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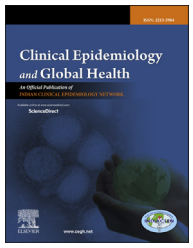

Commentary on Evidence Summaries

Evidence in health-care practice! Missing the forest for the trees?

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ABSTRACT

A Cochrane review (published in 2014) reported that daily therapy is comparable to intermittent therapy in children with tuberculosis. This is contrary to another systematic review (published in 2010) that included the same trials and dataset, based on which the World Health Organization recommended daily treatment in preference to intermittent therapy. This commentary explores the practical challenges involved in using secondary research (from systematic reviews) to inform decisions by various stakeholders in health-care. These include the technical and statistical jargon associated with systematic reviews, the distinction between reviews providing answers to clinical questions as opposed to decision questions, the place of 'tertiary research' to facilitate evidence-informed health-care, and the hierarchy within systematic reviews. A potential solution to overcome these challenges and enable stakeholders to use evidence to inform decisions, is to empower them with knowledge and skills to interpret such research, in parallel with its production and dissemination.

1. Introduction

The recent Cochrane review comparing daily versus intermittent anti-tuberculosis therapy in children[1] reported that there is no obvious difference between the two treatment regimens. The authors also highlighted the poor quality of individual trials, leading to this result. This review's conclusion is completely different from that published in a previous systematic review by another group[2] despite examination of the same trials and dataset.[3–6] The main reason for this difference has been explained in the Cochrane review[1] as an error in data extraction (and hence meta-analysis) by the authors of the previous systematic review.[2] In that respect, the Cochrane review[1] is a valuable addition to scientific literature and can be taken as the current best evidence on the subject.

The other obvious importance of the new review[1] relates to the guidance issued by the World Health Organization[7] in favour of daily treatment in children (based on the older systematic review). In fact, very recently (March 2014), the Government of India also has deliberated on the issue and is expected to issue a new guideline favouring daily treatment (D Behera, personal communication). This raises an interesting conundrum. Recent years witnessed an orientation in favour

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of intermittent treatment (through the DOTS strategy) rather than the traditional daily regimen (although this was probably for programmatic reasons rather than based on a careful examination of evidence).[8] If these guidelines were changed to favour daily therapy on the basis of the previous systematic review,[2] it follows that these could be flipped back since the new review[1] did not observe any difference between the two treatment regimens.

However, the real value of this review[1] is that it raises several interesting points to ponder over, although these go beyond the scope and reach of the review itself. Some of these are highlighted below.

2. Secondary research: clearing the fog or confusing the issue?

Secondary research (systematic reviews with or without meta-analysis) is designed (and expected) to facilitate scientifically valid conclusions to be drawn from primary research, in order to make evidence-informed decisions. As has been emphasized before,[9] such research addresses clinical questions (usually expressed in the famous PICO format), but not necessarily decision questions (i.e. what should I do?). In a well-developed health-care system wherein stakeholders (including health-care professionals, policy-makers and health-consumers) are empowered with knowledge and skills to understand the nuances of secondary research, the distinction between addressing clinical questions and decision questions is fairly clear. Such stakeholders are able to derive/deduce answers to their specific decision questions, from the evidence (secondary research) generated in response to clinical questions. In fact, the art of practicing evidence-informed health-care rests on this oft-neglected aspect.

In contrast, where stakeholders (at all levels) are not sufficiently empowered, secondary research appears too complicated to understand, and include into decision-making. Stakeholders may not recognize the distinction between answers to clinical (as opposed to decision) questions. In such situations, methodological refinements of the kind presented in the Cochrane review[1] and the distinction (more importantly the basis for the same) from the older systematic review[2] may be lost upon the stakeholders. Personal discussion suggests that this tends to drive them away from evidence-based practice altogether and instead fall back to the traditional 'experience-based' or 'eminence-based' systems of decision-making.

3. Tertiary research!

This creates the need for a unique brand of analysis that (for want of a better term) I'm going to call 'tertiary research', i.e. research and analyses conducted to demystify secondary research. Commentaries in response to this[1] and other systematic reviews could be considered under this category. On the one hand, this is a welcome step as it could lighten the fog for stakeholders who may lack the skill and time required to understand and interpret secondary research. On the other hand, since tertiary research sometimes involves data-mangling and interpretation-wrangling, there is the risk that personal bias(es) of individual tertiary researcher(s) could creep in. For example, the current Cochrane review[1] could be interpreted by one tertiary researcher as evidence supporting intermittent therapy (on the basis that it delivers similar effects as daily therapy). However, another could interpret that the available evidence is too limited in quality and quantity, to make a decision to change from current practice (and hence the status quo should be maintained). A third could successfully argue that the available trials are of low methodological quality and also not really comparable (in terms of trial inclusion criteria, type of intermittent regimen used and definition of the outcome), thereby precluding pooling them in a meta-analysis. All three arguments would be right and a tertiary researcher could pitch whichever aspect he/she prefers.

In short, tertiary research expressed in simplified terms has the potential to clarify matters, but can also reflect (perhaps amplify) the personal bias of the researcher. If this happens, would it be very different from the 'expert opinions' that currently form the bottom rung of the evidence hierarchy?

4. High quality evidence, but for whom?

At the end of the day, I believe that the key conclusion from this Cochrane review[1] is that current data are "insufficient to support or refute the use of intermittent twice- or thrice-weekly, short-course treatment regimens over daily short-course treatment in children with TB" (verbatim quote). This is of course wholly true, a point which was well-accepted even before the review was initiated (and hence the justification to undertake the review). The only difference is that a systematic approach (consuming considerable time, talent, energy, and funds) has been used to arrive at this conclusion, as opposed to a common-sense or gut-feeling (dare I say experience?) based approach.

Of course, we are now 'certain that we are uncertain' which points to the need for better quality primary research, followed by another round of secondary (and perhaps tertiary) research.

Experts in secondary and tertiary research could have a field day arguing over the subtleties in one or the other review.[1,2] For example, the Cochrane review[1] has reported an intention-to-treat analysis but in one trial[6] failed to include all the randomized subjects, in the denominator (on the grounds that many were randomized before obtaining consent and hence did not receive the intended intervention). Although the obvious selection bias was recognized in the Cochrane review,[1] some would argue that this is not enough and all randomized subjects should have been included in the analysis. Similarly, a four-way analysis including best and worst-case scenarios was not undertaken.

But ultimately how does all this help the physician who has to decide what to do in his/her practice; the policy-maker (Government, NGO, professional society) who has to choose either intervention for an entire health-care system; or the patient who has to choose between adhering (or not!) to a daily versus intermittent regimen?