CADTH Lecture Series

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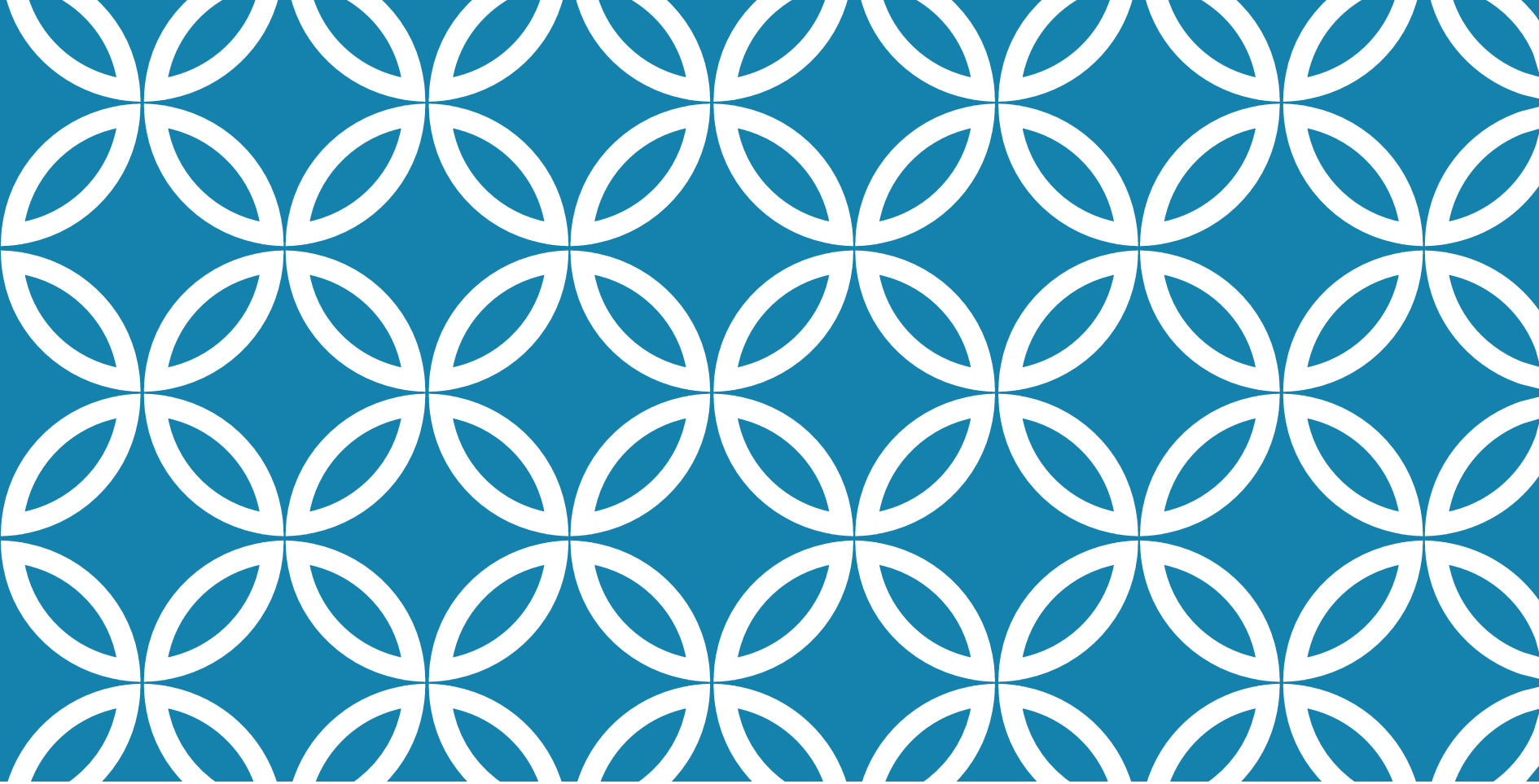
#CADTHTalks

CADTH Evidence Driven.

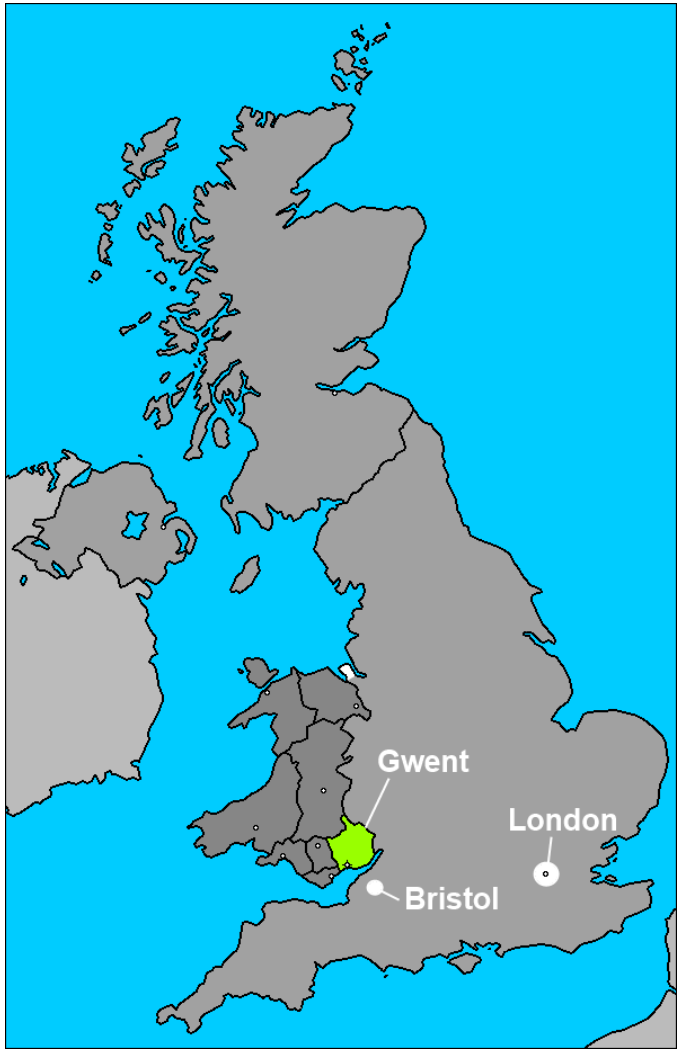


ALL THAT GLITTERS IS NOT GOLD - ARE SYSTEMATIC REVIEWS FOOL'S GOLD?

Jon Brassey


CADTH

WHERE IT STARTED



ATTRACT

GIG CYMRU NHS WALES
Iechyd Cyhoeddus Cymru
Public Health Wales

ATTRACT

Receive question

Rapid search

Crude appraisal

Narrative synthesis

10,000 CLINICAL QUESTIONS

Clinicians want easy access to robust answers to their clinical questions

= rapid reviews

~70% users are health professionals
(50% are doctors)

~30% are information specialists

Trip

www.tripdatabase.com

110,000
registered
users

100 million+ searches

OUTLINE OF PRESENTATION

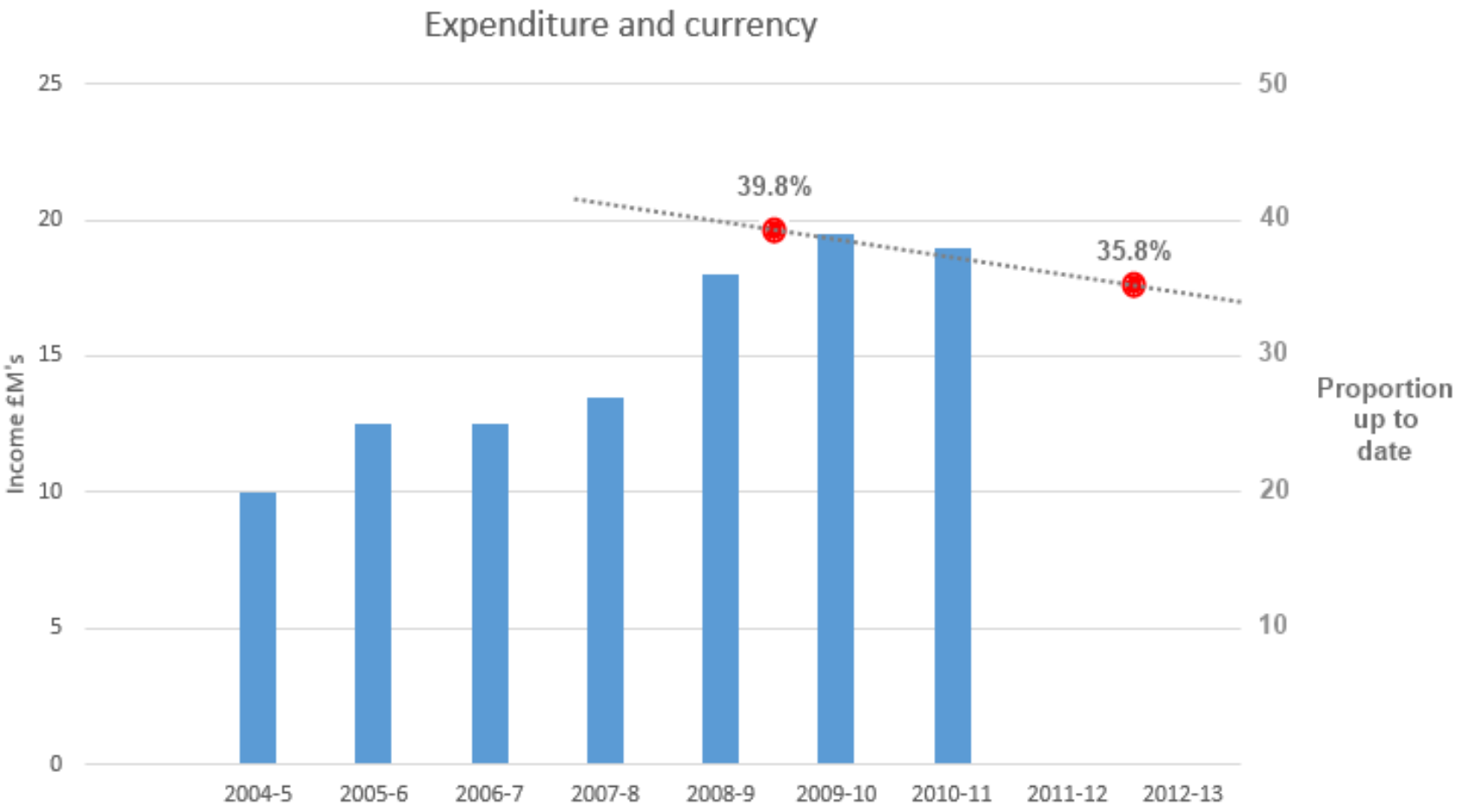
1. **Problems with current systematic review systems**
2. **Rapid reviews**
3. **Trip – some interesting areas of work we're currently involved in**

SYSTEMATIC REVIEW DEFINITION

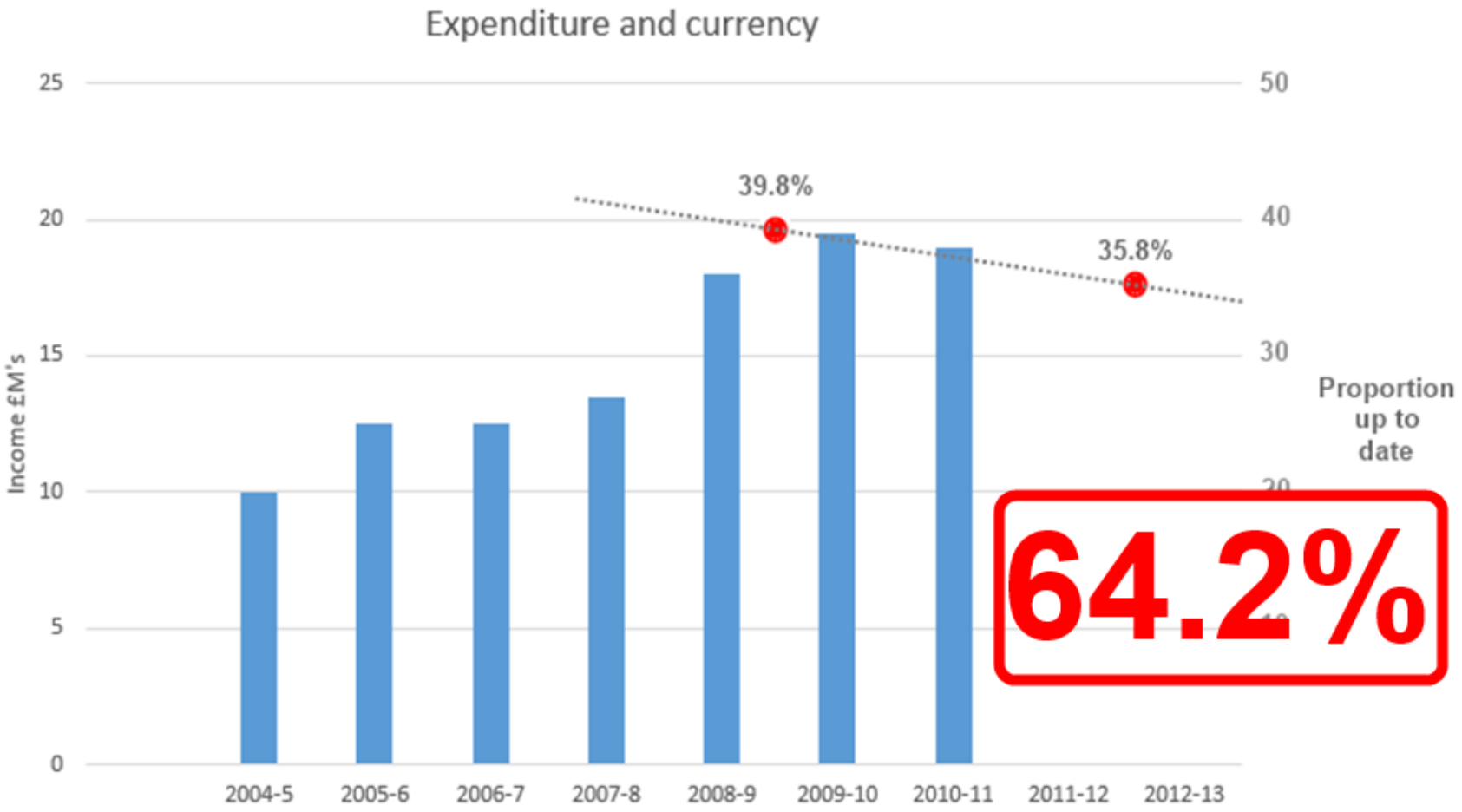
A systematic review is a high-level overview of primary research on a particular research question that tries to identify, select, synthesize and appraise **all** high quality research evidence relevant to that question in order to answer it.

Cochrane Collaboration

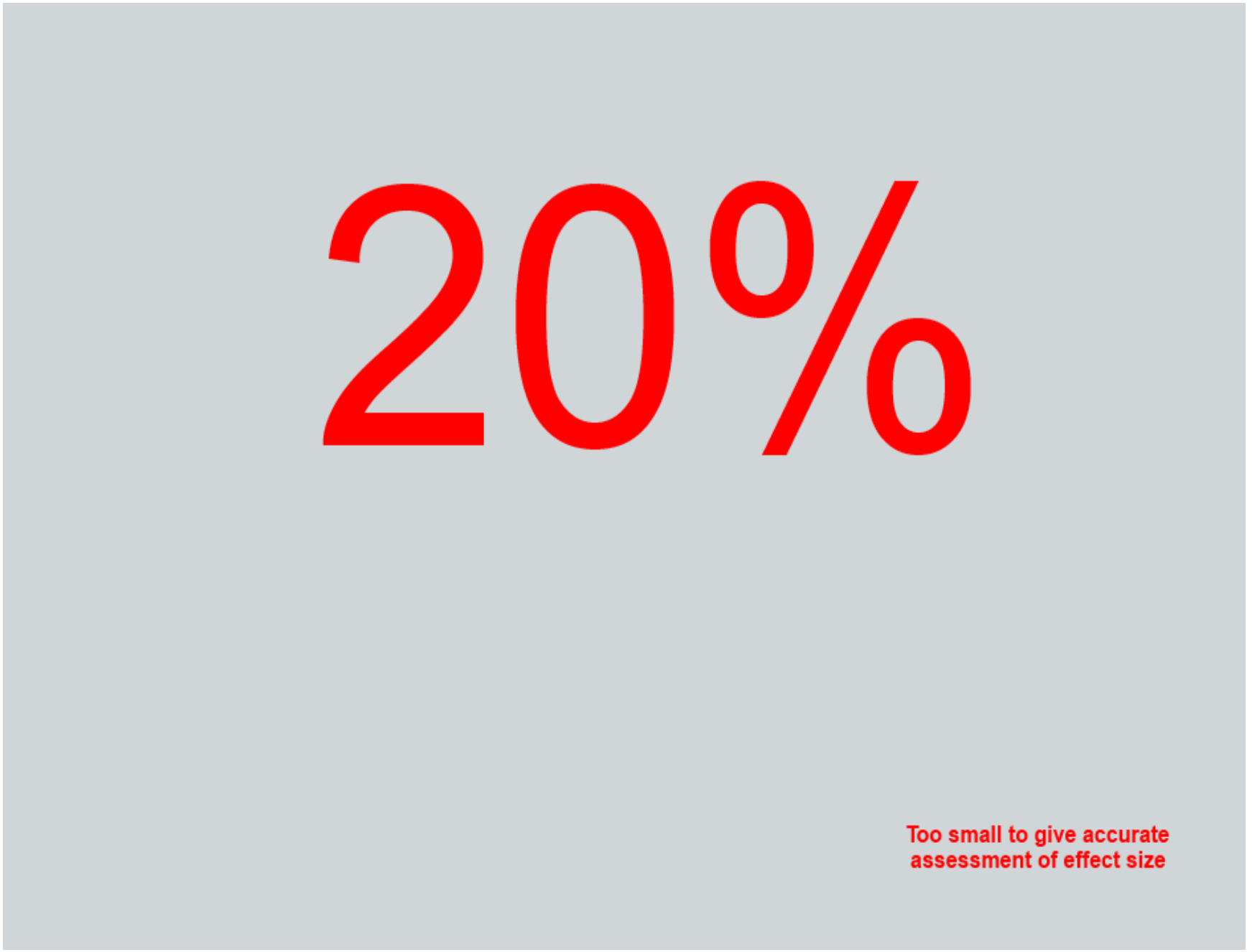

Systematic reviews
Not evidence based
Untenable
Absurd
Not fit for purpose
Unsustainable



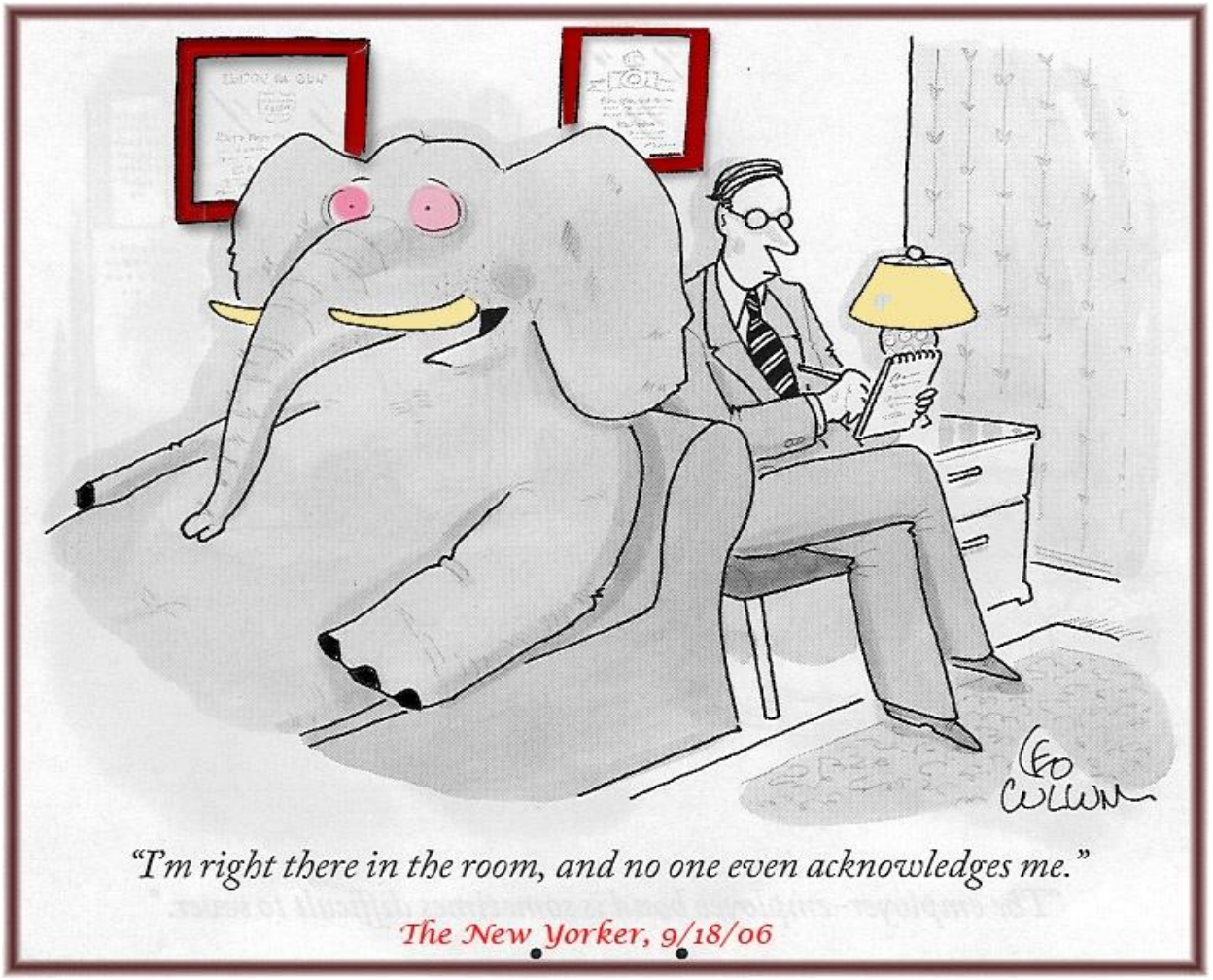
Sources: The Cochrane Library and Oversight Committee. Nov 14, 2012 and Annual Report and Financial Statements 2010/11



Sources: The Cochrane Library and Oversight Committee. Nov 14, 2012 and Annual Report and Financial Statements 2010/11


20%
Too small to give accurate
assessment of effect size

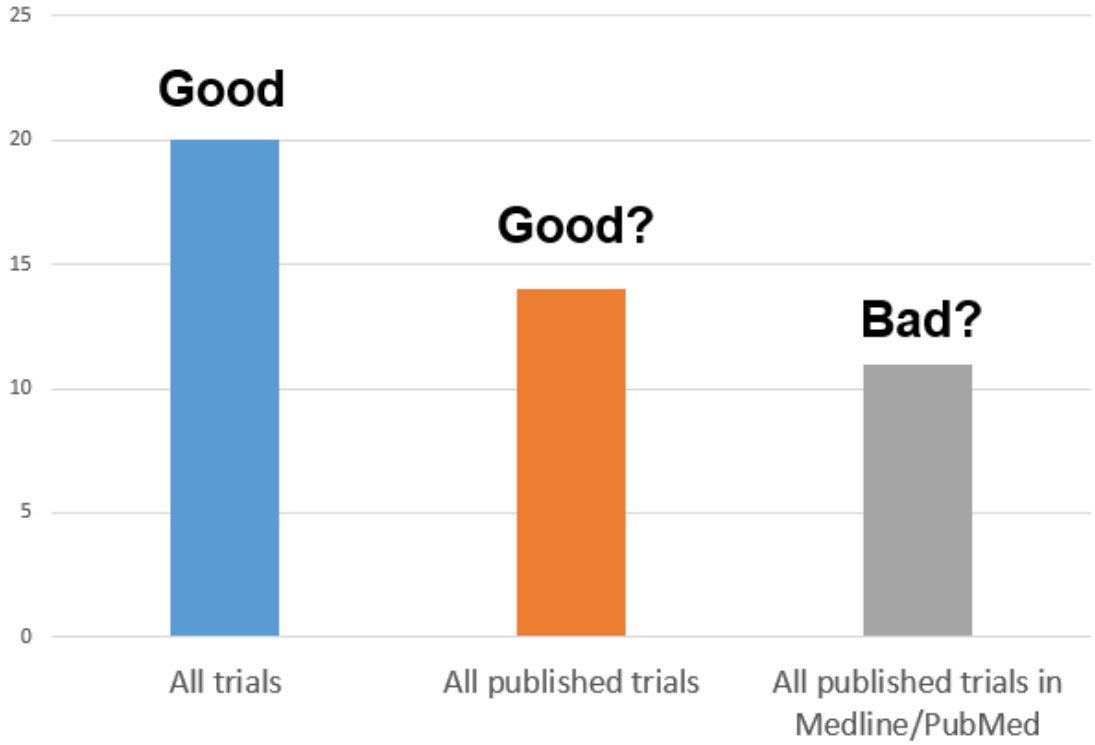
UNPUBLISHED TRIALS



"I'm right there in the room, and no one even acknowledges me."

The New Yorker, 9/18/06

UNPUBLISHED TRIALS



Schroll JB, Bero L, Gøtzsche PC.

Searching for unpublished data for

Cochrane reviews: cross sectional study.

BMJ. 2013 Apr 23;346

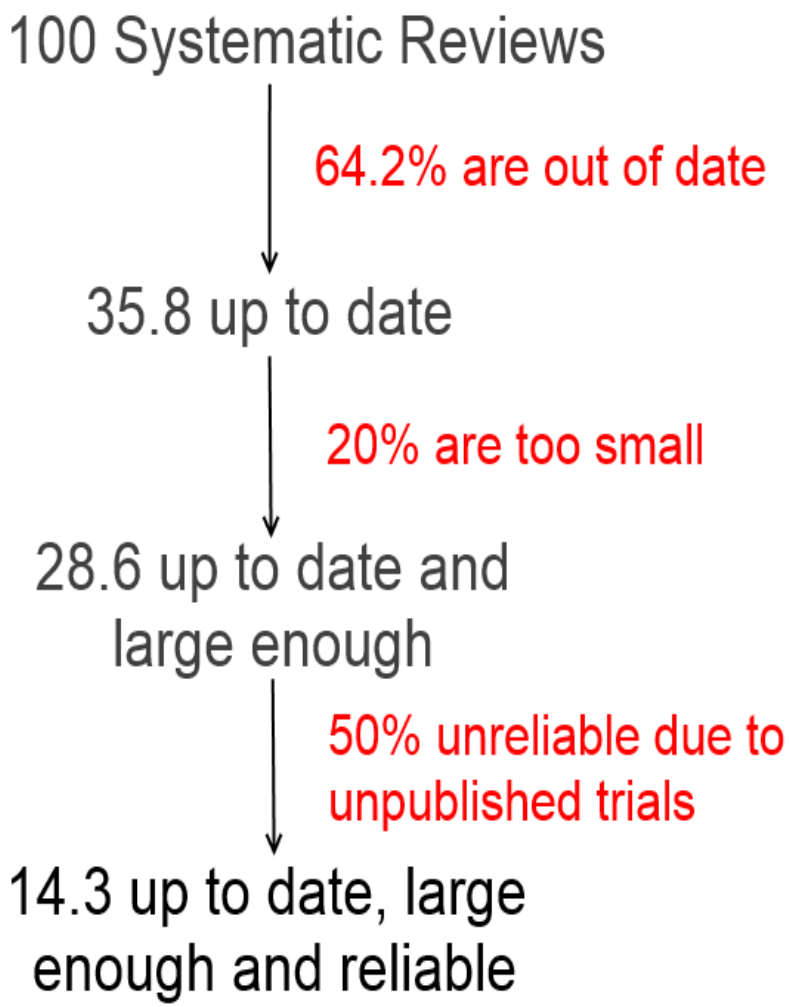
UNPUBLISHED TRIALS

- Turner et al. Selective publication of antidepressant trials and its influence on apparent efficacy. NEJM 2008
- Compared outcomes and effect sizes from published trials with those registered with FDA
- 31% of FDA-registered studies not published
- 37 v 1 – published v unpublished for +ve studies
- 3 v 33 - published v unpublished for -ve studies
- Overall 32% increase in effect size for meta-analyses of published trials versus FDA

UNPUBLISHED TRIALS

- Hart et al. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. BMJ 2011
- 42 meta-analyses for nine drugs across six drug classes were reanalysed
- 3/41 (7%) gave identical estimates of effect
- 19/41 (46%) showed lower efficacy of the drug
- 19/41 (46%) showed greater efficacy of the drug
- In ~50% of cases the difference was greater than 10%

50% unreliable


100 Systematic Reviews
64.2% are out of date
35.8 up to date
20% are too small
28.6 up to date and large enough
50% unreliable due to unpublished trials
14.3 up to date, large enough and reliable

YET MORE DATA

- **Year on year increase in number of RCTs being carried out**
- **AllTrials initiative**
- **Clinical Study Reports (Nordic Cochrane Centre)**


Tamiflu® 75 mg
capsules, hard
Oseltamivir
Roche
10 capsules
www.bmj.com/tamiflu

RESOURCE NEEDS TO BE MANAGED

Gatekeeper role before large resource expenditure:

- Outcomes relevant to patients
- Effect size likely to be clinically significant
- No forthcoming clinical trials

If 'worthy' need to decide which method:

- 'Standard' systematic review method
- More robust Tamiflu style SR based on CSRs or Individual Patient Data (IPD)

RAPID REVIEWS - SEMANTICS

Rapid v systematic

RAPID V SYSTEMATIC

Time-based?

5 minutes

1 day

1 week

1 month

1 year

Resource based?

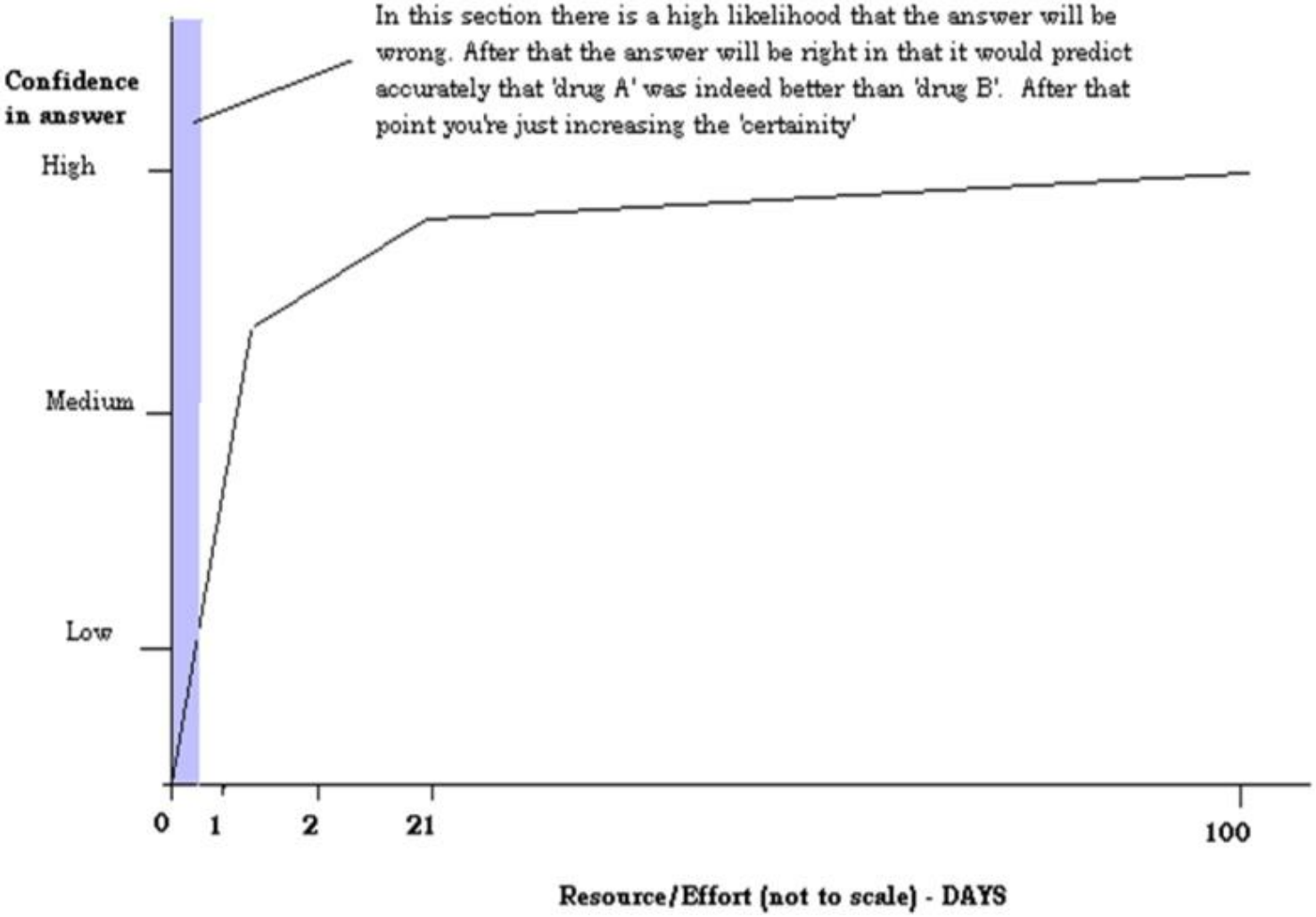
Number of databases

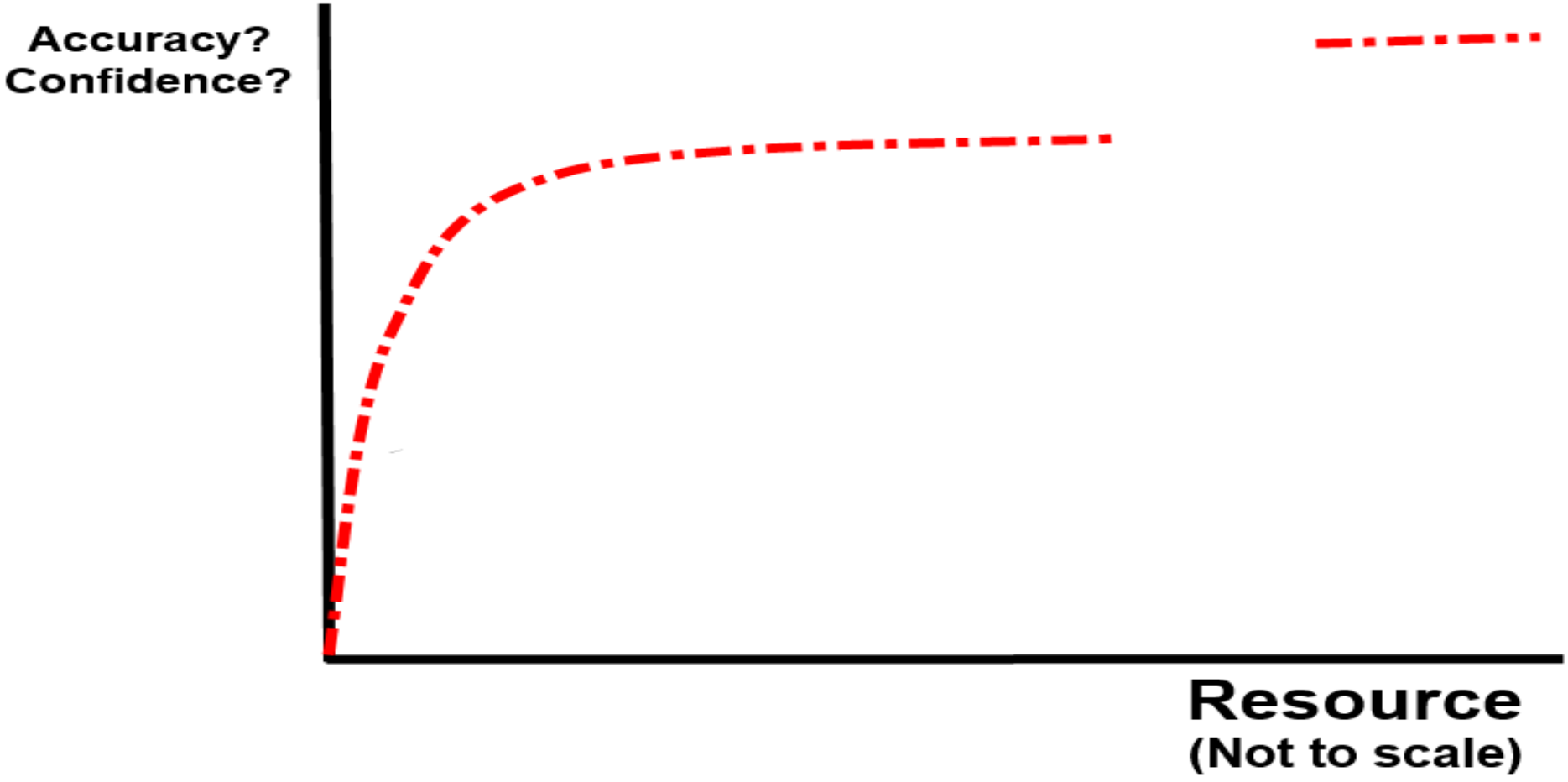
Bias detection

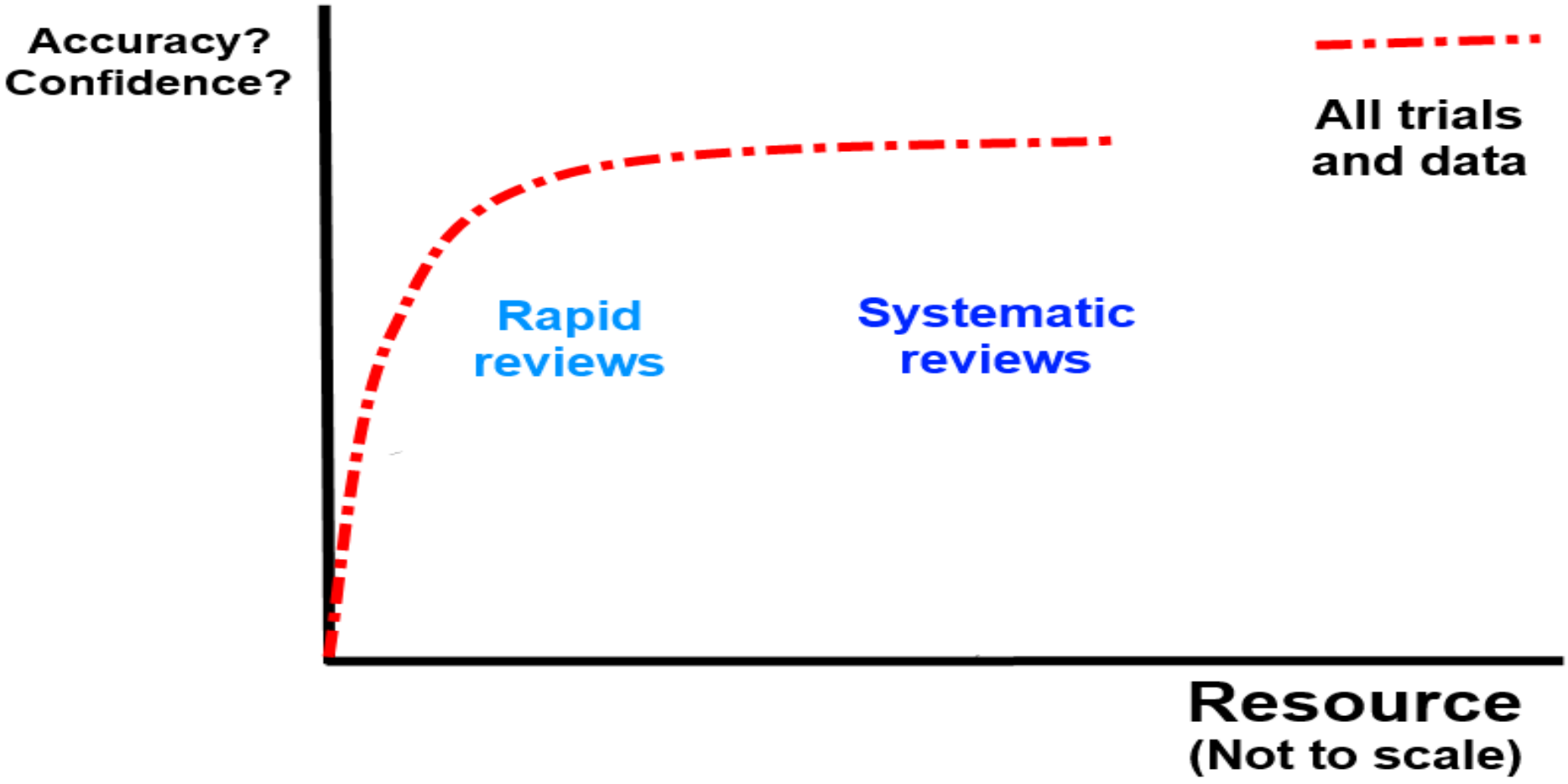
Level of synthesis

Cost

Certainly not ‘accuracy’


In this section there is a high likelihood that the answer will be wrong. After that the answer will be right in that it would predict accurately that 'drug A' was indeed better than 'drug B'. After that point you're just increasing the 'certainity'
Confidence in answer
High
Medium
Low
0
1
2
21
100
Resource/Effort (not to scale) - DAYS


Accuracy?
Confidence?
Resource
(Not to scale)


Accuracy?
Confidence?
All trials
and data
Rapid
reviews
Systematic
reviews
Resource
(Not to scale)

WHAT IS THE ANSWER?

WHAT IS THE QUESTION?

WHY ARE YOU DOING THE REVIEW?

1. Know if intervention A is better than intervention B
2. To quantify how much better A is over B
3. To see what research has been carried out before to avoid waste
4. Assess for adverse events

RAPID REVIEWS ARE PROBLEMATIC

- Semantics
- Diversity of methods
- Little evidence base to guide methods
- No obvious rapid review intellectual core
- Sometime poor perception

WHAT TO DO?

- Coordination
- Develop an intellectual core to guide development
- Develop robust, transparent methods
- Develop a clear narrative

MY INVOLVEMENT IN RAPID REVIEWS

- 4 hour manual rapid review
- Random selection of Cochrane systematic reviews
- Quick search of PubMed Clinical Queries
- Abstracts not appraised simply scored

  +2 = positive and significant

  +1 = positive

  0 = no clear benefit

  -1 = negative

  - 2 = negative and significant
- 85% agreement with Cochrane systematic reviews

WHAT ABOUT 5 MINUTE REVIEWS?

- Mirrored the previous approach but semi-automated it
- Used machine learning/sentiment analysis to learn what was a positive study and what was negative
- Also used machine reading to identify study size and adjusted the score accordingly
- Result = average score
- 85% agreement with Cochrane reviews

AUTOMATION – OTHER GROUPS

- Paul Glasziou 'The automation of systematic reviews', BMJ 2013
  - Citation analysis/matching
- EPPI Centre
  - Machine-learning assisted screening process
- Many others:
  - Auto-detection of effect sizes
  - Auto assessment for bias
- Typically follow the systematic review methods/principles
- All problematic

MACHINE LEARNING – CURRENTLY LIMITED

- The pooled NNT for response across all trials (as defined by a Clinical Global Impressions-Improvement score of 'very much improved' or 'much improved') for LDX vs. placebo was 3 (95% CI 3-4), and NNT for remission (as defined by 4-week cessation of binge eating) for LDX vs. placebo was 4 (95% CI 4-6). http://www.ncbi.nlm.nih.gov/pubmed/25752762?dopt=Abstract
- Treatment efficacy was better in the S-14 group than it was in the T-14 group in both the ITT analysis (number needed to treat of 12·0 [95% CI 7·2-34·5]; p=0·003) and PP analyses (13·7 [8·3-40], p=0·003). http://www.ncbi.nlm.nih.gov/pubmed/23158886
- Patients in the intervention group were nearly twice as likely to report at least a 30% improvement in their pain score by 12 months (51.7% vs 27.1%; relative risk, 1.9 [95% CI, 1.4 to 2.7]), with a number needed to treat of 4.1 (95% CI, 3.0 to 6.4) for a 30% improvement. http://www.ncbi.nlm.nih.gov/pubmed/25027139
- The number needed to treat (NNT) with FB-CBT vs FB-RT was estimated as 3.2 (95% CI, 2.2-5.8). http://www.ncbi.nlm.nih.gov/pubmed/24759852?dopt=Abstract

Allan Hanbury, Vienna University of Technology and lead for KConnect

"this is rather difficult"

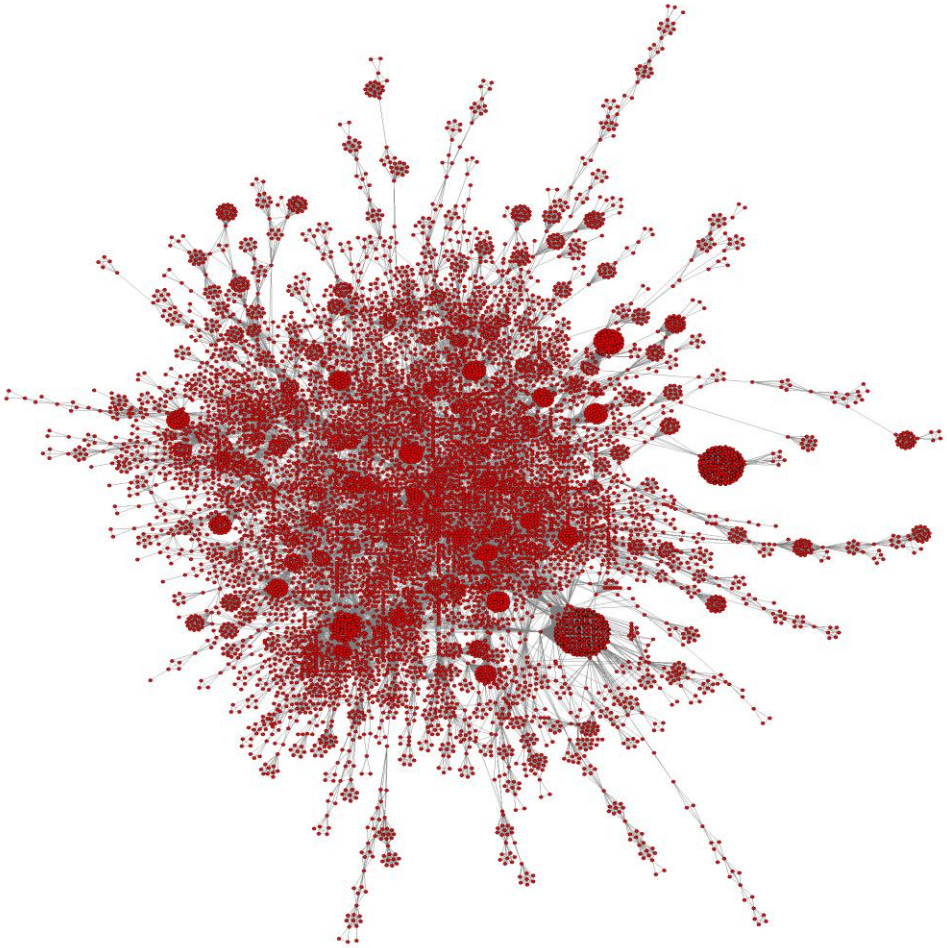
MOVING FORWARD

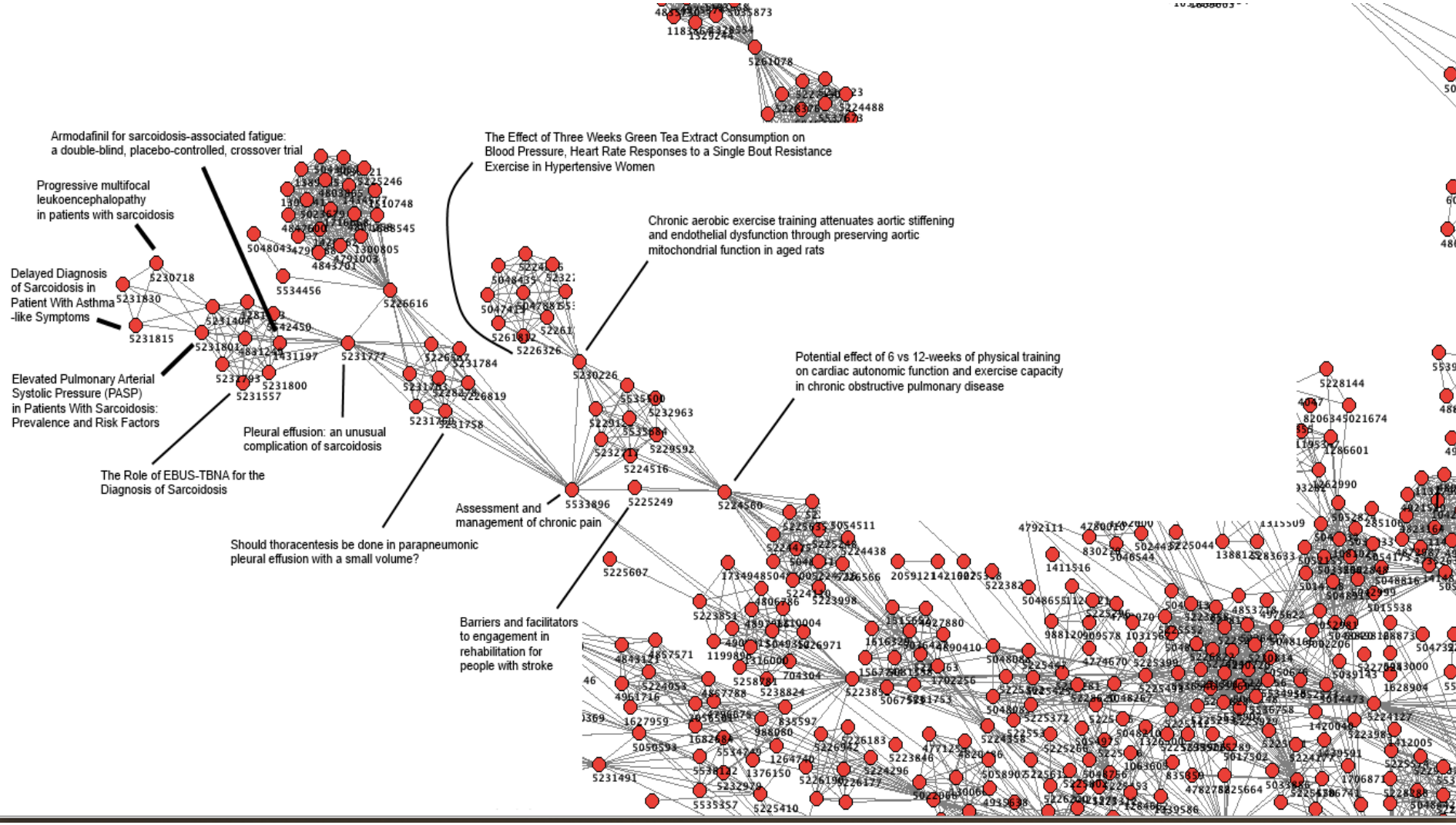
KCONNECT

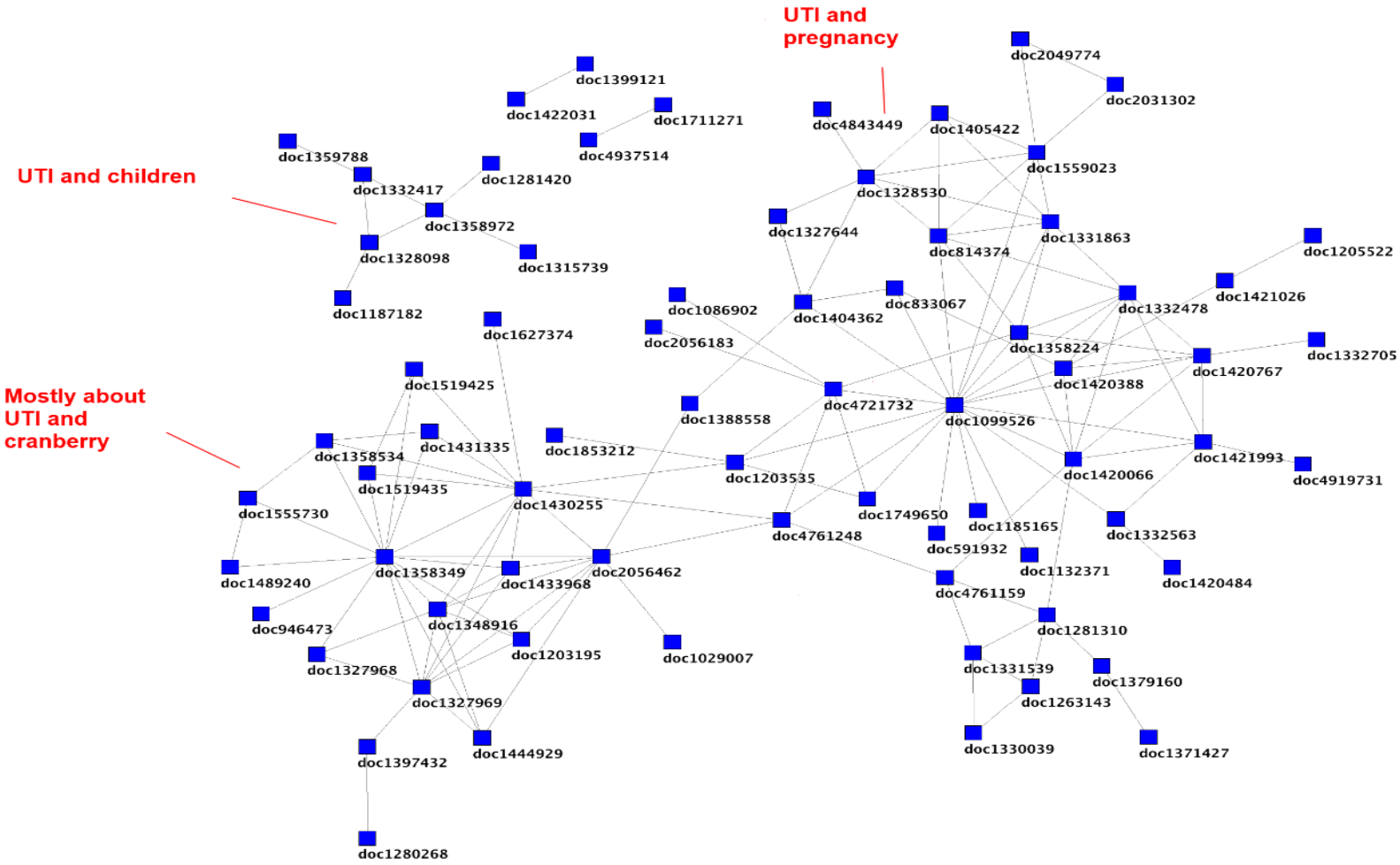
- EU Funded via Horizon 2020
- Improved methods including head-to-head trials
- Relatedness – 'auto aggregate' new studies with existing reviews
- Machine reading and semantic annotation of CSRs
- Multilingual

CLICKSTREAM DATA

- A user searches and clicks on documents 1, 4 and 5
- We say, for that user's **intention**, they are connected
- By aggregating these connections we can map the medical literature
- Structure is rich and relatively untapped




Armodafinil for sarcoidosis-associated fatigue: a double-blind, placebo-controlled, crossover trial
Progressive multifocal leukoencephalopathy in patients with sarcoidosis
Delayed Diagnosis of Sarcoidosis in Patient With Asthma -like Symptoms
Elevated Pulmonary Arterial Systolic Pressure (PASP) in Patients With Sarcoidosis: Prevalence and Risk Factors
The Role of EBUS-TBNA for the Diagnosis of Sarcoidosis
Pleural effusion: an unusual complication of sarcoidosis
Should thoracentesis be done in parapneumonic pleural effusion with a small volume?
The Effect of Three Weeks Green Tea Extract Consumption on Blood Pressure, Heart Rate Responses to a Single Bout Resistance Exercise in Hypertensive Women
Chronic aerobic exercise training attenuates aortic stiffening and endothelial dysfunction through preserving aortic mitochondrial function in aged rats
Assessment and management of chronic pain
Barriers and facilitators to engagement in rehabilitation for people with stroke
Potential effect of 6 vs 12-weeks of physical training on cardiac autonomic function and exercise capacity in chronic obstructive pulmonary disease


UTI and pregnancy
UTI and children
Mostly about UTI and cranberry
doc1399121
doc1422031
doc1711271
doc4937514
doc1359788
doc1332417
doc1281420
doc1358972
doc1328098
doc1315739
doc1187182
doc1627374
doc1519425
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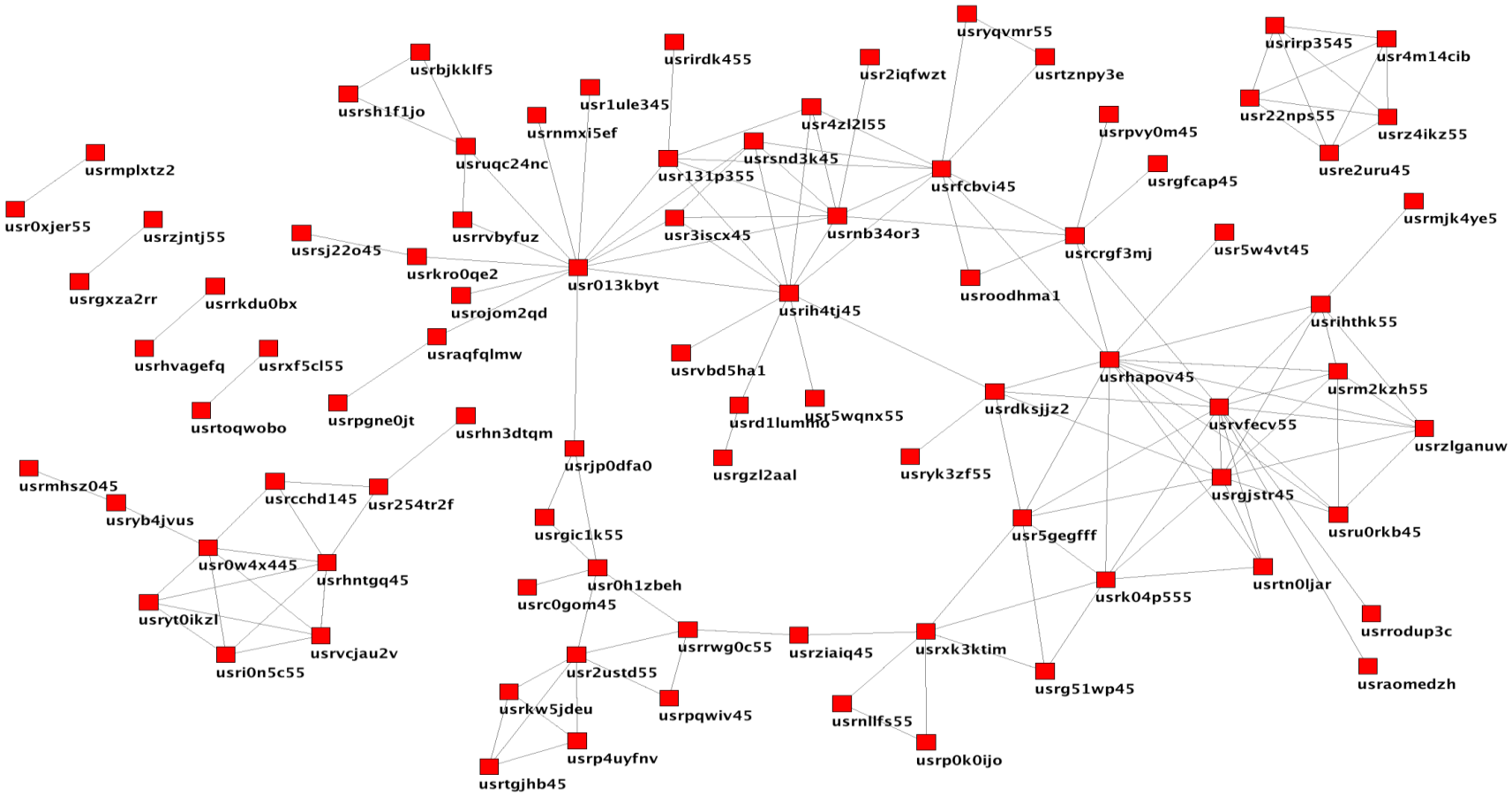
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usrrodup3c
usrrwg0c55
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usrxk3ktim
usrvcjau2v
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usr2ustd55
usrg51wp45
usraomedzh
usrkw5jdeu
usrpqwiv45
usrnllfs55
usrp4uyfnv
usrp0k0ijo
usrtgjhb45


PET Advance


Tuning:
Gain 2 (controls noise)
Clicks from last 785 days
User traffic Not logged in (85%)
Search for:
antibiotics
Search
= reordered text match
= click-related non-text match
Estimated improvement:
@ CTR dropoff 2 (typically about 2)
176.25 % (increase in integrated relevance*CTR)
Text Match Results:
Antibiotics
Antibiotics
Antibiotics
Antibiotics
COC and antibiotics
Antibiotics Ototopical
Antibiotics penicillins
Antibiotics for trachoma
Antibiotics in cat bites
Antibiotics for Sinusitis
Swine flu and antibiotics.
Antibiotics for sore throat
Antibiotics for sore throat
antibiotics in otitis media
Antibiotics for sore throat.
Antibiotics for acute asthma
Antibiotics for Animal Bites
Antibiotics for Otitis Media
Results enhanced by clickstream data
Natural results for our test system
Click-Through Filter Results:
4991388 Antibiotics for acute otitis media in children 1327489
1139696 Antibiotics in Acute Sinusitis 4975546
1099722 Antibiotics for sore throat 1404458
938645 Antibiotics for sore throat 1327299
1162923 Antibiotics for COPD Exacerbation 1081654
815158 Antibiotics for acute bronchitis 1327509
938647 Antibiotics for Animal Bites 1254916
1328227 Antibiotics for acute maxillary sinusitis 1327507
793524 Antibiotics for Sinusitis 1081662
1081662 Can UTIs be managed without antibiotics? 5623859
955554 Short-course antibiotics for acute otitis media 1327823
1404458 Antibiotics for sore throat. 5030518
1327299 Antibiotics for whooping cough (pertussis) 1329853
1162485 Antibiotics for acute otitis media in children. 4827461
5030518 Antibiotics for otitis media with effusion in children 1381026
1328583 Antibiotics for acute bronchitis 1404606
1254916 Antibiotics for Acute Bronchitis 1300700
Tuning:
Gain 2 (controls noise)
Clicks from last 785 days
User traffic Dentists (0.2%)
Search for:
antibiotics
Search
= reordered text match
= click-related non-text match
Estimated improvement:
@ CTR dropoff 2 (typically about 2)
139.34 % (increase in integrated relevance*CTR)
Text Match Results:
Antibiotics
Antibiotics
Antibiotics
Antibiotics
COC and antibiotics
Antibiotics Ototopical
Antibiotics penicillins
Antibiotics for trachoma
Antibiotics in cat bites
Antibiotics for Sinusitis
Swine flu and antibiotics.
Antibiotics for sore throat
Antibiotics for sore throat
antibiotics in otitis media
Antibiotics for sore throat.
Antibiotics for acute asthma
Antibiotics for Animal Bites
Antibiotics for Otitis Media
Results enhanced by clickstream data of dentists
Natural results for our test system
Click-Through Filter Results:
4991388 Antibiotics for acute bronchitis 1327509
1139696 Guideline Summary: Clinical practice guideline on acute bronchiolitis. ... 1411536
1099722 Preoperative antibiotics may decrease dental implant failure 1266300
938645 Interventions for replacing missing teeth: antibiotics at dental implan ... 1329661
1162923 Study suggests that systemic antibiotics are not necessary for single d ... 1411737
815158 Interventions for replacing missing teeth: antibiotics at dental implan ... 4793999
938647 Efficacy of prophylactic antibiotics for dental implants: a multicentre ... 1726219
1328227 Review suggests that antibiotics are beneficial for reducing failure of ... 4793573
793524 Antibiotics 4991388
1081662 Antibiotics 1139696
955554 Antibiotics 1099722
1404458 Antibiotics 938645
1327299 Improving diagnostic testing and reducing overuse of antibiotics for ch ... 527821
1162485 The application of ozone in dentistry: a systematic review of literature. 5121429
5030518 Evidence-based guidelines for cone beam CT for dental and maxillofacial ... 1410966
1328583 Review suggests that incomplete caries removal advantageous particularl ... 1411608
1254916 Effectiveness of prophylactic antibiotics at placement of dental implan ... 1644242

WHERE TRIP IS HEADING

- Personalised results
- Instant answers
- ‘Sensemaking’ of results
- Community to seek answers
- Sound business model

THE FUTURE

Exciting

Both for Rapid Reviews and Trip

IN CONCLUSION

- **Current methods for evidence synthesis are flawed**
- **Needs innovation and reflection**
- **Rapid reviews are a necessity**
- **There needs to be a coherent rapid review position including nomenclature**
- **Automation will be a huge help**
- **Trip hopes to play a leading role**

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