Cochrane reviews
Methodology

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Methods editor
Cochrane Drugs and Alcohol Review Group
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Contents

My contribution to the review

Cochrane Structure and Organization

Cochrane methodology for the production of systematic reviews
My contribution to the alcohol marketing review

Methodological support in the development of the protocol

Methodological support in the conduct of the review:

• Risk of bias assessment
• Data extraction
• Evaluating the quality of the evidence (GRADE)
• Writing the text of the full review: adherence to the MECIR standard of reporting and to the Cochrane methodological and editorial rules
What is Cochrane?


Involves about 40,000 contributors from more than 130 countries (researchers, clinicians, patients)

**Mission**: to produce and disseminate high-quality, relevant, accessible systematic reviews and other synthesized research evidence to improve quality of health care

Acknowledged as one of the world’s leading organizations in the health sector, with a reputation for producing high-quality, credible information to inform health decision making; Cochrane reviews are used by many guidelines producers and by wide range of stakeholders in diverse products and activities
Strategy to 2020

It defines the organization’s direction for the next years and provides the framework for strategic decision making to further improve their products and their relevance for health care decision making.

The Strategy to 2020 is based around achieving four key goals:

**GOAL 1: Producing evidence**

- Investing in quality (increasing quality)
- Making reviews more relevant for decision makers: prioritization (topics clinically relevant)
- Increase efficiency: shorten the time for publication
- New review questions: more diagnosis, prognosis, qualitative and economic
Strategy to 2020

GOAL 2: Making our evidence accessible

To make Cochrane evidence accessible and useful to everybody, everywhere in the world.

Open access

• Since February 2013, all new Cochrane Reviews became free to access for all readers 12 months after publication
• all the reviews will be free by 2020

Translation

• We will translate key content into at least the five other official languages of the World Health Organization (Spanish, French, Russian, Chinese and Arabic)
GOAL 3: Advocating for evidence

- Increase **media coverage**
- make Cochrane the ‘go-to’ place for evidence to inform health decision making by **offering a range of evidence-informed products and resources**, and by making Cochrane Library more easy to browse

GOAL 4: Building an effective & sustainable organisation

- Create an **online learning** environment
- Organizing **training program** for editors and new contributors
- Greater involvement of **low income countries** contributors
Independency

Cochrane does not accept commercial or conflicted funding. This is vital to generate authoritative and reliable information, working freely, unconstrained by commercial and financial interests.

Primary authors of the reviews and co-ordinator editors must be free from any conflict of interest
Review groups

52 composed by reviewers who make Cochrane reviews

Each Cochrane Review Group focuses on a specific topic area and is led by a Co-ordinating Editor(s) and an editorial team including a Managing Editor and Trials Search Co-ordinator.

The Cochrane Review Groups provide authors with methodological and editorial support to prepare Cochrane Reviews, and manage the editorial process, including peer review.
Methods groups

Through continuous research they provide methodological advice to Cochrane on how validity, precision and applicability of Cochrane reviews can be improved and to ensure that they meet the highest standards of quality.

They provide training, peer review and specialist advice, contribute to software developments, and conduct methodological research.

The 16 Methods Groups tackle a wide variety of issues ranging from statistical methods to information retrieval (e.g. diagnostic tests, inclusion of NRS, priority setting, prognosis, economics, qualitative data, etc).
What are systematic reviews?
A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, through the assessment of risk of bias;
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

Informed decisions.
Better health.
What are Cochrane reviews?

Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care resources. They investigate the effects of interventions for prevention, treatment, and rehabilitation. They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting.
Where you can find Cochrane reviews? Cochrane Library

http://www.cochranelibrary.com/
Which are the differences?

Publication of the **protocol** before undergoing the review

Only **one review** for each clinical question

Regularly **updated** every two years

Very **comprehensive bibliographic search** of primary studies without language and date restriction and search also for unpublished studies

Strong rigor on **methodology** and **quality of conduct**

**Transparency** and high quality of reporting

Severe **editorial process** to guarantee high quality reviews

**Plain language summary** for lay people
What is a protocol?

Detailed description of the review aim and methods:

Objective of the review

Inclusion criteria of primary studies (PICO)

Bibliographic search strategy

Methods for study selection and data extraction

Criteria for assessing risk of bias

Method used to analyze and pool the data (meta-analysis)

Method used to assess the quality/certainty of the evidence

- To increase validity by minimizing the risk of selection and reporting bias of the review
The Cochrane process

Title
- Define question
- Competence of author team

Protocol
- PICO
- Plan search
- Describe methods
- Peer review
- Publish

Review
- Undertake search
- Screen results
- Identify included studies
- Risk of bias of included studies
- Extract and analyse data
- Write up and submit

Editorial process
- Peer review
- Revision
- Copy edit
- Publish

Updating
Severe editorial process to guarantee high quality reviews

Cochrane groups internal review (methods): Quality advisor, statistician, managing editor

External referees for content and clinical relevance

Central Editorial Unit: assess reviews considered of highest clinical relevance and a random sample of all the other reviews

Complete editorial process performed both at the protocol stage and at the full review stage
Update

Only one review for each clinical question: to avoid duplication of the effort

Regularly updated every two years: relevant clinical question; new trials continue to be published on the topic

Withdrawn reviews: no more relevant clinical question (treatment no more used or superseded); important flaws discovered after publication

Stable reviews: robust results about effectiveness or ineffectiveness, no more trials expected to be published; question still relevant for clinical practice
Rigor on methodology and quality of conduct
Transparency and high quality of reporting

**Cochrane Handbook**: authors must follow the methods reported in the handbook; handbook regularly updated

**RevMan**: Cochrane reviews must be done only using the RevMan software; both for writing the text and for undergoing risk of bias assessment and statistical analyses.

**Fixed format**: fixed headings and subheadings for each section; fixed format of tables and figures
Rigor on methodology and quality of conduct
Transparency and high quality of reporting

MECIR (Methodological Expectations of Cochrane Intervention Reviews): document containing standards for both conduct and reporting; detailed guidance on what and how do /report in each phase/section of the review;

Mandatory items: means that a new review will not be published if this is not done/reported

Highly desirable items: means that this should generally be done, but that there are justifiable exceptions

To be used by authors when undergo the review and write the draft and by the quality advisor to check quality of conduct and reporting
# Standards for Reporting

<table>
<thead>
<tr>
<th>Section of the review</th>
<th>N items</th>
<th>mandatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and authors</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abstracts</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Background and objectives</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Searching for studies</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Data collection and analysis</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Results- description of studies</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>risk of bias</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Effects of interventions</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Discussion</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Conclusions</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>101</strong></td>
<td><strong>69</strong></td>
</tr>
</tbody>
</table>
Our vision is that healthcare decision-making throughout the world will be informed by high quality, timely research evidence.

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**R13 Abstract, Main results: adverse effects**

Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.

The Abstract of the review should aim to reflect a balanced summary of the benefits and harms of the intervention.

See *Handbook 11.8*

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**R14 Abstract, Main results: format of numerical results**

Present summaries of statistical analyses in the same way as they are reported in the review and in a standard way, ensuring that readers will understand the direction of benefit and the measurement scale used, and that confidence intervals are included where appropriate.

The standard format for reporting the results of statistical analysis includes an indication of the summary measure, point estimate and confidence interval, e.g. odds ratio 0.75 (95% confidence interval 0.62 to 0.89).
Objective – inclusion criteria

The review question must specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

The acronym PICO (Participants, Interventions, Comparisons and Outcomes) must be used

- Methods
  - Criteria for considering studies for this review
  - Types of studies

- Types of participants

- Types of interventions

- Types of outcome measures

- Primary outcomes

- Secondary outcomes
Bibliographic search

Very sensitive and comprehensive

At least three databases (Medline, Embase, CENTRAL, subject specific database)

Reference list of existing reviews and included studies

Search for ongoing and unpublished studies (national and international trials registers, Subject-specific trials registers, Conference abstracts, contact with authors)

No language restriction (studies in languages other than English should be translated)

No date restriction

It is the responsibility of each CRG to support review authors, and most CRGs employ a Trials Search Coordinator to design search strategies and run the searches
Bibliographic search

Both free-text and subject headings should be used (for example Medical Subject Headings (MeSH) and EMTREE).

**Limiting to RCTs:** Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE combined in AND with the keywords related to patients and intervention (PICO)

**Including non-randomised studies (NRS):**

same strategy for PICO without filter for RCTs or any other filter
Study selection

Two phases process:

1. **Screening of titles and abstracts**: at least two authors independently; disagreement resolved by discussion

Potentially relevant studies acquired in full text

2. **Full text evaluation for final inclusion**: at least two authors independently; disagreement resolved by discussion

Complete the PRISMA flow diagram

Report **reasons for exclusion** for studies read in full (Table of excluded studies)
Data extraction

Use a pre-specified **data collection form** which has been piloted

Populate a table of ‘**Characteristics of included studies**’, one for each study (details of participants, interventions and comparators, outcomes and study design.)

Extract outcomes data (**two authors independently** or at least checked by a second reviewer)
### Characteristics of included studies table

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>Country: USA</td>
<td></td>
</tr>
<tr>
<td>Participants: cocaine abusers (DSM-III)</td>
<td></td>
</tr>
<tr>
<td>N = 42</td>
<td></td>
</tr>
<tr>
<td>Age: 27 years old (mean age)</td>
<td></td>
</tr>
<tr>
<td>Sex: males 74%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity: white 76.2%</td>
<td></td>
</tr>
<tr>
<td>Marital status: married 17.5%</td>
<td></td>
</tr>
<tr>
<td>Education level: 13 years (mean)</td>
<td></td>
</tr>
<tr>
<td>Employment: employed 65%</td>
<td></td>
</tr>
<tr>
<td>Setting: outpatients</td>
<td></td>
</tr>
<tr>
<td>History:</td>
<td></td>
</tr>
<tr>
<td>- Route: 33.3% freebase, 50% intranasal</td>
<td></td>
</tr>
<tr>
<td>- Psychostimulant use: ~ 4 g per week, for approximately 40 months</td>
<td></td>
</tr>
<tr>
<td>- Other drugs: 31% of participants also report regular use of other substances (alcohol 87.5%, marijuana 37.5%)</td>
<td></td>
</tr>
<tr>
<td>- Psychiatric comorbidity: depressive disorders (19%), antisocial personality disorders (26%)</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>1. CBT (RP), n = 21</td>
<td></td>
</tr>
<tr>
<td>2. Interpersonal therapy (IPT), n = 21</td>
<td></td>
</tr>
<tr>
<td>Duration of intervention: both interventions consisted of individual sessions of 50-60 min once a week for 3 months</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up: 3 months</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>- Dropouts</td>
<td></td>
</tr>
<tr>
<td>- Use of cocaine for at least 3 consecutive weeks at any point of treatment</td>
<td></td>
</tr>
<tr>
<td>- Use of cocaine for at least 3 consecutive weeks at endpoint of study</td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td>Funding source: National Institute on Drug Abuse Grant DA 04299</td>
<td></td>
</tr>
<tr>
<td>Conflict of interest: not stated</td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Risk of bias of primary studies

• Assessment of the internal validity of each study results, for randomized trials, the Cochrane 'Risk of bias' tool must be used
• Done at study level and then summarized across all the studies
# Risk of bias of RCTs

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Unclear risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>Authors' judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Information not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Information not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Blinding of participants and personnel impossible for the types of intervention</td>
</tr>
<tr>
<td>subjective outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>objective outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: “to maintain a single blind for psychotherapy, the clinical evaluator saw subjects in a office physically separated from the office in which therapy was conducted and instructed subjects not to disclose details of their therapist or treatment”</td>
</tr>
<tr>
<td>subjective outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: “to maintain a single blind for psychotherapy, the clinical evaluator saw subjects in a office physically separated from the office in which therapy was conducted and instructed subjects not to disclose details of their therapist or treatment”</td>
</tr>
<tr>
<td>objective outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>4% dropout</td>
</tr>
<tr>
<td>All outcomes except retention in treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All the declared outcomes in the Methods section were reported in the Results. All the declared outcomes in the Methods section were reported in the Results</td>
</tr>
</tbody>
</table>
Risk of bias of RCTs

Caption
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Risk of bias of non-randomised studies

No strict rules

1. For experimental and controlled studies, and for prospective cohort studies, the six domains in the standard ‘Risk of bias’ tool could usefully be assessed, whether allocation is randomized or not. Than further domains could be added (e.g. comparability of groups at baseline for confounding and prognostic factors, adjustment for confounding performed)
Risk of bias of non-randomised studies

2. ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions
developed by members of the Cochrane Bias Methods Group and the Cochrane Non-Randomised Studies Methods Group

To evaluate risk of bias of NRS that compare the health effect of two or more interventions (i.e. effectiveness, not aetiology, prognosis, risk factor)
Not yet mandatory; very complex and time consuming
For cohort studies, case control, cross sectional
Risk of bias of non-randomised studies

**Interrupted time series (ITS) studies**: criteria developed by the Effective Practice and Organization of Care (EPOC) Group (www.epoc.cochrane.org);

**Uncontrolled case series**: no suggested checklist; not useful study design to assess efficacy or causal relationship
**Data synthesis**

**Clinical heterogeneity:** Undertake a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful.

**Statistical heterogeneity:** random versus fixed effect model; exploration for heterogeneity by subgroup analysis

**Robustness of the results:** consider sensitivity analysis (impact of imputed data and high risk of bias studies)

Do not pool RCTs and NRS results together
Quality/certainty of the evidence (GRADE approach)

Extensive evaluation of the evidence considering not only the estimate of the effect and risk of bias but also other relevant domains to make a final judgment about the confidence in the overall estimate when we have to generalize from the samples analyzed in the retrieved studies to the general population that is the target of the review.

GRADE working group: born in 2000; now involves about 200 members who meet regularly twice a year. Elaborated a new method for grading the evidence and the strength of the recommendations of clinical practice guidelines. To be used by guidelines producers and systematic review authors.

Mandatory since 2016 to include the Summary of findings in a Cochrane review.
Quality/certainty of evidence assessment based on GRADE approach

• RCTs ☐☐☐☐

• Observational studies ☐☐☐☐☐

• 5 factors that can lower quality
  1. Limitations in detailed study design and execution (*risk of bias criteria*)
  2. Inconsistency (*or heterogeneity*)
  3. Indirectness (*PICO and applicability*)
  4. Imprecision
  5. Publication bias

• 3 factors can increase quality
  1. Large magnitude of effect
  2. Opposing plausible residual bias or confounding
  3. Dose-response gradient
GRADE Domains: downgrade the evidence

- **Inconsistency (heterogeneity) between studies results:** Point estimates vary widely across studies; Confidence intervals (CIs) minimal or no overlap; statistical test for heterogeneity $P < 0.10$; The $I^2$ : 60 e 90% : substantial, 75 e 100% : considerable

- **Directness of Evidence (generalizability, transferability, applicability):** differences between PICO and available evidence in populations/patients, interventions, outcomes

- **Publication bias:** find only small “positive” studies, mainly if sponsored by industry Funnel plot showing asymmetry

- **Imprecision of the overall estimate:** Wide confidence intervals. Small number of events. Small sample size
GRADE Domains: upgrade the evidence

- Only for observational studies
- **Large magnitude of effect** (RRR 50%/RR 2) or very large (RRR 80%/RR 5); modeling studies suggests that confounding alone is unlikely to explain associations with a RR greater than 2 (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2).
- **Dose response relation**
- **Residual confounding** not adjusted for that could increase the association e.g.: effect of condom use on HIV infection among men who have sex with men RR: 0.34 [0.21, 0.54] (RRR: 66%) in favor of condom use vs no condom use. Condom users were more likely to have more partners (but studies did not adjust for this confounding factor). Considering the number of partners would, if anything, strengthen the effect estimate in favor of condom use.
Quality (certainty) of evidence assessment based on GRADE approach

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Quality</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>★★★★★</td>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect</td>
</tr>
<tr>
<td>★★★★</td>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</td>
</tr>
<tr>
<td>★★★</td>
<td>Low</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td>★★</td>
<td>Very low</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</td>
</tr>
</tbody>
</table>
Quality (certainty) of evidence assessment based on GRADE approach

• Assessment done at the outcome level – no at study level – across all the studies.
• For the most relevant primary outcomes (up to seven)
• One SoF for each comparison (up to four)
### Summary of findings table

**Summary of finding: antibiotics for acute otitis media in children**

Antibiotics compared with placebo for acute otitis media in children

**Patient or population:** Children with acute otitis media  
**Setting:** High- and middle-income countries  
**Intervention:** Antibiotics  
**Comparison:** Placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Estimated risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at 24h</td>
<td>Placebo: 367 per 1,000</td>
<td>Intervention risk: 330 per 1,000 (286–382)</td>
<td>RR 0.9 (0.78–1.04)</td>
<td>1229 (5)</td>
</tr>
<tr>
<td>Pain at 2–7 d</td>
<td>Placebo: 257 per 1,000</td>
<td>Intervention risk: 185 per 1,000 (159–213)</td>
<td>RR 0.72 (0.62–0.83)</td>
<td>2791 (10)</td>
</tr>
<tr>
<td>Hearing, inferred from the surrogate outcome abnormal tympanometry—1 mo</td>
<td>Placebo: 350 per 1,000</td>
<td>Intervention risk: 311 per 1,000 (262–375)</td>
<td>RR 0.89 (0.75–1.07)</td>
<td>927 (4)</td>
</tr>
<tr>
<td>Hearing, inferred from the surrogate outcome abnormal tympanometry—3 mo</td>
<td>Placebo: 234 per 1,000</td>
<td>Intervention risk: 227 per 1,000 (178–290)</td>
<td>RR 0.97 (0.76–1.24)</td>
<td>808 (3)</td>
</tr>
<tr>
<td>Vomiting, diarrhea, or rash</td>
<td>Placebo: 113 per 1,000</td>
<td>Intervention risk: 156 per 1,000 (123–199)</td>
<td>RR 1.38 (1.09–1.76)</td>
<td>1,401 (5)</td>
</tr>
</tbody>
</table>
Plain Language for lay people

Summary of the review written in plain language able to be understood by lay people without knowledge of technical terminology (400 to 700 words)

Title: rewritten in plain language

Which is the review question?: objective

What was studied in the review?: background

What are the main results?: study characteristics, funding source, effect of treatment without figures

Search date: currency of the review

Quality of the evidence: (based on GRADE approach)

Key messages: conclusions