Children With Chronic Wet or Productive Cough—Treatment and Investigations
A Systematic Review

Chang AB, Oppenheimer JJ, Weinberger M, Rubin BK, Irwin RS.
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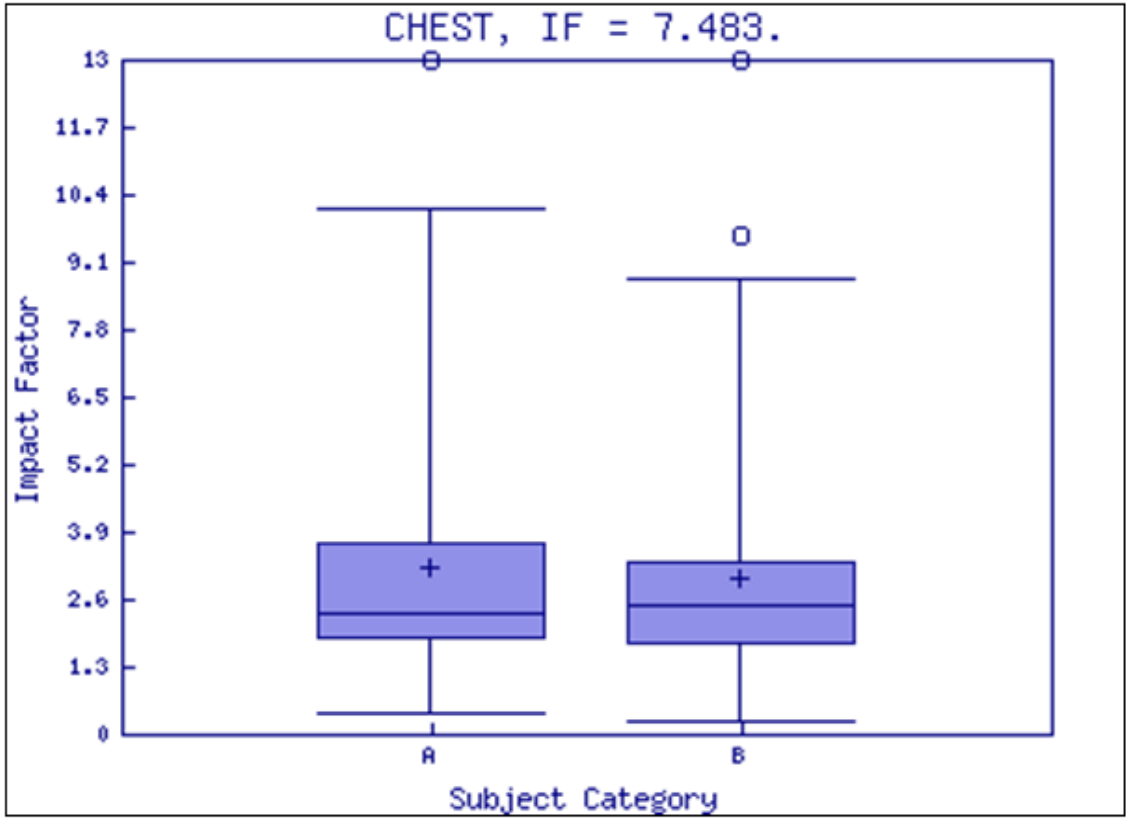
CHEST	0012-3692	45169	7.483	6.558	1.771	345	9.4	6.6

Cited Journal | Citing Journal | Source Data | Journal Self Cites



Ke
A -
B -

Background

- Systematic reviews were conducted to examine two related key questions (KQs) in children with chronic (> 4 weeks' duration) wet or productive cough not related to bronchiectasis:

- ✓ KQ1—How effective are antibiotics in improving the resolution of cough?
  If so, what antibiotic should be used and for how long?
- ✓ KQ2—When should they be referred for further investigations?

步驟１：系統性文獻回顧探討的問題為何？

P

- Children aged ≦14 years
- Chronic cough (> 4 weeks duration) with wet or productive cough

I

- Antibiotics

C

- Do not use antibiotics

O

- Improve cough resolution

步驟 2：系統性文獻回顧的品質如何？(FAITH)

F - 研究是否找到 (Find) 所有的相關證據？

最好的狀況是？
良好的文獻搜尋至少應包括二個主要的資料庫(如：Medline, Cochrane考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH字串及一般檢索詞彙(text words)。

P.121
Duplicates found between Scopus and PubMed searches were identified and removed by the librarians before sending the abstracts to the two authors (A. B. C. and J. J. O.) who reviewed the abstracts.

For randomized controlled trials (RCTs), both reviewers independently assessed the risk of bias criteria by using measures in Cochrane reviews.

有資料庫、關鍵字及MeSH字串及一般檢索詞彙

F - 研究是否找到 (Find) 所有的相關證據？

SEARCH strategy for KQ1
PubMed
("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough") AND (antibiotics OR anti-bacterial agents)
Filters: Humans; English; Child: birth-18 years

Web of Science:
TOPIC: ((chronic cough OR idiopathic cough OR refractory cough OR unresponsive cough OR intractable cough OR psychogenic cough OR unresolved cough OR unexplained cough OR wet cough OR productive cough) AND (antibiotics OR anti-bacterial agents)) AND TOPIC: (child OR children OR adolescent OR infant OR neonate) Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE OR REVIEW OR PROCEEDINGS PAPER)

SCOPUS:
TITLE-ABS-KEY(("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough") AND (antibiotics OR "anti-bacterial agents") AND (child OR children OR infant OR neonate OR adolescent)) AND (LIMIT-TO(LANGUAGE,"English"))

Cochrane CENTRAL
("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough") AND (antibiotics OR "anti-bacterial agents") AND (child OR children OR infant OR neonate OR adolescent)

F - 研究是否找到 (Find) 所有的相關證據？

SEARCH strategy for KQ2

PubMed

("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough" OR (cough AND chronic disease[mh])) AND (diagnostic tests, routine[mh] OR referral and consultation[mh] OR referral[tiab] OR consultation[tiab] OR decision trees[mh] OR clinical pathways[mh] OR investigation* OR algorithms[mh]) Filters: Humans; English; Child: birth-18 years

Web of Science

(("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough" OR (cough AND chronic disease))) AND TOPIC: ((routine diagnostic tests OR referral and consultation OR referral OR consultation OR decision trees OR clinical pathways OR investigation* OR algorithm*)) AND TOPIC: ((child OR children OR adolescent OR infant OR neonate))
Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR MEETING ABSTRACT OR REVIEW)

SCOPUS

TITLE-ABS-KEY(("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough" OR (cough AND chronic disease)) AND ("diagnostic tests, routine" OR "routine diagnostic tests" OR "referral and consultation" OR referral OR consultation OR "decision trees" OR "clinical pathways" OR investigation* OR algorithm*) AND (child OR children OR infant OR neonate OR adolescent) AND (human OR humans)) AND (LIMIT-TO(LANGUAGE,"English"))

CENTRAL (Cochrane)

(("chronic cough" OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "wet cough" OR "productive cough" OR (cough AND chronic disease)) AND ("diagnostic tests, routine" OR "routine diagnostic tests" OR "referral and consultation" OR referral OR consultation OR "decision trees" OR "clinical pathways" OR investigation* OR algorithm*) AND (child OR children OR infant OR neonate OR adolescent)) in Title, Abstract, Keywords

評讀結果： ■ 是 □否 □不清楚

Figure1- Selection of studies that addresses KQ1:

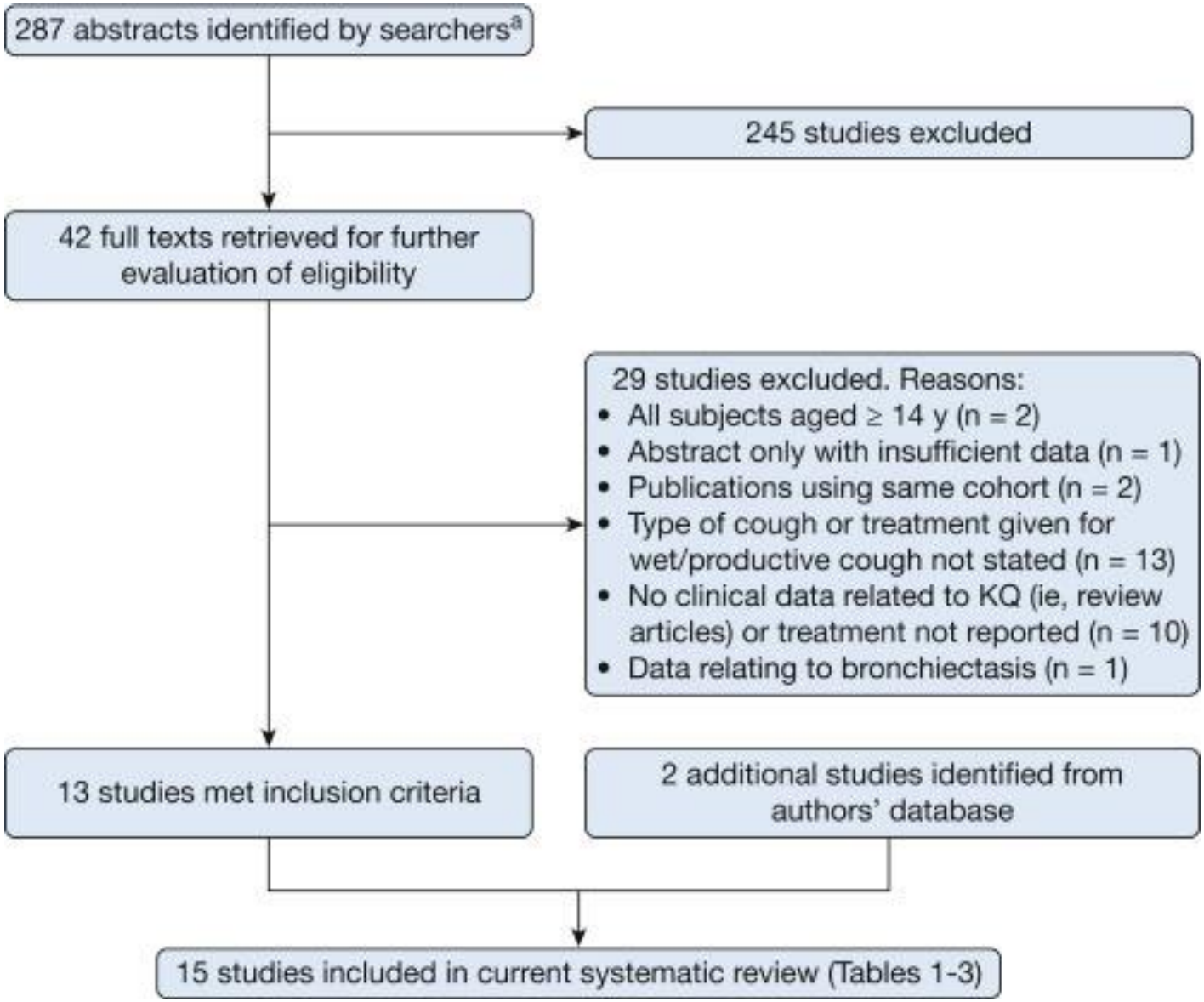
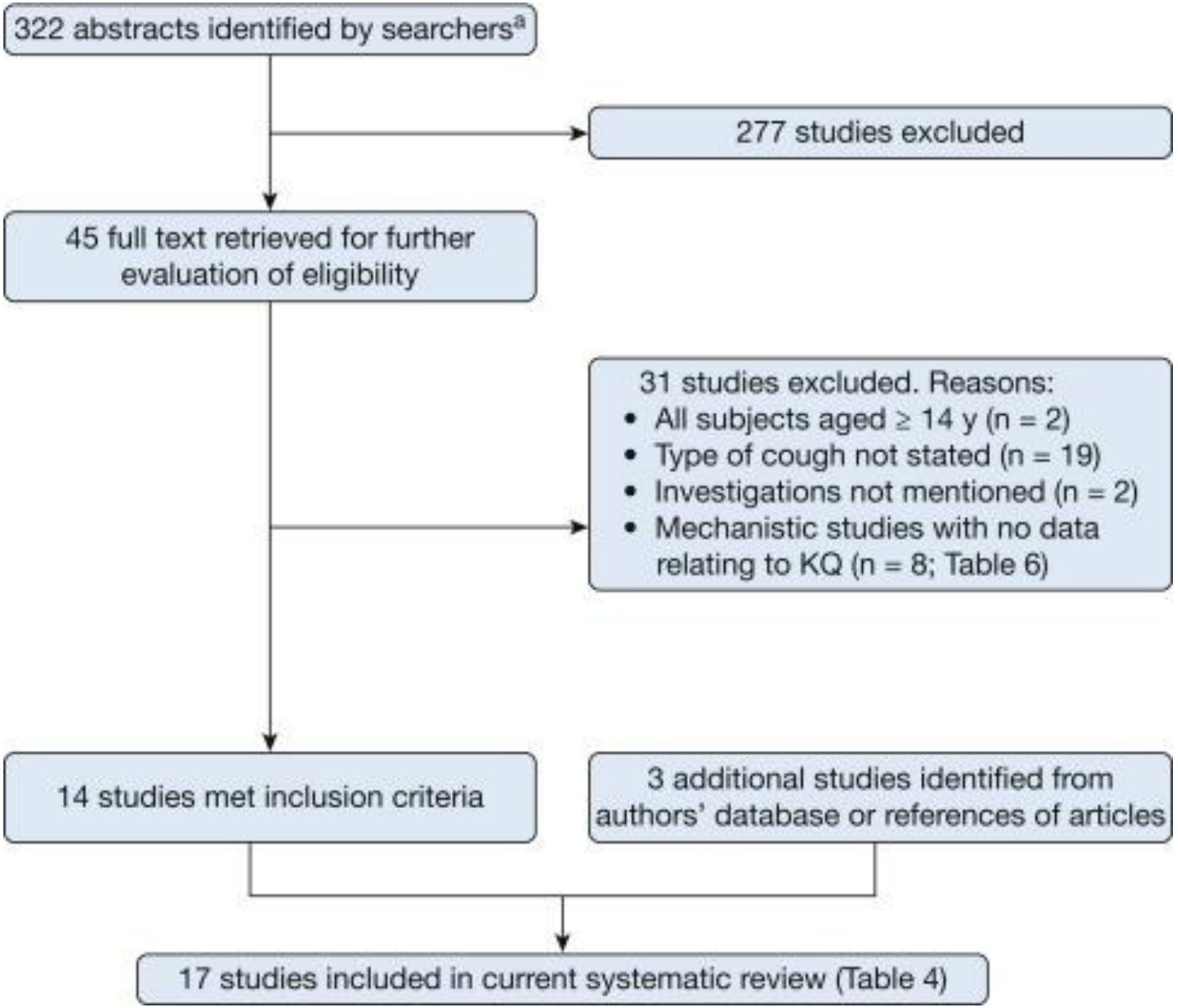


Figure2- Selection of studies that addresses KQ2:



步驟 3：系統性文獻回顧的品質如何？(FAITH)

A - 文獻是否經過嚴格評讀 (Appraisal)？

最好的狀況是？

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。P.121

➢Validity assessment (1)-Cochrane risk of bias tool

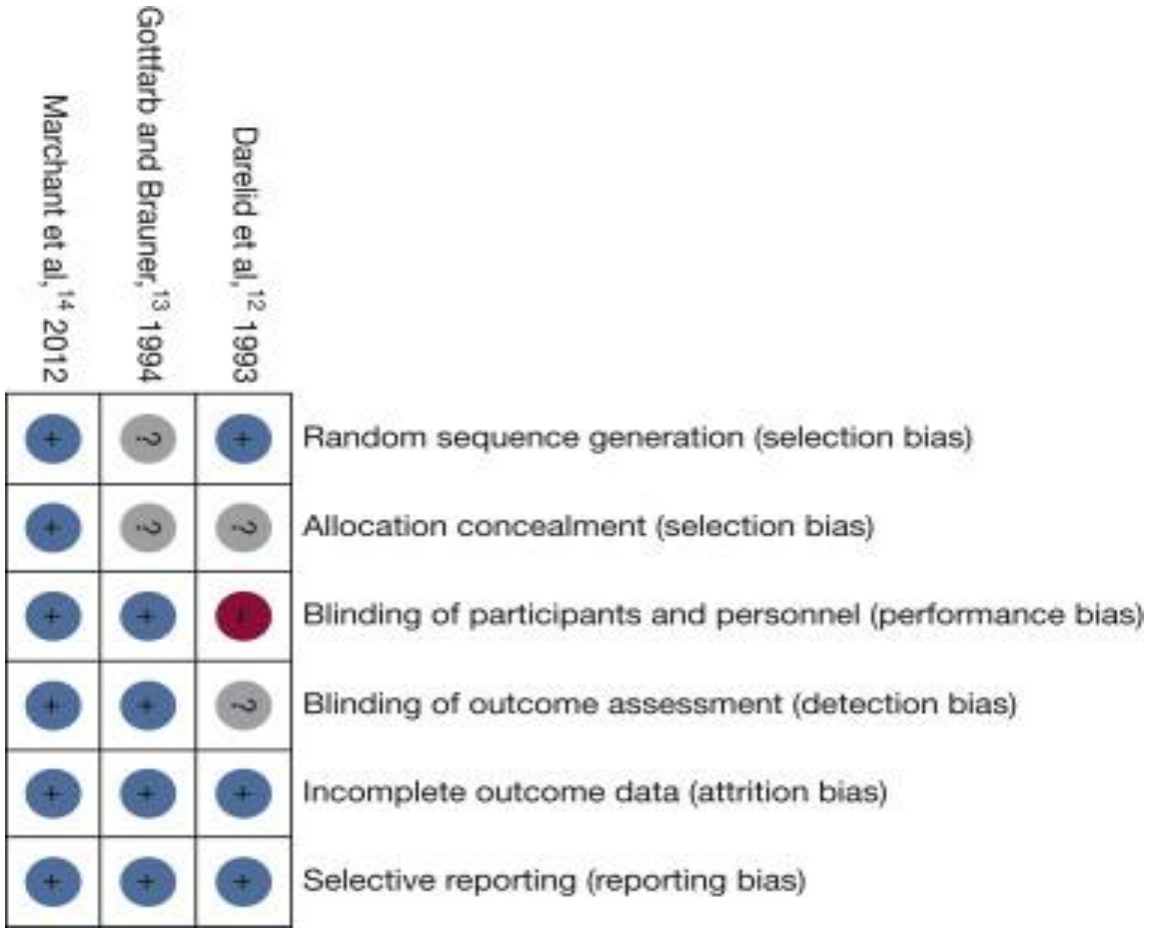
For randomized controlled trials (RCTs), both reviewers independently assessed the risk of bias criteria by using measures in Cochrane reviews.

The criteria used were: 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),and selective reporting (reporting bias).

➢Validity assessment(2)-cohort studies

For cohort studies, data were extracted by a single author (A. B. C.) and checked by a second author (J. J. O.). In cohort studies, the study's setting, number enrolled and completing the study, inclusion and exclusion criteria,and main results related to the respective KQs are reported(Tables 1-4).

Figure3-Risk of bias summary



Risk of bias summary: judgments of review authors (A. B. C. and J. J. O.) regarding each risk of bias item for the randomized controlled trials (Marchant et al,14 Darelid et al,12 and Gottfarb and Brauner13) included (KQ1).

評讀結果： □ 是 □否 ■不清楚

步驟 4：系統性文獻回顧的品質如何(FAITH)

I - 是否只納入 (included) 具良好效度的文章？

最好的狀況是？
僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

Data were presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowcharts, and the summaries were tabulated.
Fifteen studies were included in KQ1 (three systematic reviews, three RCTs, five prospective studies, and four retrospective studies) and 17 in KQ2 (one RCT, 11 prospective studies, and five retrospective studies).

評讀結果：■是□ 否 □不清楚

TABLE 2] Prospective Studies in Children With Chronic Wet Cough That Included Mx (Dx and Rx and Excludes Mechanistic Studies) (KQ1)

Author, Publication Year/Country	Setting; Study Design	Inclusion Criteria; EXC or Definitions	No. Enrolled, No. Completed; FU Length; Age	Main Aim(s) of Study	Primary Findings Related to KQ	Specimen; Bacteria Types[b] and AB Used	Other Main Findings or Comment
Darelid et al,[12] 1993/ Sweden	3 centers; pediatric OPD; open RCT	Aged 0.5-6 y, persistent cough > 10 days EXC, pneumonia, allergy, acute otitis media, tonsillitis, cardiac disease, clinical suspicion of pertussis	N cohort = 88; n completed = 87[c] FU = 3 mo Median age group = 13-24 mo (IQR, NR)	Whether 7 d of erythromycin clinically improves children aged 0.5-6 y with a cough > 10 d	88% cured (day 7) in erythromycin group vs 36% in control subjects ($P < .006$)	Nasopharyngeal swab Hi = 38%; Spn = 48%; Mcat = 75%; pertussis = 5% Erythromycin	Study included because 50% had a cough > 21 d. Authors confirmed that the cough was wet (as in Cochrane review[15])
Gottfarb and Brauner,[13] 1994/ Sweden	3 centers; pediatric ~~OPD; DB~~ RCT	Lower resp tract infection with cough >10 d, >11 coughing attacks in 24 h EXC, pneumonia, acute otitis media, clinical suspicion of pertussis	N cohort = 52; n completed = 52[c] FU = 14 d Median age = 2.6-2.7 y (IQR, NR)	"To investigate the nasopharyngeal flora of children with persistent cough and the effects of treatment with AMC"[(p545)]	"AB treated group had significantly better recovery in both the pediatricians estimation ($P = .02$) and independent parental judgement ($P = .002$)"[(p545)]	Nasopharyngeal swab Hi = 30%; Spn = 20%; Mcat = 71% AMC	Study included because the mean duration of cough was 3-4 wk (range NR). Authors confirmed that the cough was wet (as in Cochrane review[15])
Marchant et al,[14] 2012/ Australia	Single-center; pediatric and resp ~~OPD; DB~~ RCT	Aged 0.5-18 y, physician-observed wet cough > 3 wk EXC, chronic lung, cardiac neuro-development disease, ABs in last 2 wk, acutely unwell	N cohort = 50; n completed = 47 FU = 2 wk Mean age = 1.8-2.8 y (IQR, 0.9-5.3)	Efficacy of 2 wk of oral AMC (compared with placebo) in achieving cough resolution in children with chronic wet cough	AMC effective for wet cough: cough resolution rates (48%) in AMC group vs placebo (16%), $P = .016$	BAL Hi = 38%; Spn = 24%; Mcat = 19% All AMC sensitive	BAL in subgroup (n = 37) indicate PBB

步驟 5：系統性文獻回顧的品質如何(FAITH)

T - 作者是否以表格和圖表「總結」(total up) 試驗結果？

最好的狀況是？應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近，可針對結果進行統合分析(meta-analysis)，並以「森林圖」(forest plot)呈現研究結果，最好再加上異質性分析。

TABLE 2] Prospective Studies in Children With Chronic Wet Cough That Included Mx (Dx and Rx and Excludes Mechanistic Studies) (KQ1)

Author, Publication Year/Country	Setting; Study Design	Inclusion Criteria; EXC or Definitions	No. Enrolled, No. Completed; FU Length; Age	Main Aim(s) of Study	Primary Findings Related to KQ	Specimen; Bacteria Types[5] and AB Used	Other Main Findings or Comment
Darelid et al,[12] 1993/ Sweden	3 centers; pediatric OPD; open RCT	Aged 0.5-6 y persisten > 10 day EXC, pneur allergy, a media, to cardiac d clinical su pertussis	N cohort = 88;	Whether 7 d of	88% cured (day 7) in	Nasopharyngeal	Study included
Gottfarb and Brauner,[13] 1994/ Sweden	3 centers; pediatric OPD; DB RCT	Lower resp infection >10 d, > coughing					

TABLE 3] Retrospective Studies on Children With Chronic Wet Cough That Included Mx (Dx and Rx But Excludes Research Mechanistic Studies) (KQ1)

Author, Publication Year/Country	Setting	Inclusion Criteria; EXC	N; Age; FU Length	Main Aim(s)	Primary Finding Relating to KQ	Specimen Type; Bacteriology[1] and AB Used	Other Major Findings	Comment
Donnelly et al,[26] 2007/England	Single-center; resp OPD; review of clinic letters (random)	"Persistent, wet cough present for 1 mo that resolves with appropriate AB treatment"(p80)	N = 81 Median age = 3.8 y (range, 0.4-14.8 y); FU = NR	To present "results of a retrospective review of outcomes in 81 randomly selected patients with a	95% cured with AB use; 48% reported "wheeze" but had "ruttle"	Nonquantitative BAL (n = 19), cough swab (n = 51) Of infected specimens (approximately 50%):	59% symptomatic for > 1 y; BE in 4 of 14 who had chest CT scan; 31% with concomitant "asthma"	

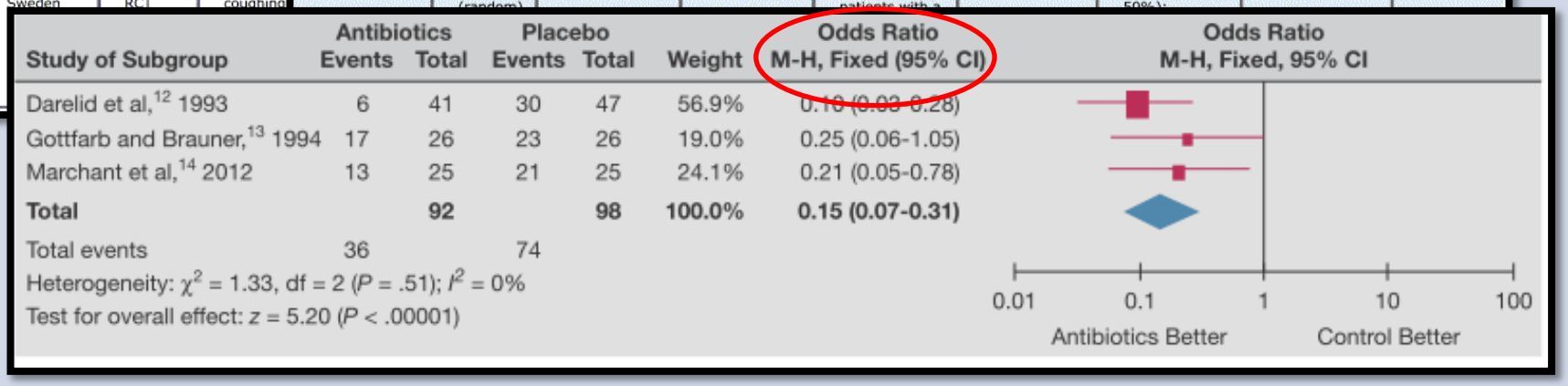


Figure 4 – Forest plot from the three randomized controlled trials (Marchant et al,14Darelid et al,12and Gottfarb and Brauner13). Data show that the use of antibiotics significantly improved cough resolution (odds ratio, 0.15 [95% CI,0.07-0.31]).

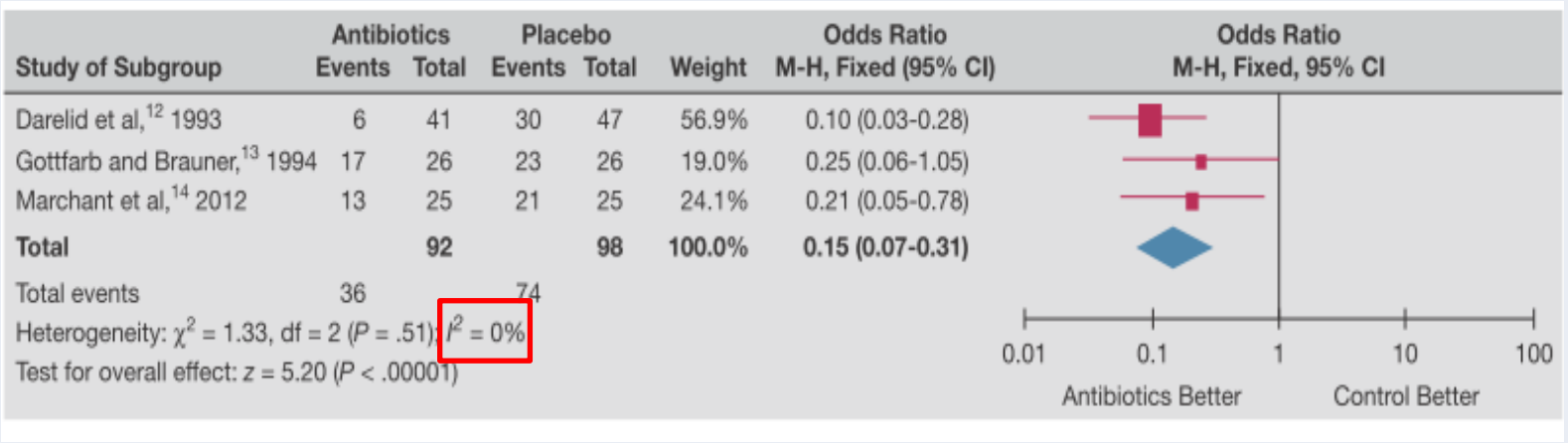
評讀結果：　■是 □否□ 清楚

步驟 6：系統性文獻回顧的品質如何(FAITH)

H - 試驗的結果是否相近 - 異質性 (Heterogeneity)？

最好的狀況是？

在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的PICO及研究方法，探討造成異質性的原因。



Study of Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed (95% CI)
Darelid et al,[12] 1993	6	41	30	47	56.9%	0.10 (0.03-0.28)
Gottfarb and Brauner,[13] 1994	17	26	23	26	19.0%	0.25 (0.06-1.05)
Marchant et al,[14] 2012	13	25	21	25	24.1%	0.21 (0.05-0.78)
Total		**92**		**98**	**100.0%**	**0.15 (0.07-0.31)**
Total events	36		74			

Heterogeneity: $\chi^2 = 1.33$, df = 2 ($P = .51$); $I^2 = 0\%$

Test for overall effect: $z = 5.20$ ($P < .00001$)

評讀結果： ■ 是 □否 □不清楚

RESULT

- Data were presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowcharts, and the summaries were tabulated.
- Fifteen studies were included in KQ1 (three systematic reviews, three RCTs, five prospective studies, and four retrospective studies) and 17 in KQ2 (one RCT, 11 prospective studies, and five retrospective studies).
- Combining data from the RCTs (KQ1), the number needed to treat for benefit was 3 (95% CI, 2.0-4.3) in achieving cough resolution.
- In general, findings from prospective and retrospective studies were consistent, but there were minor variations.

CONCLUSIONS

- **There is high-quality evidence that in children aged # 14 years with chronic (> 4 weeks' duration) wet or productive cough, the use of appropriate antibiotics improves cough resolution.**
- There is also high-quality evidence that when specific cough pointers (eg, digital clubbing) are present in children with wet cough, further investigations (eg, flexible bronchoscopy, chest CT scans, immunity tests) should be conducted.
- When the wet cough does not improve by 4 weeks of antibiotic treatment, there is moderate-quality evidence that children should be referred to a major center for further investigations to determine whether an underlying lung or other disease is present.

臨床運用

- Discussion Point:
  - 台灣的醫療環境，不會等咳嗽到4週才使用抗生素
  - 小兒咳嗽，先評估家中環境或是否有二手菸、燒香、塵蹣? (環境評估)
  - 文獻指出，抗生素種類需以當地常見的致病菌種為主。
  - 國內檢驗可以很快知道結果，對於兒童慢性濕咳之治療，建議依據臨床症狀及檢驗報告(黴漿菌肺炎、肺炎鏈球菌)結果來投藥
  - 家屬對給予抗生素的擔心?

小兒濕咳四週要使用抗生素嗎?

- ✓同意：4 人
- ✓懷疑：12 人
- ✓不同意：7人

Thank you!