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Continuing Education

Reading systematic reviews to answer clinical questions

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ABSTRACT

Healthcare decisions need to be informed by reliable research. This requires practitioners to phrase clear questions when being faced with a knowledge gap, find the evidence that will best answer the question, critically appraise the evidence for validity and reliability and apply the findings to the unique setting. Systematic reviews are often the first point of reference when seeking healthcare answers.

This article provides a short guide on finding, reading and interpreting systematic reviews, as well as applying the results, illustrated by a clinical scenario (multiple micronutrient powders for health and nutrition in children under two years of age).

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1. Introduction

You are a healthcare professional working in a rural area. A woman and her 12-month old boy come for a routine check-up. She mentions that she has introduced solid food to the baby's diet, after having exclusively breastfed him for 6 months. His diet consists mainly of porridge, since the woman is a single parent on a low wage and cannot afford much. You are concerned about the risk of anaemia and enquire about the use of any form of vitamin supplements. She answers that she was told to give him iron drops at her previous visit, but that he does not like the taste and refuses to eat anything that contains the drops. So she stopped using the drops months ago. You remember that you have recently listened to a presentation on the use of powders containing iron and a variety of vitamins at a conference, and wonder whether the use of these micronutrient powders would be an effective way to supplement his diet, in order to

prevent anaemia. You decide to find out what research evidence exists before making recommendations about its use.

Which study should you be reading? Where will you find a suitable study? In the past you might have turned to expert opinion, a text book, or sought for a relevant study on MEDLINE. However, over the last 20 years, good evidence has emerged that expert opinion and text books, based on expert opinion, may be wrong and out of date. What is more, whilst one study may help inform your answer, it is important that decisions are made based on the totality of the evidence around a particular question. For this, you will need to access a systematic review of all relevant evidence, critically appraised and summarized. So skills in finding, reading, appraising and interpreting systematic reviews are critical to health professionals in staying up to date and using the best research evidence in their decision making.

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In the following article, using the scenario above as an example, we will attempt to answer these questions and provide you with a short guide of systematic reviews – what they are, why read them, where to find and how to read them.

2. What is a systematic review?

A systematic review is a study “in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method”.¹ The key characteristics of a systematic review include a clearly stated set of objectives with pre-defined eligibility criteria for studies; explicit, reproducible methodology; a comprehensive 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; and a systematic presentation and synthesis of the characteristics and findings of the included studies.^{2,3}

3. Why do we need to read systematic reviews?

Evidence-based medicine, according to David Sackett (1996) is “the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients”.⁴ It therefore means incorporating the current, best available evidence to help answer our questions in clinical practice. Systematic reviews are considered an excellent source of evidence, and are often the first point of reference when seeking healthcare answers.

4. Where does one start?

Before we can find an answer, we need to have a clearly formulated question. The five steps of evidence-based health care (EBHC) are a very helpful process when being faced with a knowledge gap: It requires us to ask an answerable question; access the literature to find an answer to this question; critically appraise the literature for validity and reliability; apply the results to our practice and lastly evaluate our practice.

Phrasing clear questions is a key first step. Structuring the question in a way that incorporates all the essential elements, helps us to find relevant information that can answer our question. A widely adopted format for phrasing questions is the “PICO” format, where the “P” stands for the population, patient or participant; the “I” for the intervention; the “C” for the comparison; and the “O” for the main outcome of interest.³

Thinking back to our scenario, the “PICO” would thus be:

P: 12-month old at risk of developing anaemia

I: routine supplementation with micronutrient powders containing minerals and vitamins

C: no routine supplementation

O: anaemia

The corresponding question would thus be: *In infants at risk of developing anaemia, does routine supplementation with micronutrient powders containing minerals and vitamins, compared to no routine supplementation, reduce the incidence of anaemia?*

In addition to the information about the population, intervention, comparison and outcomes (PICO) in questions, it is imperative that we are clear about the type of question we are asking. This is important since it will determine the type of primary study that will best answer our question. Since our question is a question on treatment or prevention, the best study design to answer this question would be a randomized controlled trial (RCT).

A systematic review is even more useful than the best single study to answer a question, since it aims to find all studies relevant to the question at hand. It therefore gives us a more holistic picture of the current evidence and the various studies that have been done. The most well-known and probably most commonly used, are systematic reviews of healthcare interventions, answering questions about effectiveness of medical interventions. Systematic reviews can also summarize other types of studies providing answers to questions of risk factors,⁵ diagnostic accuracy,⁶ incidence⁷ or prevalence⁸; and qualitative studies.⁹

Further examples of PICO questions and references to systematic reviews that can be consulted to answer these questions are presented in Table 1.

5. Where can we find systematic reviews?

After having phrased a clear question, we need to find the best available evidence. Since a systematic review is considered best evidence, we need to attempt to find one that would answer our question. If no systematic review is available, we can look then for single, primary studies that would answer the question.

When searching for systematic reviews, it is helpful to use the PICO elements as keywords, combining them with Boolean operators (AND, OR, NOT). Adding synonyms to the keywords will broaden the search and will decrease the chance of missing important studies.¹⁰

The *Cochrane Database of Systematic Reviews* is the best place to start looking for systematic reviews of healthcare interventions. We searched The Cochrane Library using the following keywords in our search: *infant AND (micronutrient OR vitamin) AND anaemia* and found the following systematic review:

De-Regil LM, Suchdev PS, Vist GE, Walleiser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD008959. DOI: [10.1002/14651858.CD008959.pub2](https://doi.org/10.1002/14651858.CD008959.pub2).¹¹

The TRIP database (www.tripdatabase.com) is another very useful database, since it filters the search according to synthesised (systematic reviews, guidelines) and primary research. It also allows you to enter the PICO components of your question in a very user-friendly manner.

Table 1 – Examples of questions, PICO elements and systematic reviews.

Question		PICO	
Type of question			
Intervention/ treatment	How effective are community-based intervention packages in reducing maternal and neonatal morbidity and mortality? ¹²	P	Women of reproductive age and pregnant women
		I	Intervention packages: additional training (other than the usual training) of community outreach workers
		C	Usual maternal and newborn care from local government and non-government facilities
		O	Maternal and neonatal mortality and morbidity
Intervention/ treatment	How effective is rifampicin monotherapy or rifamycin combination therapy compared to INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB? ¹³	P	HIV-negative people at risk of developing active TB (without active TB at the time of enrolment)
		I	Treatment with rifampicin or rifamycin-containing drug combinations (any dose or duration).
		C	INH monotherapy.
		O	Rate of active TB
Intervention/ prevention	How effective are rotavirus vaccines approved for use for preventing rotavirus diarrhoea in children living in low and middle income countries? ¹⁴	P	Children from low and middle income countries
		I	Approved rotavirus vaccines
		C	Placebo, no vaccine, or other vaccine
		O	Rotavirus diarrhoea
Diagnostic accuracy	How accurate is Xpert® MTB/RIF assay (Xpert) in detecting pulmonary TB in adults? ¹⁵ How accurate is Xpert® MTB/RIF assay (Xpert) in detecting rifampicin resistance in adults with a positive TB diagnosis? ¹⁵	P	Adult patients suspected of having pulmonary TB or MDR-TB, with or without HIV infection.
		I (index test)	Xpert® MTB/RIF assay (Xpert)
		C (reference standard)	Solid media and/or liquid culture system (for TB detection). Phenotypic drug susceptibility testing methods as recommended by the WHO
		O (target condition)	Active pulmonary TB and rifampicin resistance

6. How do we read and interpret systematic reviews?

Understanding the results of a systematic review is probably the most daunting tasks of all, but a little insight into how a systematic review is constructed can be very helpful in reading the review.

When reading a systematic review, you need to ask yourself the following:

1. Will this review answer my question?
2. Is the review well conducted?
3. What are the results of the review?
4. How do the results from this review apply to my patients?

For each of these, there are a number of additional questions that will help you along the way. We will go through each question to illustrate the process of critical appraisal, using the systematic review by De-Regil et al¹¹ as an example.

1. Will this review answer my question?

This key step is to assess whether the systematic review is addressing the question you are interested in. You therefore need to compare your PICO question to that of the systematic review. In this case, the objective of the review is to “assess the effects and safety of home (point-of-use) fortification of foods with multiple micronutrient powders on nutritional, health and developmental outcomes in children under two years of age”, which seems similar to the question we are asking.

Furthermore, detailed information about the study designs, participants, interventions, comparisons and outcomes of the included studies will also help you to decide whether the studies included in the review are appropriate to answer your question. You can then proceed in reading the systematic review.

2. Is the review well conducted?

Results should always be interpreted in light of the rigour of the methods used, which is why it is imperative to always look at how the systematic review has been conducted before accepting the results.^{16,17} Questions to guide this critique of the quality are detailed in Table 2.

If you feel that the authors addressed all the important issues and that this is a valid review, you can continue to read the results. Overall, the systematic review by De-Regil et al was well conducted and we can thus proceed to have a look at the results.

3. What are the results of the review?¹⁹

Characteristics of included studies

We need to start by orientating ourselves to the included studies. What is the description of the included studies – how many studies were included, where were the studies conducted, who were the included participants, how many participants were included, which interventions were used and which outcomes were assessed? The De-Regil review included eight trials with a total of 3748 participants – male and female

Table 2 – Questions to guide the critique of the quality of a systematic review.

Question	What would be the “gold standard?”
Did the authors register the title prior to writing the protocol?	There is currently a move to register all titles of systematic reviews, not only within the <i>Cochrane Collaboration</i> (where this is mandatory) but also for non-Cochrane reviews. PROSPERO (http://www.crd.york.ac.uk/Prospero/) is an international database of prospectively registered systematic reviews in health and social care. Registering a systematic review provides a comprehensive listing of systematic reviews, avoids duplication, and enables comparison of reported review findings with what was planned in the protocol.
Did the authors write a protocol?	A protocol should be completed and peer-reviewed before starting the review process. All protocols of <i>Cochrane Systematic Reviews</i> are peer-reviewed and published in <i>The Cochrane Library</i> .
Did authors explicitly pre-specify inclusion and exclusion criteria before conducting the study?	The inclusion and exclusion criteria should be made explicit at the protocol stage of the review.
Did the authors try to find all the relevant studies (both published and unpublished)? ○ Where did they search? ○ What search terms were used? ○ Did they have language restrictions?	The search strategy needs to be explicitly described. Search terms should be mentioned or listed in the appendix and should ideally be very sensitive, including keywords as text words, MeSH terms and synonyms. There should not be any language restrictions. Authors need to search at least three electronic databases, relevant conference abstracts, trial registries and dissertation databases. They should also make an effort to contact experts in the field, identify unpublished literature, and check reference lists of included studies. Hand-searching can also supplement the search.
How did authors select studies for inclusion?	Screening of studies should be done independently by at least two authors. This should be explicitly stated. The procedure authors followed in case of disagreement should also be described. Excluded studies should be listed, with the reason for exclusion.
How did authors extract data?	For every included study, data should be extracted independently by two authors, using a standardized data extraction form.
Did authors appraise the quality of included studies?	Authors need to state whether they critically appraised the quality of included studies. This includes judging the risk of bias in different domains, depending on the types of studies included in the review. For RCTs, which is the main study design that would be used to answer a question about treatment, authors need to judge the risk of: 1. Selection bias (whether there was adequate sequence generation and allocation concealment), 2. Performance bias (adequate blinding of participants and caregivers), 3. Detection bias (blinding of outcome assessors), 4. Attrition bias (rate of loss to follow-up and incomplete outcome reporting), 5. Selective outcome reporting and 6. Any other potential source of bias. Authors need to explicitly describe the procedure they followed in making judgements about risk of bias.
Did authors appropriately synthesize results?	Results of single studies can be synthesized in a meta-analysis, ¹⁸ if the studies are similar enough. If they are too heterogeneous (i.e. different), they should not be pooled and other ways of presenting results should be explored (e.g. table format, matrixes, narrative reporting).
How did authors interpret the results?	Authors should formulate appropriate conclusions when interpreting results.
Did authors declare competing interests? Did authors declare funding sources?	It is essential that all authors declare competing interests, as well as funding sources.
Is the review up-to-date?	The time period between the last search and the publication of the review should be reasonably small. Authors should also mention whether they are planning on updating the review as new trials emerge.

children ranging from 6 to 36 months of age. All included studies were conducted in low income countries in Asia, Africa and the Caribbean and tested a variety of multiple micronutrient powders, all including at least iron, zinc and vitamin A. Primary outcomes were: anaemia (included in all studies), iron deficiency, haemoglobin concentration, iron status, weight-for-age (Z-scores) and all-cause mortality.

Risk of bias of included studies

Next, we need to look at the risk of bias of included studies. If you are reading a Cochrane review, as in our case, the risk of bias will be summarized in risk of bias tables, illustrated in a figure and reported in the results section. It includes the judgement of the authors on every domain, for every study,

Fig. 1 – A forest plot taken from De-Regil.¹¹ Permission has been obtained to use Figure 1 in this article. Copyright © 2011 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

Explanation: Fig. 1

- 1: The intervention (MNP) and the control (no intervention/placebo)
- 2: The measure of effect used in the meta-analysis. For dichotomous outcomes, this is usually the risk ratio (RR) or the odds ratio (OR). For continuous outcomes, this can be the mean difference or standardized mean difference. This also shows what type of meta-analysis was done, in this case random-effects meta-analysis (as opposed to fixed-effect meta-analysis) and the 95% CI interval.
- 3: The individual studies included in the meta-analysis are listed on the left of the forest plot. Each study typically identified by the surname of the first author and the year of publication. The total amount of events (in this case deaths) and the total sample size per group, the weight of the study in the pooled result, as well as the point estimate and corresponding confidence interval is listed.
- 4: This is the line of no effect. For ratios (RRs and ORs), the line of no effect is at 1. This means, that there would be no difference between the effect of the intervention and the control. For mean differences this line would be at 0.
- 5: The result of each individual study is plotted on the graph. The square in the middle represents the point estimate of the effect and the horizontal line through the square represents the corresponding 95% CI. The length of the line represents the width of the CI: the longer the line, the wider the CI and the less precise the result. If this line crosses the vertical line of no effect, it means that the CI includes the measure of no effect (1 for ratios and 0 for differences) and that the result is not statistically significant. The size of the square represents how much weight the study has in the pooled result. This depends on the variance.
- 6: These are all the results for the individual studies presented graphically.
- 7: This is the pooled result for the outcome anaemia. This result (RR 0.69, 95% CI 0.60–0.78) means that the average risk for anaemia in children taking MNP supplements is 0.69 the risk of children taking placebo or no supplements. In other words, for the outcome anaemia, there is an average relative risk reduction (RRR) in anaemia of 31% in children taking MNP supplements when compared to children taking placebo or no supplements. The 95% CI of 0.60–0.78 shows that we can be 95% certain, that the average RR in the population (the “true” value) lies somewhere between 0.60 (i.e. a RRR of 40%) and 0.78 (i.e. a RRR of 22%). Since this interval does not include the value of no effect (in this case 1 for the RR), we can say that this is a statistically significant result.²⁰
- 8: The diamond is the graphical representation of the pooled result. The vertical apexes represent the pooled effect estimate (in this case the pooled risk ratio), while the horizontal apexes represent the corresponding confidence intervals. If the diamond touches the vertical line of no effect, the pooled result is considered as not being statistically significant.
- 9: If the results of the individual studies as well as the pooled result lie to the left side the vertical line of no effect, the values of the point estimates are less than the value of no effect, and in this case, favour the intervention. This way, by looking at the graph and without going into much detail, you have an idea of the direction of the effect.

10: If the results are plotted to the right of the line of no effect, the values of the point estimates are greater than the value of no effect, and in this case, favour the control or the placebo. Usually, this is written at the bottom of the forest plot.

11: Heterogeneity is reported with the help of the τ^2 , χ^2 and the I^2 statistic²:

- The τ^2 statistic is a measure of between-study variance in a random-effects meta-analysis. If this measure is greater than 1, it suggests the presence of substantial heterogeneity.
- The χ^2 test assesses whether observed differences in results are compatible with chance alone. A low P-value, usually less than 0.10, provides evidence of heterogeneity of intervention effects.
- The I^2 statistic quantifies inconsistency by describing the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. Guide for interpretation:
 - 0%–40%: might not be important
 - 30%–60%: may represent moderate heterogeneity
 - 50%–90%: may represent substantial heterogeneity
 - 75%–100%: considerable heterogeneity

In this forest plot, there is no evidence of the presence of significant clinical heterogeneity, ($\tau^2 = 0.01$; $\chi^2 = 6.17$ ($P = 0.29$); $I^2 = 19\%$) meaning that there is not much variation between the results of individual studies.

indicated as low risk of bias, high risk of bias, or unclear risk of bias where there was insufficient information to judge the risk of bias. The authors of this review judged all trials, except for

one, as having low risk of bias according to the pre-specified criteria. We would therefore be happy to continue reading the effects of the intervention.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Patient or population: children 6 to 23 months

Settings: community settings

Intervention: home fortification with multiple micronutrient powders

Comparison: placebo/no intervention

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Anaemia	RR 0.69 (0.60 to 0.78)	1447 (6 studies)	moderate ¹
Iron deficiency	RR 0.49 (0.35 to 0.67)	586 (4 studies)	high ²
Haemoglobin (g/L)	MD 5.87 (3.25 to 8.49)	1447 (6 studies)	moderate ^{1,3}
Iron status (ferritin concentrations in ng/mL)	MD 20.38 (6.27 to 34.49)	264 (2 studies)	low ^{1,4}
Weight-for-age Z-score	MD 0 (-0.37 to 0.37)	304 (2 studies)	moderate ^{1,5}
All-cause mortality	0	0 (0 studies)	None of the trials reported on this outcome.

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ One study (Adu-Afarwuah 2007) has serious risk of bias.

² Because of the consistent and large effect of the intervention RR 0.49 (95 % CI 0.36 to 0.67), we have refrained from downgrading because of the high risk of bias in one of the four studies.

³ There was considerable statistical heterogeneity attributable to one study (Lundeen 2010). However, because of the clear conclusion and consistency in the results, assessors chose to not downgrade.

⁴ There was imprecision in the results.

⁵ There was considerable unexplained statistical heterogeneity, but given the lack of clinical significance of the different results reported in the trials (i.e. all children are within the desirable Z scores), assessors chose to not downgrade

Fig. 2 – Summary of findings table, taken from De-Regil 2011.¹¹ Permission has been obtained to use Figure 2 in this article. Copyright © 2011 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

Effects of the intervention

When examining the results of a systematic review, we need to consider both the effect estimates e.g. risk ratios, mean differences (the numerical result); the confidence intervals (CI); and the presence of heterogeneity.

A forest plot (a graphical representation of the results) can be used to display the results of a meta-analysis. It displays the results of the single studies, as well as the pooled result. Fig. 1, illustrates and explains the main features of a forest plot¹¹ and looks at the results for the outcome: anaemia.

Quality of evidence

When interpreting the results, we not only need to look at the pooled effect estimate and the CIs, but in addition need to consider the quality of the evidence. We need to ask ourselves: How trustworthy are these results? More and more Cochrane reviews include a summary of findings table (SoF), like the one in Fig. 2, presenting all the results per outcome. The SoF table gives an overview of the main outcomes of the review; the relative effects and the corresponding 95% CIs; as well as the number of participants and studies included. In addition, it presents the quality of the evidence per outcome, using the GRADE approach which makes use of a transparent and explicit approach to rate the quality of evidence.²¹

GRADE describes four categories of evidence: high, moderate, low and very low quality of evidence (see Box 1).²² According to the GRADE approach, the quality of a body of evidence is rated across each outcome and can be downgraded due to study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence and likelihood of publication bias. GRADE evidence quality in a particular systematic review is specific to each outcome.^{23–27}

Box 1 GRADE definitions of quality of evidence level.²²

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Looking at Fig. 2, the SoF table of the De-Regil review,¹¹ we can thus interpret the results for the outcome *Anaemia* as follows: There is evidence of moderate quality that home fortification with MNP decreases the risk for anaemia in children by 31%, when compared to placebo or no

intervention. The confidence interval shows, that this reduction can lie anywhere between 40% and 22%. We also see that 1447 participants (in 6 studies) contributed to this result. Footnotes are used to provide reasons for downgrading the evidence. For the outcome *Anaemia* the footnote explains that the quality of evidence was downgraded because one of the studies had a high risk of bias.

4. How do the results from this review apply to my patients?

Now that we have interpreted the results, we need to consider whether we can apply it to the patients in our clinical setting. This requires us to consider a number of additional factors besides the epidemiological evidence. These include patient preferences and values, policy issues, availability and cost of the intervention, as well as individual clinical considerations like co-morbidities and disease profile.

Applying the results of systematic reviews in practice, or practising EBHC, is thus more than merely following a recipe. It requires critical thinking, sound clinical judgement and communication skills. In our scenario, we would need to consider, for example, the cost and affordability of the supplements; that the use of these powders requires hygienic preparation of food; and whether using the powder as a supplement is acceptable to the woman and her family – in addition to the current best available evidence.

7. Conclusion

When faced with a knowledge gap in clinical practice, systematic reviews are an excellent first point of reference. A well-conducted, up-to-date systematic review presents all the available evidence pertaining to a specific question and thus has the ability to give more reliable answers than single studies. Once you have familiarized yourself with the approach, the structure and the terminology of systematic reviews, they are likely to become indispensable to your practice.

Results of systematic reviews should be used to inform the healthcare decision making while considering patient's preferences and values, as well as your own clinical expertise when making decisions.

Conflicts of interest

All authors have none to declare.

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