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Epidemiologia e  
Bioestatística



# *Revisão Sistemática e Meta-análise*

## *2019*

# Revisão tradicional x 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 critérios de qualidade
- Extração dos dados de forma padronizada
- Sumarização dos dados em forma de tabelas e gráficos
- **Análise (medida sumário)\*\***

# Revisão Sistemática

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**Revisão de estudos através de uma estratégia que limita o viés na reunião sistemática, com avaliação crítica e síntese de todos os estudos relevantes sobre um tópico específico.**

### a) Pergunta bem formulada:

- Hipótese
- Exposição e desfechos definidos?

# Influenza vaccines for preventing acute otitis media in infants and children (Review)

Norhayati MN, Ho JJ, Azman MY

## **OBJECTIVES**

To assess the effectiveness of influenza vaccine in reducing the occurrence of acute otitis media (AOM) in infants and children.

- **Hipótese:** Influenza vaccines might be an effective way of reducing this risk by preventing the development of AOM.
- **Exposição:** influenza vaccine with placebo or no treatment
- **Desfecho:** acute otitis media

# Etapas

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## b) Definir critérios de inclusão e de exclusão de estudos

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

# Artigo: critérios de inclusão e exclusão

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## **Types of studies**

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

## **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.

# Artigo: critérios de inclusão e exclusão

## 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.

## 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.



# Etapas

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## 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: 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/

# Etapas

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## d) Seleção de estudos

- Segundo critérios de inclusão/exclusão de artigos
- Pela avaliação da qualidade do estudo



**Apresentação de fluxograma**

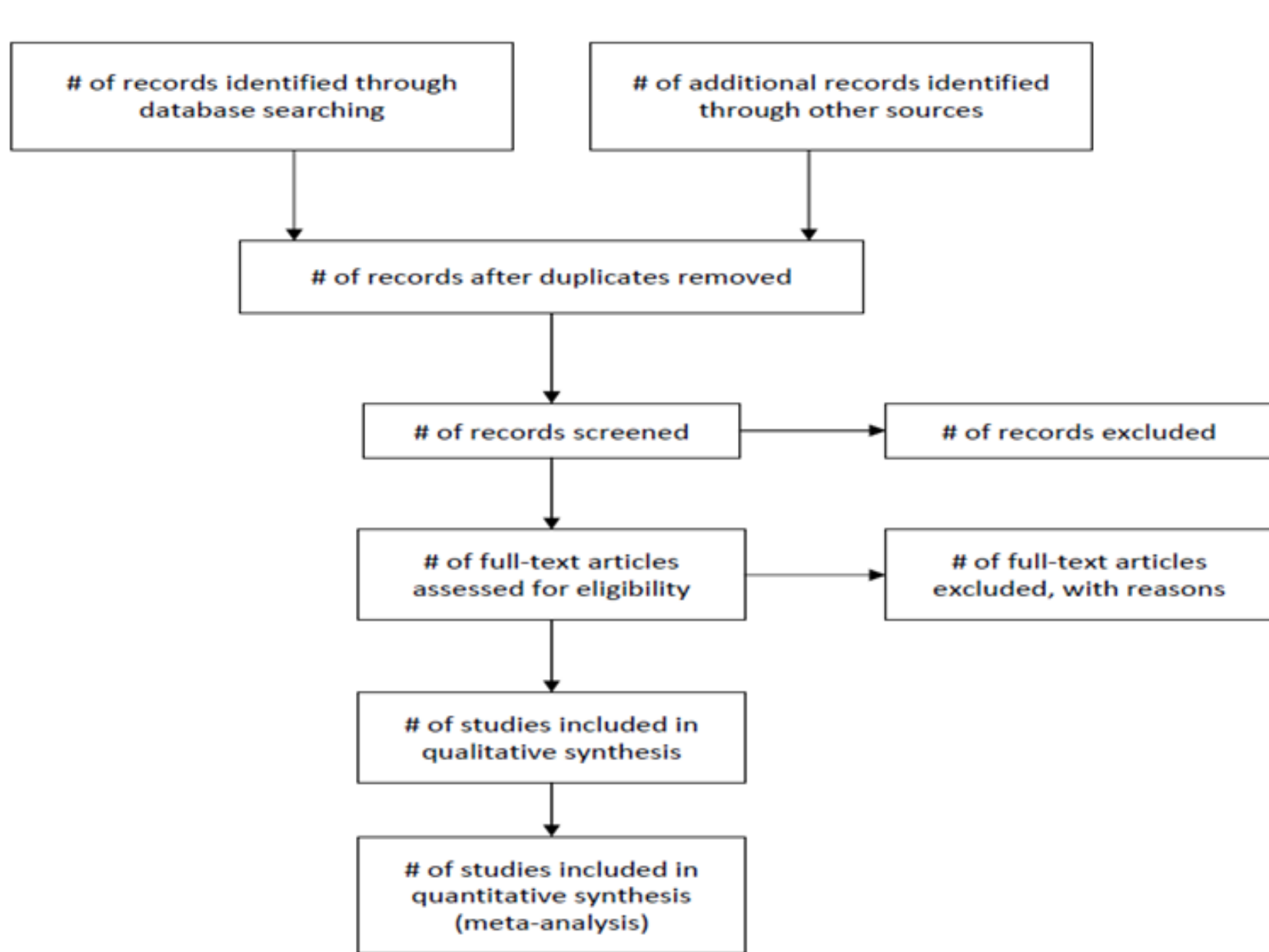
# Seleção de estudos

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## **Selection of studies**

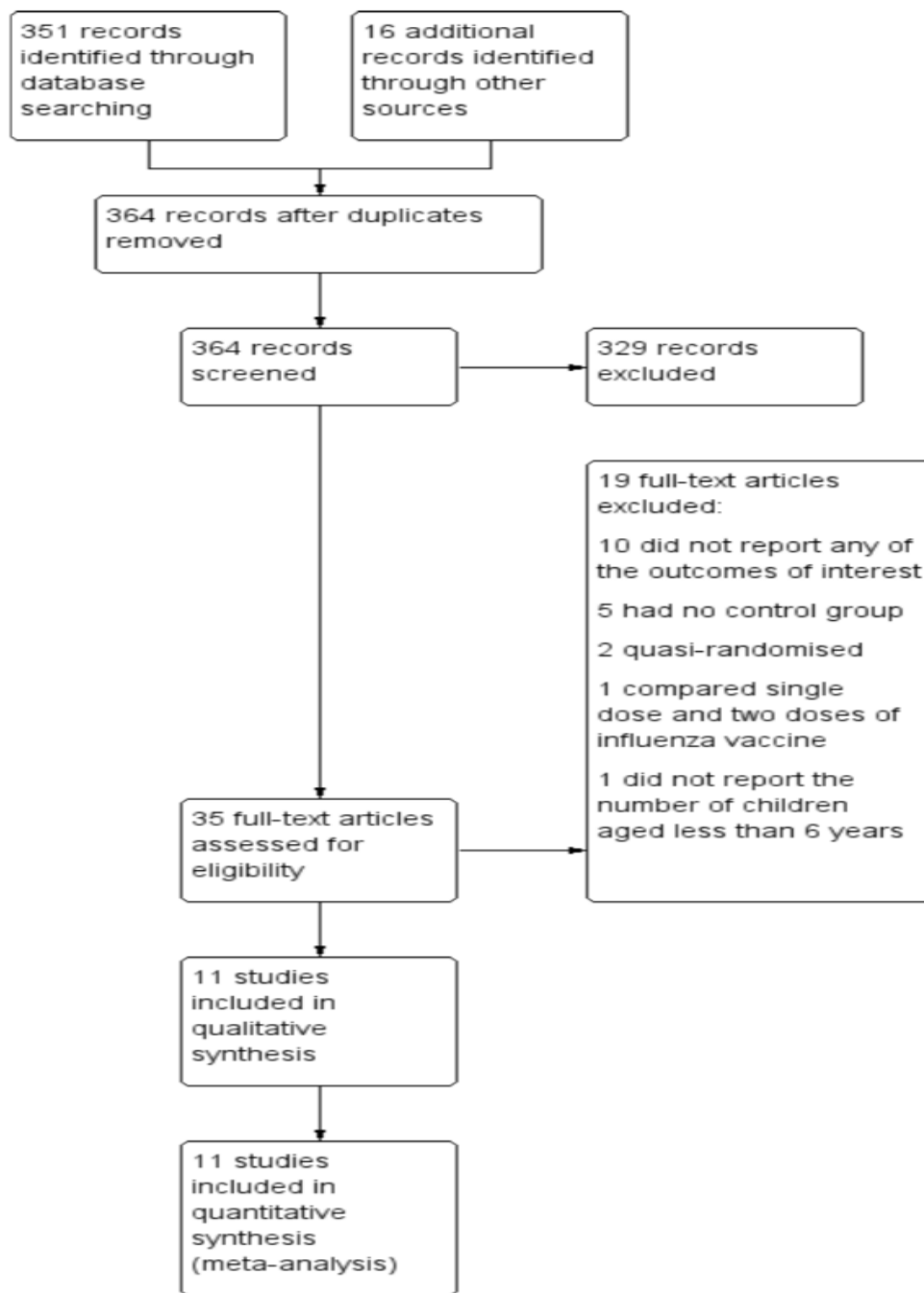
Two review authors (MNN, MYA) independently scanned the titles and abstracts identified by the searches, obtaining the full-text articles for records that appeared to meet the eligibility criteria or for which information was insufficient to assess eligibility. We independently assessed the eligibility 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.

# PRISMA – proposta de fluxograma



# Fluxograma

Figure 1. Study flow diagram.



# Etapas

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## d.1. Avaliação da qualidade dos estudos

Diferentes instrumentos:

Checklists

Escores



# Avaliação de qualidade

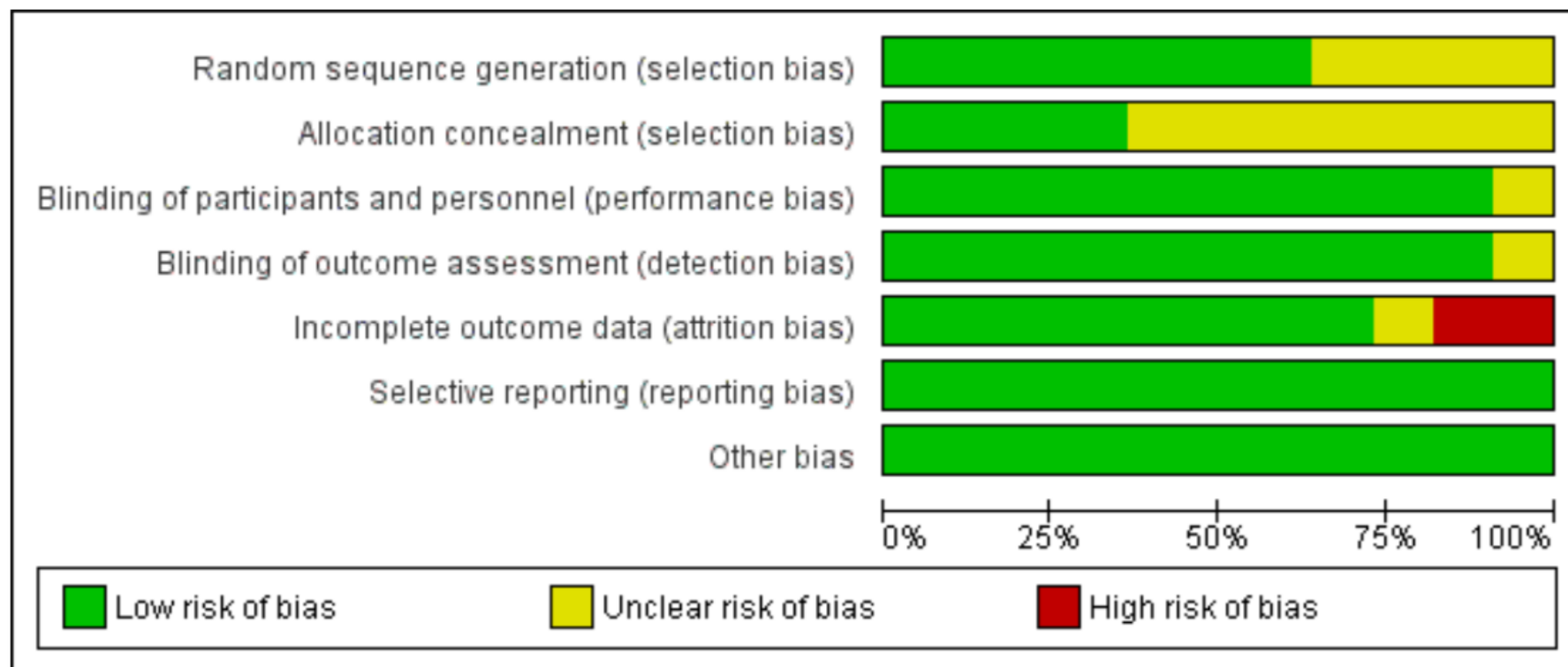
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## **Assessment of risk of bias in included studies**

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).

# Avaliação de qualidade

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



# Avaliação de qualidade

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	+	+	+	+	+	+	+

# **Etapas**

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## **e) Extração da informação**

- **Formulário para extração de dados**
- **Mínimo de 2 investigadores**

# Artigo: 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.

# Etapas

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## f) Análise

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

# Descrição

## artigos

Methods	Randomised, parallel-group trial
Participants	<p>133 children aged 1 to 5 years with a history of recurrent AOM (defined as <math>\geq 3</math> episodes in the preceding 6 months or <math>\geq 4</math> 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"> <li>1. Occurrence of AOM within the 6-month period</li> <li>2. Occurrence of febrile respiratory illnesses</li> <li>3. Use of antibiotics</li> </ol>
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

## f) Análise

- Quantitativa: Meta-análise \*\*
- Combina e integra os resultados de estudos independentes, considerados homogêneos.
- Explora fontes de heterogeneidade
- Escolha da medida de associação (RR, OR) ou efeito
- **Há cálculo de medida-sumário**



# Meta-análise

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- Combina estudos homogêneos,
- 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).

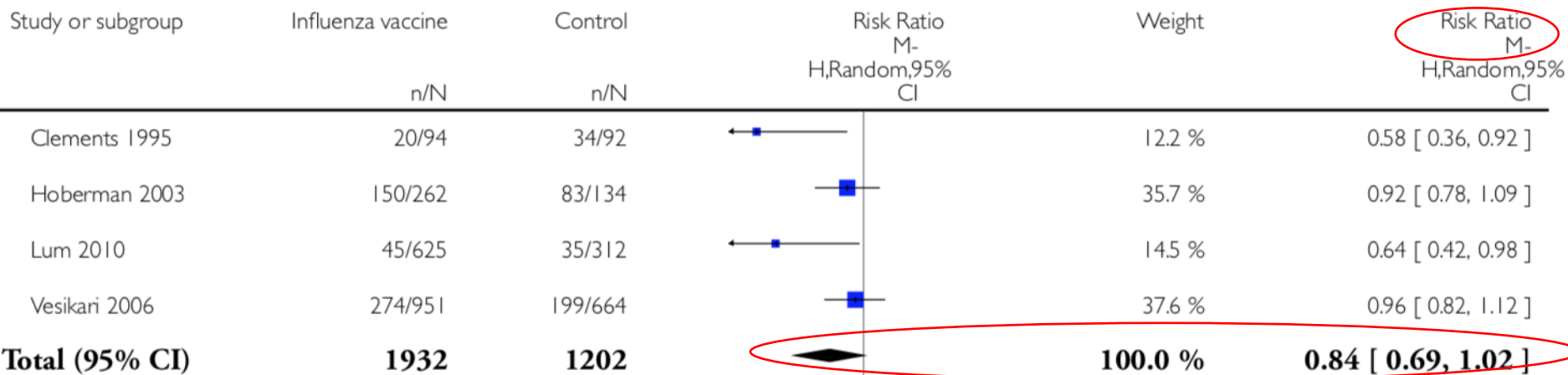
# Artigo: meta-análise com forest plot

## 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

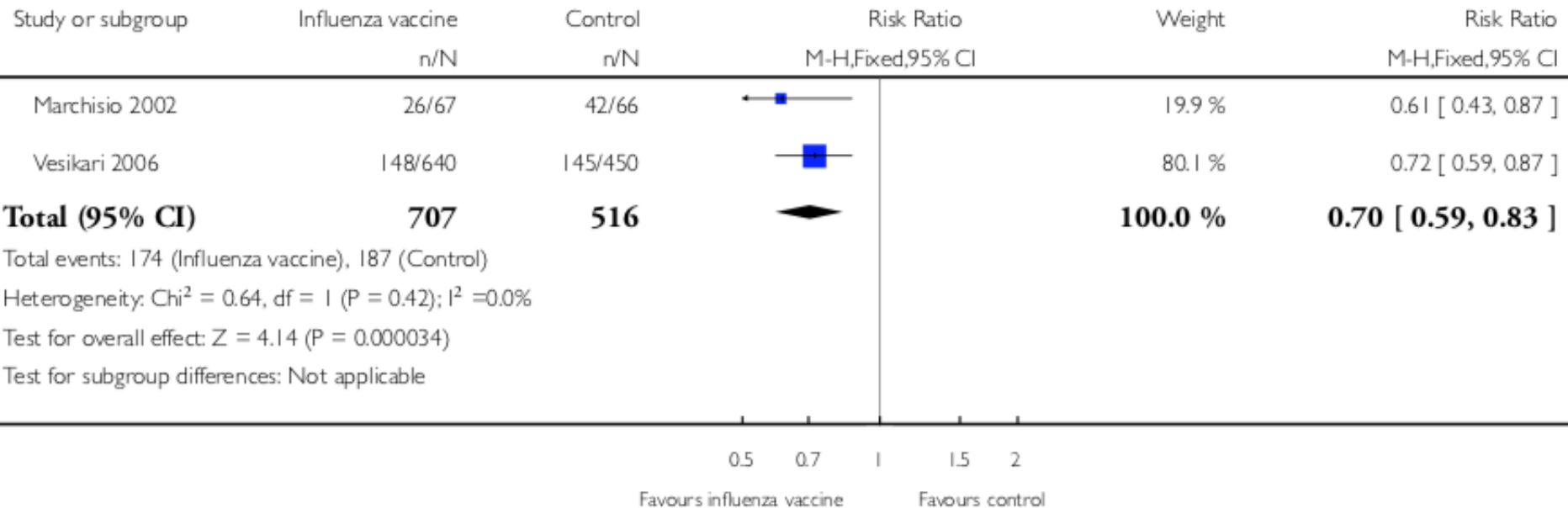
# Artigo: meta-análise com forest plot

## 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

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- 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

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## 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**

# Manejo da Heterogeneidade

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- 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 sub-grupos
  - Combinar estudos usando efeitos aleatórios - conhecer um efeito médio.
  - META-REGRESSÃO - análise estatística que relaciona o tamanho do efeito às características do estudo, por exemplo, média de idade, proporção de mulheres, dose do medicamento

## 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](#)).

### Data synthesis

We examined heterogeneity using both fixed-effect and random-effects models, depending on the degree of significant clinical or statistical heterogeneity, in Review Manager 5 software ([RevMan 2014](#)). Our results are reported with the fixed-effect model unless it is stated that we have used the random-effects model. Thresholds for the interpretation of the  $I^2$  statistic can be misleading, since the importance of inconsistency depends on several factors. We used the guide to interpret heterogeneity as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ( [Higgins 2011](#)): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity.

# **Possibilidade de síntese da evidência**

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## **Estudos “descritivos”**

- **Prevalência ou incidência de desfechos relevantes**

## **Estudos “analíticos”**

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



# **Etapas**

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## **g) Interpretação dos resultados**

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

# Relevância

## Authors' conclusions

Influenza vaccine results in a small reduction in AOM. The observed reduction in the use of antibiotics needs to be considered in light of current recommended practices aimed at avoiding antibiotic overuse. Safety data from these trials were limited. The benefits may not justify the use of influenza vaccine without taking into account the vaccine efficacy in reducing influenza and safety data. We judged the quality of the evidence to be low to moderate. Additional research is needed.

## Quality of the evidence

The overall quality of the evidence was low to moderate.

## 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.

## **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**

# Validade interna:

## 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

# Validade interna: Vieses de informação

## *Revisão Sistemática e Meta-análise*

### 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).

# Colaboração Cochrane



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[Tutorial: How to read a forest plot](#)

