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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.

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1. Introduction

The recent Cochrane review comparing daily versus intermittent anti-tuberculosis therapy in children¹ 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 group² despite examination of the same trials and dataset.^{3–6} The main reason for this difference has been explained in the Cochrane review¹ as an

error in data extraction (and hence meta-analysis) by the authors of the previous systematic review.² In that respect, the Cochrane review¹ 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 review¹ relates to the guidance issued by the World Health Organization⁷ 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 review¹ did not observe any difference between the two treatment regimens.

However, the real value of this review¹ 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.

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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 review¹ and the distinction (more importantly the basis for the same) from the older systematic review² 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.

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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 this¹ 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 review¹ 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?

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4. High quality evidence, but for whom?

At the end of the day, I believe that the key conclusion from this Cochrane review¹ 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 review¹ has reported an intention-to-treat analysis but in one trial⁶ 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?

5. Mirror , whose evidence is the fairest?

Given that the two reviews^{1,2} arrived at opposite conclusions despite peer review, it also raises the question about which evidence is superior (i.e. closer representation of the truth). In this case, the methodological error in the older review² and its correction in the new review¹ suggest that the latter is superior. Traditionally also, Cochrane reviews are accorded the greatest respect owing to methodological rigour that includes a stringent peer review process at every stage. In addition, there are other methodological refinements (representing data using different measures, intention-to-treat analysis, fixed effect and random effects models, sensitivity analyses etc).

However, two points are worth noting. Cochrane reviews are also not entirely free from errors, inconsistencies, discrepancies etc despite the multi-level peer review process. For example, in the present review,¹ one of the trials⁵ is described as having 137 participants (in the review text), whereas the meta-analysis shows 140! No doubt there would be an explanation for this apparent discrepancy, but the question is whether stakeholders reading the review would grasp it.

Recently a Cochrane review was withdrawn¹⁰ after nearly two years of publication when an error in data analysis was discovered, although it did not affect the conclusion. In contrast, another review¹¹ with errors in data analyses (that could alter the conclusions) was retained. This raises the second point viz the absence of a clear policy even within the Cochrane Collaboration to deal with errors reported/discovered after publication. If this is true, how would stakeholders judge the validity of published secondary research?

6. Evidence: what is appropriate and how much?

Systematic reviews evaluating interventions generally include only randomized trials (which are regarded as the best study design, least prone to bias), and exclude other study designs (on account of lower methodological quality). Following this pattern, the ‘current best evidence’¹ also includes RCTs, thereby ignoring other forms of evidence, albeit of lower methodological quality. But (as in this situation) should inferior quality RCTs really be considered superior to other inferior study designs?

In the case of daily versus intermittent tuberculosis treatment, it would appear that decisions affecting thousands, perhaps millions of patients (individual treatment decisions, health-system practice decisions, nation-wide policy decisions) are expected to be made from analyses of four trials in around 500 subjects.^{3–6} This raises questions specific to this review viz “Is the evidence enough?” as well as pertaining to all reviews viz: “How much evidence is enough?” Too little (as in this case) and we would clamour for more to make robust conclusions (and decisions). Too much and the ethical issue (of exposing people to an inferior intervention) becomes a challenge.

There is also the challenging issue of what the (secondary) research evidence actually means in real-life. Systematic

reviews (in general) deal with *efficacy* (and sometimes safety) of interventions, but not necessarily *effectiveness*. This distinction has been highlighted previously also¹² and is critically important because interventions should not only be efficacious (in research settings) but also effective in real-life settings. Assessment of the latter requires a careful consideration of additional issues like the health-care setting, feasibility, logistics and cost considerations of the intervention (and its alternatives), social aspects and other issues; that together now form an entirely distinct branch of science referred to as Health Technology assessment (HTA).^{12,13}

7. What is the way forward?

Perhaps the way forward lies in a single word: empowerment. Stakeholders including consumers of health-care require guidance, education and empowerment to understand the relevant points from primary and secondary research. Perhaps we need to focus our energies not only on production of systematic reviews, but also to create a milieu wherein these can be understood and applied by the end user. In other words, the emphasis should be on empowering ‘users’ and not only ‘doers’ (of systematic reviews). The advantage with this dual focus is that empowered stakeholders have the potential to stimulate better quality research (primary and secondary) by demanding answers to their decision questions, which would be addressed through the clinical questions in primary and secondary research.

Of course, tertiary research has the potential to address stakeholders’ needs to some extent, although it does not empower them in the manner desired. Further, unless methodologies are developed to eliminate the potential bias(es), such research could cut either way.

In the context of examining the ‘current best evidence’ from the Cochrane review on daily versus intermittent anti-tuberculosis therapy¹ and yet having difficulty in making a definite decision in favour of either intervention (as is the case with many such reviews), one wonders whether we might end up missing the forest for the trees!

Conflicts of interest

The author has none to declare.

REFERENCES

1. Bose A, Kalita S, Rose W, Tharyan P. Intermittent versus daily therapy for treating tuberculosis in children. *Cochrane Database Syst Rev*. 2014. <http://dx.doi.org/10.1002/14651858.CD007953.pub2>. Issue 1. Art. No.: CD007953.
2. Menon PR, Lodha R, Sivanandan S, Kabra SK. Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials. *Indian Pediatr*. 2010;47(1):67–73.
3. Kansoy S, Kurta N, Akit S, Aksoylar S, Yaprak I, Çalayan S. Superiority of intermittent-short course chemotherapy in

- childhood pulmonary tuberculosis. *Turk J Med Sci.* 1996;26(1):41–43.
4. Kumar L, Dhand R, Singhi PD, Rao KL, Katariya S. A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J.* 1990;9(11):802–806.
5. Ramachandran P, Kripasankar AS, Duraipandian M. Short course chemotherapy for pulmonary tuberculosis in children. *Ind J Tuberc.* 1998;45:83–87.
6. Te Water Naude JM, Donald PR, Hussey GD, et al. Twice weekly vs. daily chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J.* 2000;19(5):405–410.
7. World Health Organization. *Rapid Advice. Treatment of Tuberculosis in Children.* Geneva: World Health Organization; 2010.
8. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. <http://libdoc.who.int/hq/2006/WHO.HTM.TB.2006.371.eng.pdf>.
9. Mathew JL, Singh M. Evidence based child health: fly but with feet on the ground!. *Indian Pediatr.* 2008;45:95–98.
10. El Dib R, Mathew JL, Martins RH. WITHDRAWN: interventions to promote the wearing of hearing protection. *Cochrane Database Syst Rev.* 2013 Nov 13. <http://dx.doi.org/10.1002/14651858.CD005234.pub6>. Issue 11. Art. No.:CD005234.
11. Lassi ZS, Haider BA, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. *Cochrane Database Syst Rev.* 2010. <http://dx.doi.org/10.1002/14651858.CD005978.pub2>. Issue 12. Art. No.:CD005978.
12. Mathew JL. Beneath, behind, besides and beyond evidence-based medicine. *Indian Pediatr.* 2010;47:225–227.
13. Mathew JL. KNOW ESSENTIALS: a tool for informed decisions in the absence of formal HTA systems. *Int J Tech Assess Health Care.* 2011;27:139–150.