Cochrane Central Register of Controlled Trials, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register (CENTRAL; 2017, Issue 1) in the Cochrane Library (searched 15 February 2017);
- MEDLINE Ovid (1946 to 15 February 2017);
- Embase.com (1947 to 15 February 2017);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to 15 February 2017);
- LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to 15 February 2017);
- Web of Science (1955 to 15 February 2017).

We checked the reference lists of all related studies for further references in order to find unpublished trials or trials not identified

Estratégias de busca (palavras-chave)

Appendix I. MEDLINE (Ovid) search strategy

1 exp Otitis Media/

2 otitis media.tw.

3 (OM or OME or AOM or CSOM).tw.

4 glue ear*.tw.

5 (middle ear* adj5 (infect* or inflam*)).tw.

6 or/1-5

7 exp influenzavirus a/ or exp influenzavirus b/ or influenzavirus c/

8 Influenza, Human/

9 (influenza* or flu).tw.

10 or/7-9

11 exp Vaccines/

12 exp Vaccination/

13 (laiv or tiv).tw.

14 exp Immunization/

15 (vaccin* or immuni* or innocul*).tw.

16 or/11-15

17 10 and 16

18 Viral Vaccines/

d) Seleção de estudos

- Segundo critérios de inclusão/exclusão
- Pelo menos 2 pesquisadores



Apresentação de fluxograma

Identificação

N. de relatos identificados no banco de dados de buscas

N. de relatos identificados em outras fontes

N. de relatos após eliminar os duplicados

Seleção

N. de relatos rastreados

N. de relatos excluídos

Elegibilidade

N. de artigos em texto completo avaliados para elegibilidade

N. de artigos em texto completo excluídos, com justificativa

Inclusão

N. de estudos incluídos em síntese qualitativa

N. de estudos incluídos em síntese quantitativa (meta-análise)

Fluxograma recomendado

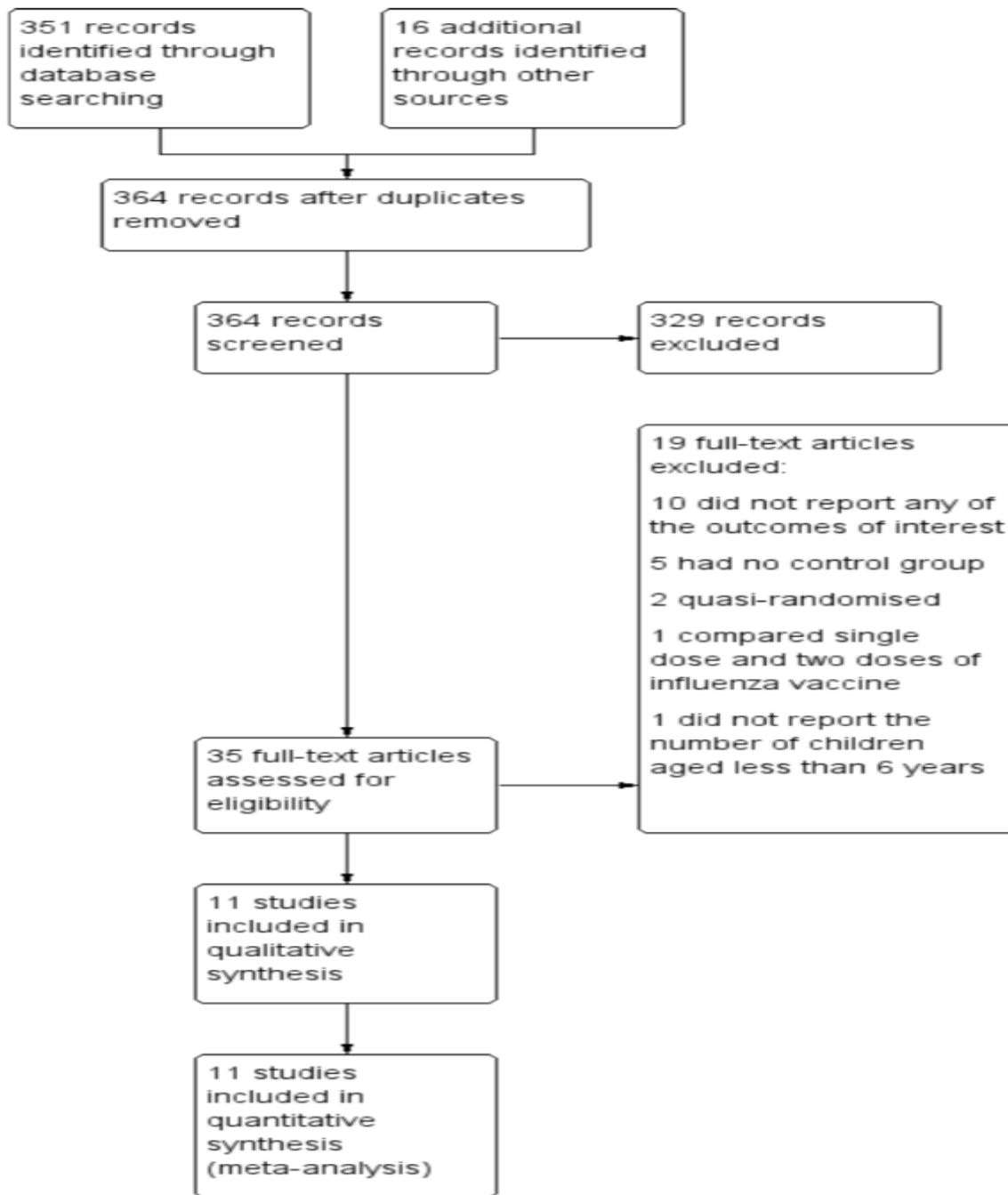
Artigo-exemplo: Seleção de estudos

Selection of studies

Two review authors (MNN, MYA) independently scanned the titles and abstracts identified by the searches, obtaining the full-text articles for records that appeared to meet the eligibility criteria or for which information was insufficient to assess eligibility. We independently assessed the eligibility of the trials and documented the reasons for exclusion. Any disagreements were resolved between the review authors by discussion. We contacted the trial authors for clarification where required. We translated papers in languages other than English with the help of the Cochrane Acute Respiratory Infections Group.

Figure 1. Study flow diagram.

Fluxograma



e) Avaliação da qualidade dos estudos (possibilidade de vieses)

- Diferentes instrumentos, de acordo com o desenho do estudo
- ✓ Checklists ou guidelines (mais adequados para submeter artigos, mas usados para avaliar a qualidade)
- ✓ Escores (elaborados para avaliar a qualidade)



Reporting guidelines for main study types

Randomised trials

CONSORT

Observational studies

STROBE

Systematic reviews

PRISMA

Study protocols

SPIRIT

Diagnostic/prognostic studies

STARD

Case reports

CARE

Clinical practice guidelines

AGREE

Qualitative research

SRQR

Animal pre-clinical studies

ARRIVE

Quality improvement studies

SQUIRE

Economic evaluations

CHEERS

Outros instrumentos para avaliar Ensaio clínico

• Escore de JADAD

1. Was the study described as **randomized** (this includes the use of words such as randomly, random, and randomization)?
2. Was the study described as **double blind**?
3. Was there a description of **withdrawals and dropouts**?

Either give a score of 1 point for each “yes” or 0 points for each “no.” There are no in-between marks.

Give 1 additional point if:

For question 1, the method to generate the sequence of randomization was described **and it was appropriate** (table of random numbers, computer generated, etc.)

and/or:

If for question 2 the method of **double blinding** was described **and it was appropriate** (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

For question 1, the method to generate the sequence of randomization was described **and it was inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or:

For question 2, the study was described as double blind but the method of blinding was **inappropriate** (e.g., comparison of tablet vs. injection with no double dummy)

Outros instrumentos para avaliar Ensaaios clínicos

- **Instrumento da Cochrane Collaboration – Risk of bias tool (ROB)**

Domain 1: Risk of bias arising from the randomization process

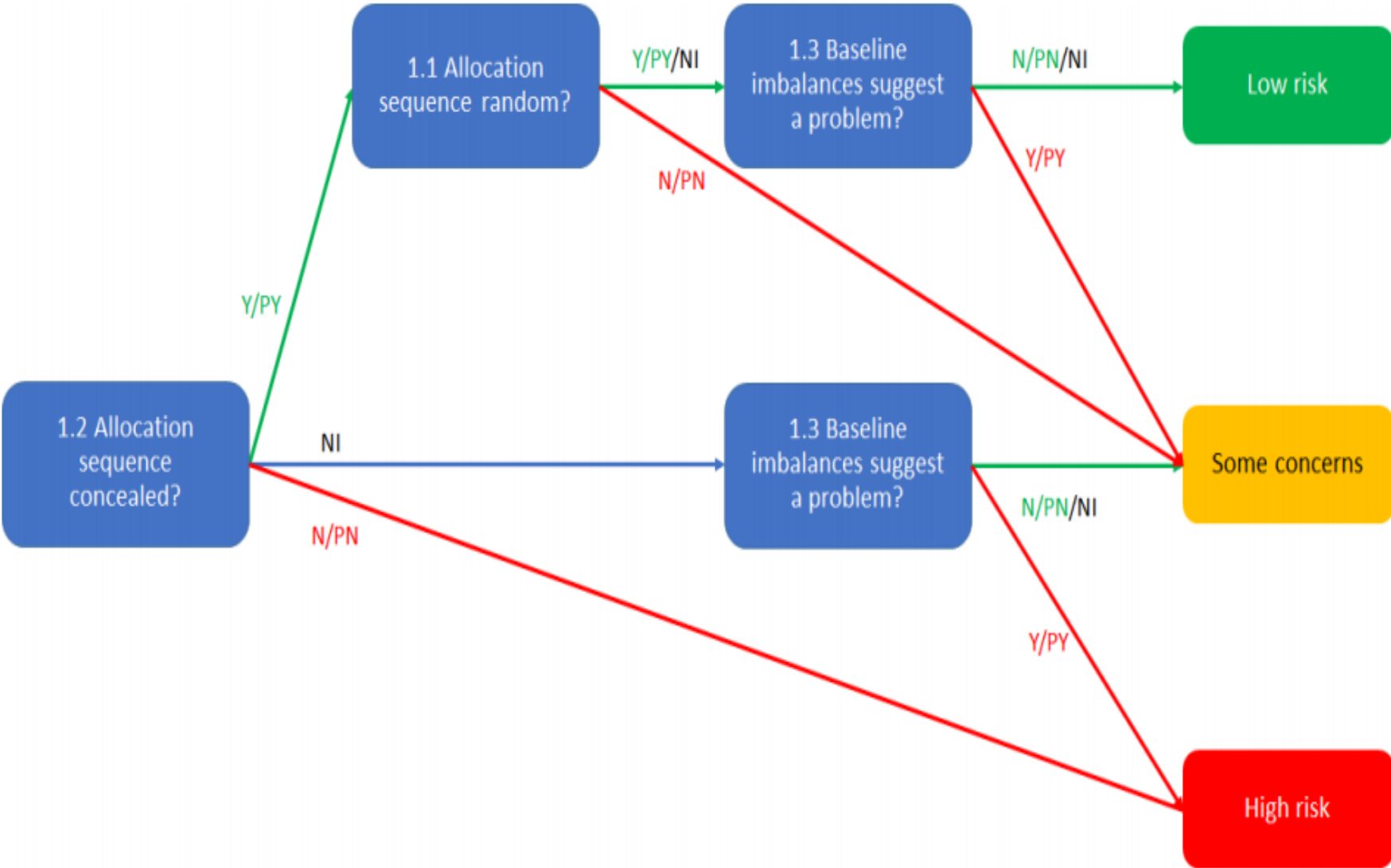
Domain 2: Risk of bias due to deviations from the intended interventions

Domain 3: Risk of bias due to missing outcome data

Domain 4: Risk of bias in measurement of the outcome

Domain 5: Risk of bias in selection of the reported result

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)



Algorithm for suggested judgement of risk of bias arising from the randomization process

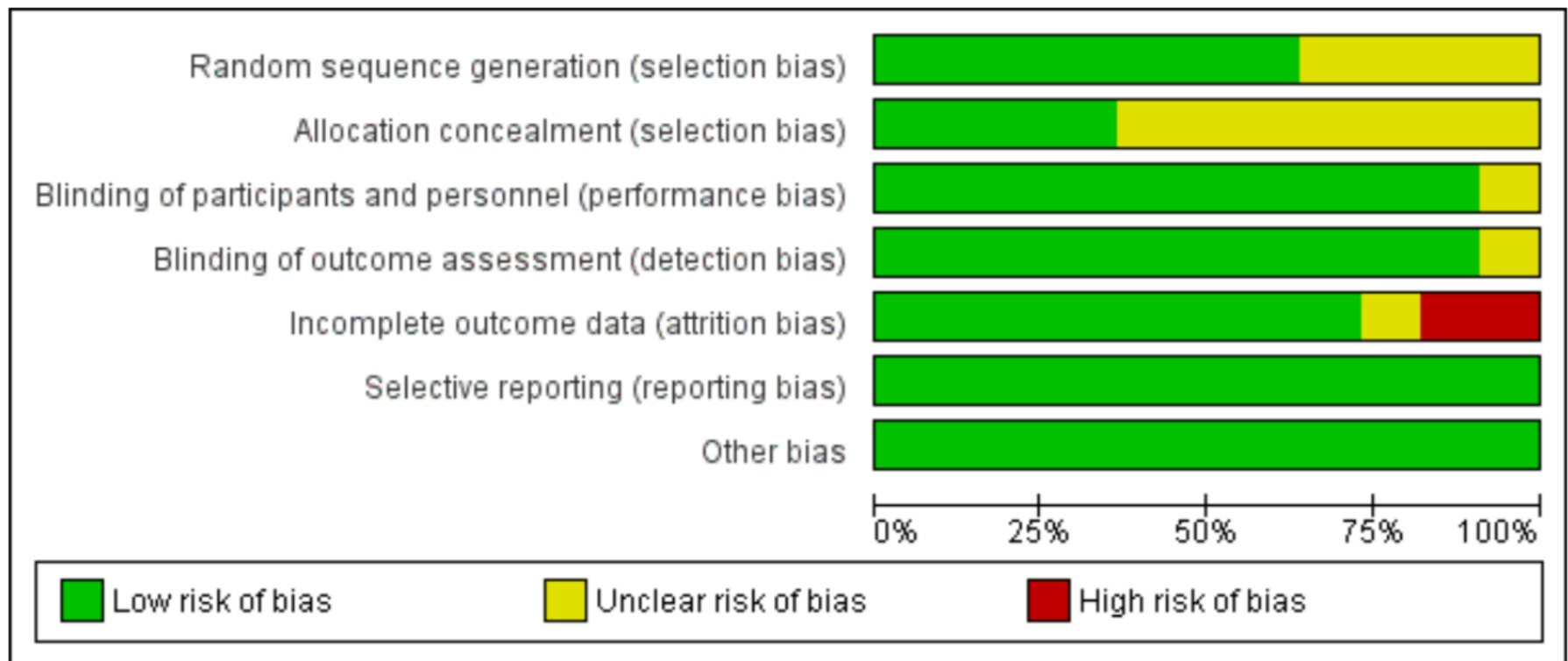
Artigo-exemplo: avaliação da qualidade dos artigos

Assessment of risk of bias in included studies

We assessed the risk of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selectivity of outcome reporting, and other bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins, 2011).

Artigo-exemplo:

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Artigo-exemplo:

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Belshe 2000	?	?	+	+	?	+	+
Bracco 2009	+	+	+	+	-	+	+
Clements 1995	?	?	?	+	+	+	+
Gruber 1996	?	?	+	?	+	+	+
Hoberman 2003	+	?	+	+	+	+	+
Kosalaraksa 2015	+	?	+	+	+	+	+
Lum 2010	+	+	+	+	+	+	+
Marchisio 2002	?	?	+	+	+	+	+
Swierkosz 1994	+	?	+	+	-	+	+
Tam 2007	+	+	+	+	+	+	+
Vesikari 2006	+	+	+	+	+	+	+

f) Extração da informação

- Formulário para extração de dados
- Mínimo de 2 investigadores

Artigo-exemplo: extração da informação

Data extraction and management

We extracted the following from each of the selected studies:

- study setting;
- participant characteristics (age, sex, ethnicity);
- methodology (number of participants randomised and analysed, duration of follow-up);
- type of vaccine used;
- method for diagnosing AOM;
- occurrence of AOM and middle ear effusion;
- antibiotics used to treat AOM and its complications;
- causative organism associated with AOM;
- utilisation of healthcare and related resources;
- number of culture-confirmed influenza cases; and
- occurrence of adverse events related to influenza vaccine (e.g. febrile illnesses).

We resolved any disagreements by discussion.

g) Análise

- Descritiva/qualitativa: Construção de tabelas com todos os artigos avaliados e principais resultados

Tabela com a descrição sumarizada dos artigos

Referência	Local e ano do estudo	População	Intervenção	Desfecho estudado	Resultados principais
Autor principal, ano ¹	Brasil, 2018	Crianças	Vacina	Níveis anticorpos	Diferença de médias favorável à vacina
2					
3					
4					
5					

Artigo-exemplo

Methods	Randomised, parallel-group trial
Participants	<p>133 children aged 1 to 5 years with a history of recurrent AOM (defined as ≥ 3 episodes in the preceding 6 months or ≥ 4 episodes in the preceding 12 months, with the most recent episode of AOM in the previous 2 to 8 weeks)</p> <p>Mean (SD) age (months): vaccine group (32.6/14.6), control group (36.2/15.9)</p> <p>Sex (male/female): vaccine group (38/29), control group (42/24)</p> <p>Exclusion criteria: acute febrile illness, severe atopy, any previous influenza vaccination, acquired or congenital immunodeficiency, recent administration of blood products, cleft palate, chronically ruptured eardrum, obstructive adenoids, sleep apnoea syndrome, and placement of tympanostomy tubes</p> <p>Setting: healthcare setting, Italy</p>
Interventions	<p>Intervention group (N = 67) received 2 doses of intranasal, inactivated, virosomal subunit influenza vaccine on day 1 and day 8</p> <p>Control group (N = 66) received no treatment.</p> <p>Duration of follow-up: every 4 to 6 weeks for 25 weeks</p>
Outcomes	<p>Acute otitis media was based on the presence of any combination of: fever, earache, irritability, and hyperaemia or opacity accompanied by bulging or immobility of the tympanic membrane</p> <p>Otitis media with effusion was based on the presence of impaired mobility, opacification, fullness, or retraction of the eardrum associated with a tympanogram with a flat tracing, and the absence of signs and symptoms of acute infection</p> <ol style="list-style-type: none"> 1. Occurrence of AOM within the 6-month period 2. Occurrence of febrile respiratory illnesses 3. Use of antibiotics
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... assigned randomly" Comments: Method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Quote: "... assignment and vaccine administration were performed by two investigators"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... the parents were instructed not to discuss group assignment with the investigator responsible for the clinical and ontological follow-up, who remained blinded to group assignment until the end of the follow-up period" Comment: We judged this to be of low risk for all outcomes except participant-reported adverse effects

g) Análise

- Quantitativa: **Metanálise ***

Combina e integra os resultados de estudos independentes, considerados homogêneos.

Explora fontes de heterogeneidade

Escolha da medida de associação (RR, OR), de eficácia (RRR), ou diferença de médias

Estimativa de medida de associação (medida-sumário)

Meta-análise

- Aumenta o número de observações,
- Aumenta o poder estatístico de detectar os efeitos.

- Medida-sumário: o efeito da intervenção / tratamento é calculado como uma média ponderada dos efeitos de cada estudo.

- Os pesos são o inverso da variância do efeito do tratamento/ intervenção de cada estudo (que está associado com o tamanho da amostra).

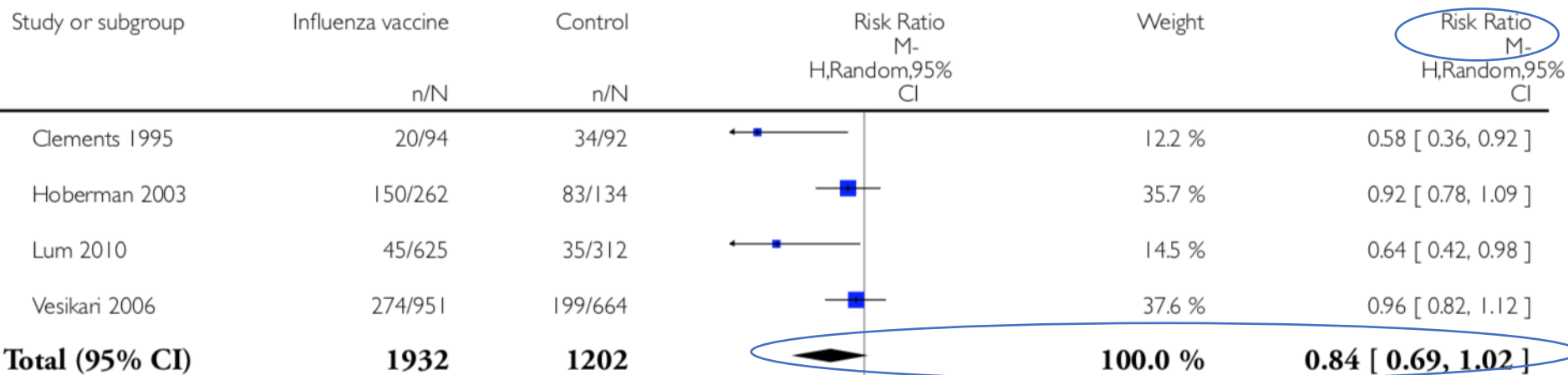
Artigo-exemplo: metanálise com forest plot

Analysis 1.1. Comparison 1 Influenza vaccine versus control, Outcome 1 At least 1 episode of acute otitis media.

Review: Influenza vaccines for preventing acute otitis media in infants and children

Comparison: 1 Influenza vaccine versus control

Outcome: 1 At least 1 episode of acute otitis media



Total events: 489 (Influenza vaccine), 351 (Control)

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 6.80$, $df = 3$ ($P = 0.08$); $I^2 = 56\%$

Test for overall effect: $Z = 1.80$ ($P = 0.071$)

Test for subgroup differences: Not applicable

0.5 0.7 1 1.5 2
Favours influenza vaccine Favours control

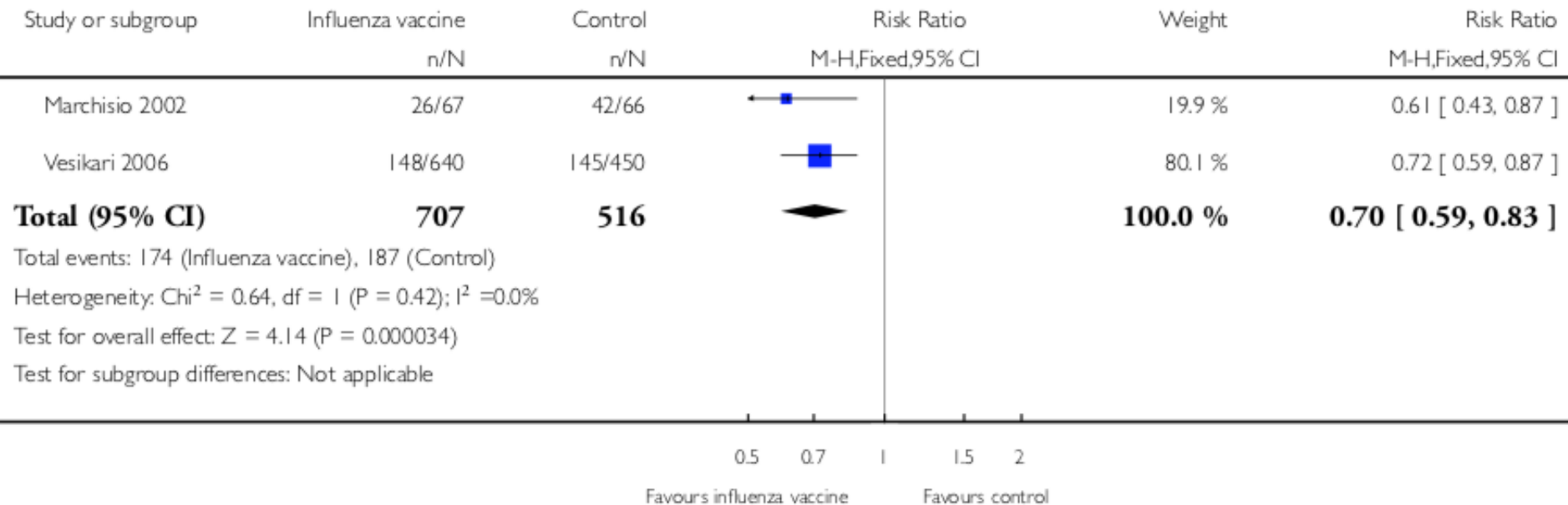
Artigo-exemplo: metanálise com forest plot

Analysis 1.4. Comparison 1 Influenza vaccine versus control, Outcome 4 Courses of antibiotics.

Review: Influenza vaccines for preventing acute otitis media in infants and children

Comparison: 1 Influenza vaccine versus control

Outcome: 4 Courses of antibiotics



Heterogeneidade clínica ou metodológica/estatística

- Estudos diferem quanto às características dos participantes (idade, severidade), intervenção (dose), duração do acompanhamento, variável de desfecho, desenho de estudo.
- Heterogeneidade estatística. Variação entre os resultados dos estudos é maior do que a esperada ao acaso.
- Intervalos de confiança de alguns estudos não englobam os riscos relativos observados por outros estudos

Testando a heterogeneidade

Qui-quadrado para heterogeneidade

- Se $p\text{-valor} > 0,10$, não rejeito a hipótese nula de igualdade
- Se $p\text{-valor} < 0,10$, rejeito igualdade e confirmo **heterogeneidade** entre os estudos

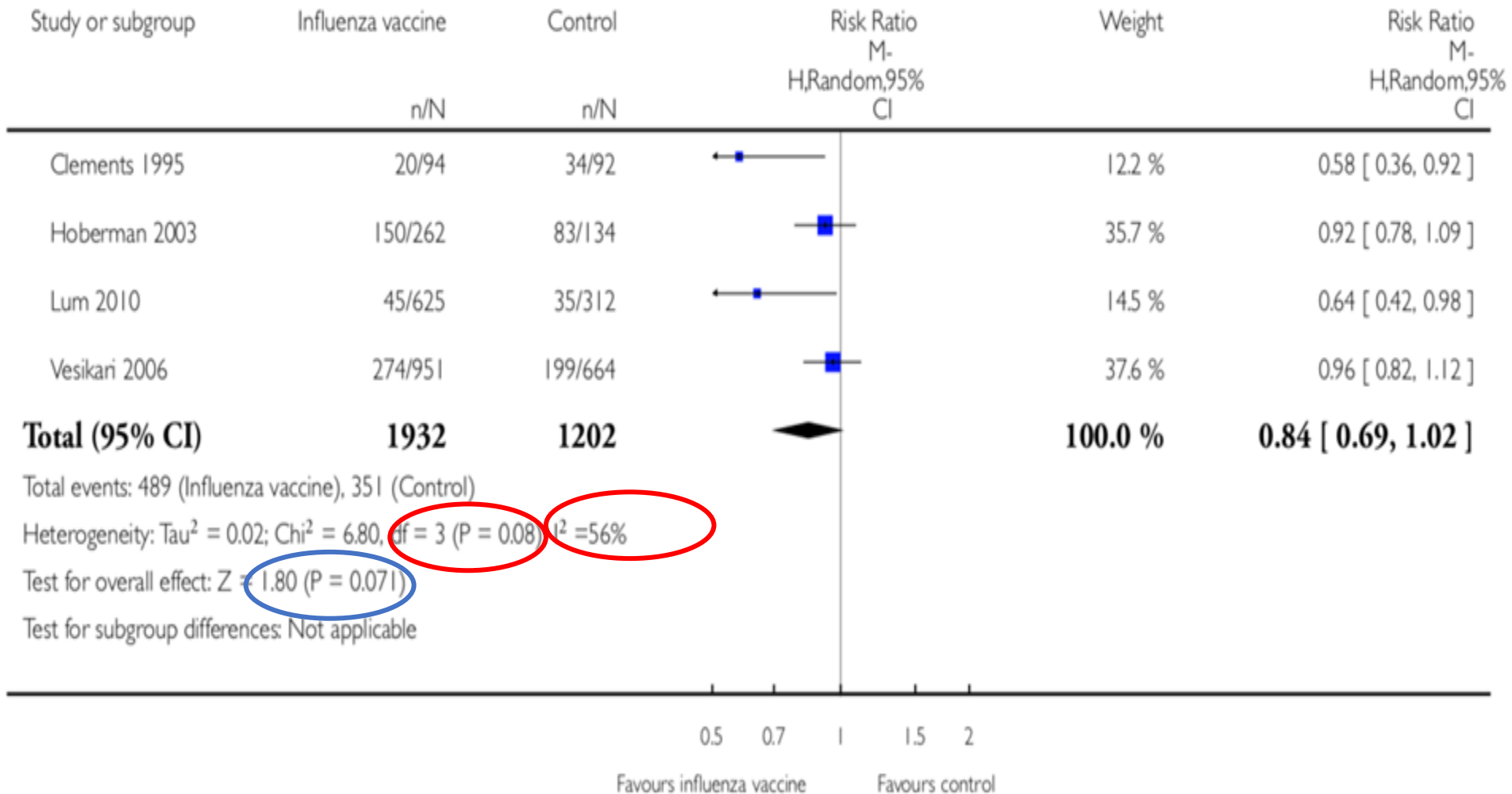
Teste I^2 – percentual de heterogeneidade que excede acaso

- 0-25% - baixa
- 26-50% - moderada
- **> 50% - alta**

Artigo-exemplo: heterogeneidade

Assessment of heterogeneity

We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions, and outcomes. Second, we assessed statistical heterogeneity by means of the I^2 statistic (Higgins 2011).



Manejo da Heterogeneidade

A presença da heterogeneidade não é um problema para a meta-análise, mas uma oportunidade para investigar por que o efeito da intervenção / tratamento varia em diferentes circunstâncias.

Possibilidades:

Não combinar resultados - explicar causas da heterogeneidade – análise de subgrupos

Combinar estudos usando efeitos aleatórios - conhecer um efeito médio.

Vieses de Seleção

1. Viés de Publicação

dados não são publicados em função do resultado obtido=>predomínio de publicações com resultados positivos.

Pode ser avaliado graficamente (gráfico de funil)

2. Viés de Idioma

Os estudos são identificados, mas excluídos em função da língua.
>parte de incluídos - inglês

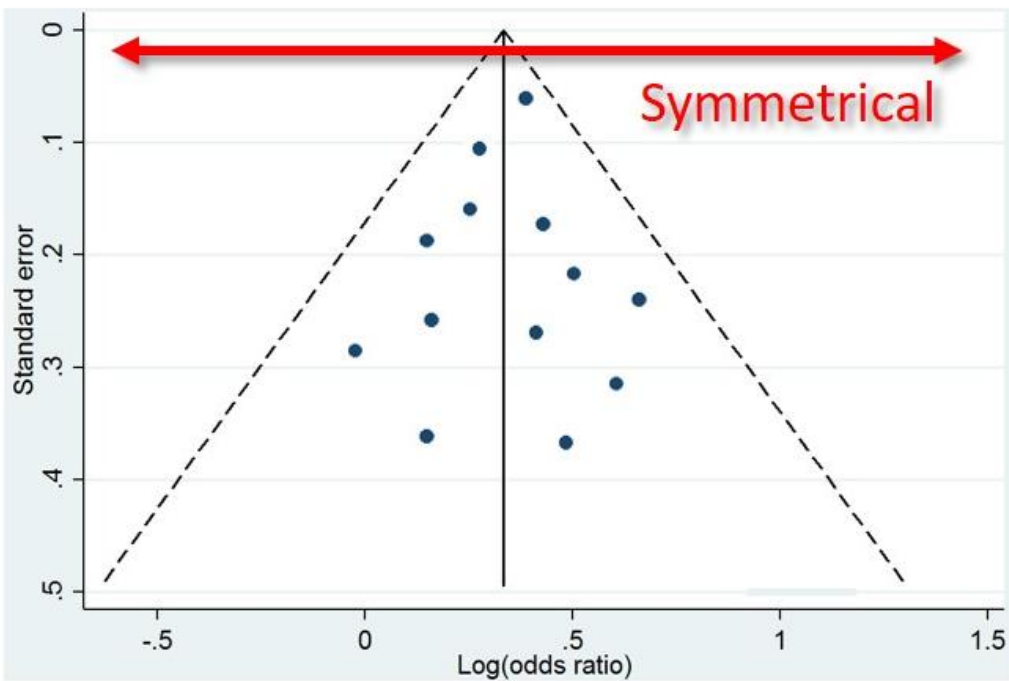
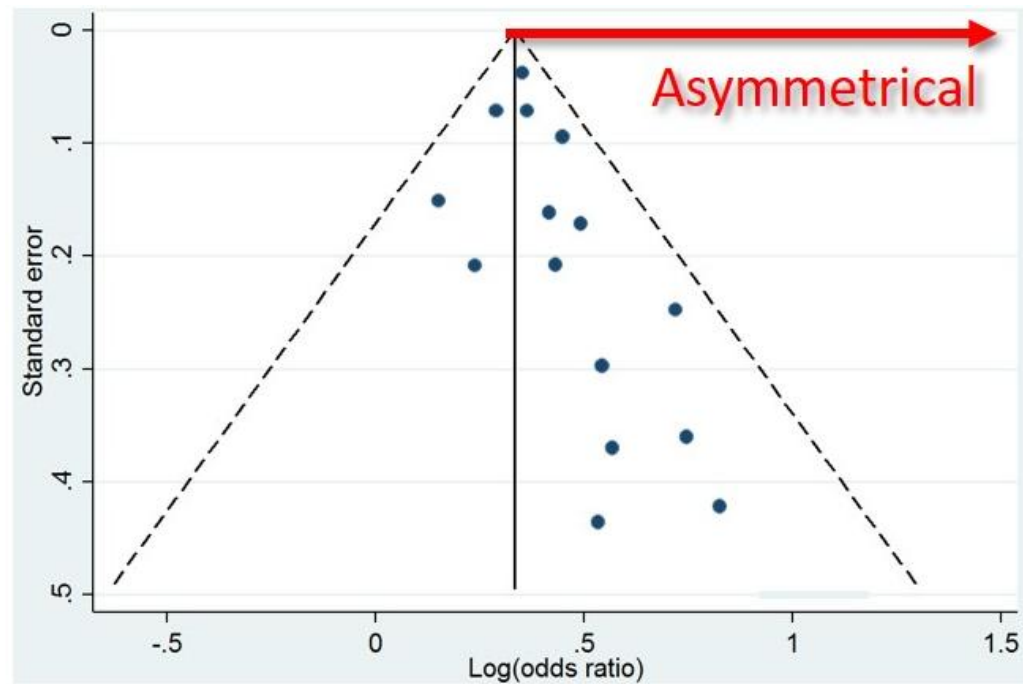


Gráfico de funil



Artigo-exemplo: Vieses de Seleção

Assessment of reporting biases

If there were sufficient studies, we intended to use funnel plots to assess the possibility of reporting biases or small-study biases, or both.

Potential biases in the review process

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases without language restriction. However, we cannot be certain that we have located all the trials in this area. Although

Vieses de informação

1. Viés de extração

- Quando estudos são avaliados de forma não padronizada, permitindo diferença na extração dos dados. Pode ser minimizado com a adoção de instrumentos validados.

2. Viés do investigador

- Quando o investigador conhece os autores e pode ficar sugestionado. Pode ser minimizado ocultando-se a identificação do artigo (avaliação mascarada).

Revisão Sistemática

Conclusões

- Força da evidência: GRADE
- Relevância para pacientes: benefícios x riscos



Welcome to the GRADE working group

From evidence to recommendations – transparent and sensible

Fatores que reduzem a qualidade da evidência

Fator	Consequência
Limitações metodológicas (risco de viés)	↓ 1 ou 2 níveis
Inconsistência	↓ 1 ou 2 níveis
Evidência indireta	↓ 1 ou 2 níveis
Imprecisão	↓ 1 ou 2 níveis
Viés de publicação	↓ 1 ou 2 níveis

Fonte: Elaboração GRADE working group - <<http://www.gradeworkinggroup.org>>.

Fatores que elevam a qualidade da evidência

Fator	Consequência
Elevada magnitude de efeito	↑ 1 ou 2 níveis
Fatores de confusão residuais que aumentam a confiança na estimativa	↑ 1 nível
Gradiente dose-resposta	↑ 1 nível

Fonte: Elaboração GRADE working group - <<http://www.gradeworkinggroup.org>>.

Artigo-exemplo - GRADE

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: at least one episode of AOM; courses of antibiotics; fever; rhinorrhoea; and pharyngitis.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes ([Atkins 2004](#)). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), employing GRADEpro GDT software ([GRADEpro 2014](#)). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.



Cochrane
Library

The Cochrane Library is a collection of databases that contain different types of high quality independent evidence

1. **Produce evidence:** We produce reviews which study all of the best available evidence generated through research and make it easier to inform decisions about health. These are called systematic reviews and we publish them in the *Cochrane Database of Systematic Reviews*. We have published over 7700 Cochrane Reviews. We also take a key role in developing new methods in evidence synthesis.
2. **Make evidence accessible:** Find out more about [Cochrane's Knowledge Translation activities](#).
3. **Advocate for evidence:** Find out more about [Cochrane's partners](#).
4. **Effective and sustainable organization:** We build networks of contributors throughout the world, known as the **Cochrane Community**. We invest in their training.



World Health
Organization

80% of WHO guidelines use Cochrane reviews.

British Journal of Obstetrics and Gynaecology

January 1990, Vol. 97, pp. 11-25

The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials

PATRICIA CROWLEY, IAIN CHALMERS, MARC J. N. C. KEIRSE



Cochrane
Library

Revisão sistemática e meta-análise



Ideias para a busca bibliográfica

Article types

clear

Clinical Trial

✓ Meta-Analysis

Review

Customize ...

Text availability

clear

Abstract

✓ Free full text

Full text

Publication dates

5 years

10 years

Custom range...

Species

Humans

Other Animals

[Clear all](#)

Format: Summary ▾ Sort by: Most Recent ▾ Per page: 20 ▾

Send to ▾

Best matches for arterial hypertension and diuretics and efficacy and (randomized or randomised):

[Thiazide Diuretics in Chronic Kidney Disease.](#)

Sinha AD et al. Curr Hypertens Rep. (2015)

[Efficacy and safety of mineralocorticoid receptors in mild to moderate arterial hypertension.](#)

Pelliccia F et al. Int J Cardiol. (2015)

[Pseudotumor cerebri: What We Have Learned from the Idiopathic Intracranial Hypertension Treatment Trial.](#)

Thakore RV et al. R I Med J (2013). (2016)

Switch to our new best match sort order

Search results

Items: 9

Article types

Clinical Trial

Meta-Analysis

Review

Customize ...

Text availability

Abstract

Free full text

Full text

Publication dates

5 years

10 years

From 2016/01/01 to 2019/12/31

Species

Humans

Other Animals

[Clear all](#)

[Show additional filters](#)

clear

Format: Summary ▾ Sort by: Most Recent ▾ Per page: 20 ▾

Send to ▾

Best matches for children and efficacy and (randomized or randomised) not protocol:

[Efficacy of Visual-Acoustic Biofeedback Intervention for Residual Rhotic Errors: A Single-Subject Randomization Study.](#)

McAllister Byun T et al. J Speech Lang Hear Res. (2017)

[Neurofeedback in Learning Disabled Children: Visual versus Auditory Reinforcement.](#)

Fernández T et al. Appl Psychophysiol Biofeedback. (2016)

[Daily Observations of Nebuliser Use and Technique \(DONUT\) in children with cystic fibrosis.](#)

Bos AC et al. J Cyst Fibros. (2016)

Switch to our new best match sort order

Search results

Items: 1 to 20 of 239

<< First < Prev Page 1 of 12 Next > Last >>

i Filters activated: Meta-Analysis, Free full text, Publication date from 2016/01/01 to 2019/12/31. [Clear all](#) to show 18045 items.

[Efficacy of tiotropium in treating patients with moderate-to-severe asthma: A meta-analysis and systematic review based on 14 randomized controlled trials.](#)

1. Meng JF, Li H, Luo MJ, Li HB.

Medicine (Baltimore). 2019 Aug;98(33):e16637. doi: 10.1097/MD.00000000000016637.

Article types

clear

Format: Summary ▾ Sort by: Most Recent ▾ Per page: 20 ▾

Send to ▾

Clinical Trial

✓ Meta-Analysis

Review

Customize ...

Text availability

clear

Abstract

✓ Free full text

Full text

Publication dates

clear

5 years

10 years

✓ From 2016/01/01 to
2019/12/31

Species

Humans

Other Animals

[Clear all](#)[Show additional filters](#)**Best matches for elderly and vaccine and efficacy and (randomized or randomised) not protocol:**

[Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a **randomised** clinical trial.](#)

Park JK et al. Ann Rheum Dis. (2018)

[Immunogenicity of high-dose trivalent inactivated influenza **vaccine**: a systematic review and **meta-analysis**.](#)

Samson SI et al. Expert Rev **Vaccines**. (2019)

[A **randomized** phase II trial of personalized peptide **vaccine** with low dose cyclophosphamide in biliary tract cancer.](#)

Shirahama T et al. Cancer Sci. (2017)

[Switch to our new best match sort order](#)**Search results****Items: 14**