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# Cochrane reviews in neonatology: Past, present and future

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## KEYWORDS

Meta-analysis;  
Review;  
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**Summary** The Neonatal Review Group of the Cochrane Collaboration is dedicated to improving outcomes of newborn infants through the collection and synthesis of the highest quality evidence. Much has been achieved with limited resources. Future challenges for the group are to maintain and extend current reviews of therapeutic interventions, to develop bridging reviews to assist clinicians in applying current evidence more easily, to expand the scope of the Cochrane Library to include diagnostic tests, and to utilize techniques such as prospective meta-analysis to answer remaining questions in the field. In future, the Neonatal Review Group needs to assist reviewers in developing countries to prepare reviews relevant to their settings that will reduce the global burden of neonatal mortality and morbidity.

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'Those who cannot remember the past are condemned to repeat it' George Santayana

## The past

### Archibald Cochrane (1909–1988)

Best known as an epidemiologist, Archie Cochrane had several careers preceding the publication of his landmark book *Effectiveness and Efficiency – Random Reflections on Health Services*. He served in the Royal Army Medical Corps in World War II and was a POW Medical Officer in Greece and Germany. Undermanned and with little equipment or

drugs, he was surprised at the low mortality rate in the camps from severe epidemics of typhoid and diphtheria. He realized that the natural defences of the human body and its recuperative powers relegated his own interventions to somewhat diminished importance. Indeed, he later worried that he 'shortened the lives of some of my friends by unnecessary intervention'.<sup>1</sup> His frustrations at his own inability to separate effective from harmful therapy evolved later in life (when such knowledge existed) to the simple principles underpinning the Collaboration named in his honour. In brief, he suggested that in providing health care we should allocate our limited resources fairly and wisely. The idea that randomized controlled trials provided more reliable information about therapies than other sources of evidence was central to this paradigm. It was in response to his well-known statement that 'It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically of

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all relevant randomized controlled trials',<sup>2</sup> that the Cochrane Collaboration was established.

### William Silverman (1917–2004)

Bill Silverman is acknowledged as the father of evidence-based newborn care. He recounted a time prior to the mid-1940s when 'neutral' care of preterm infants was the standard.<sup>3</sup> This consisted of warmth, protection from infection and careful feeding, and was performed predominantly by nurses. The 'let's try it and see' era that followed allowed he and other doctors to have a greater role in the care of premature babies. After some spectacular successes such as penicillin for congenital syphilis, the uncritical acceptance of novel therapies ultimately proved disastrous. Silverman describes an era of optimism where many new therapies were embraced without proper evaluation. In his book *Retrolental Fibroplasia: A Modern Parable*<sup>4</sup> he described the quintessential example of an untested, biologically plausible treatment: unrestricted supplemental oxygen therapy. This was almost universally used for a decade before the definitive randomized trial was performed demonstrating that this practice was responsible for tens of thousands of cases of blindness in surviving preterm infants.<sup>4</sup> As a result of this and similar experiences with other interventions, Bill Silverman became the first advocate for randomized trials in neonatal medicine. He believed that, by insisting on higher levels of evidence before widespread uptake of novel therapies, the mistakes of earlier eras could be prevented. Silverman credits one of his teachers, Richard Day, with the best answer to any of his questions: 'I don't know'. This answer provides the starting point for all clinical trials. Silverman met contrary opinion in a variety of forms: 'your trials are so boring', 'randomized trials never proved anything; all we need to do is to study the chemistry of ...'.<sup>5</sup> Nevertheless he continued to prick the consciences of clinicians and researchers until the time of his death, when he declined dialysis for renal failure saying, 'it would be an unethical waste of resources to prolong my death in this way'.<sup>5</sup>

### John Sinclair (1933–)

A pupil of Silverman, Jack Sinclair was the inaugural coordinating editor of the Cochrane Neonatal Review Group. Before The Cochrane Library was the textbook *Effective Care of the Newborn Infant*.<sup>6</sup> In the words of Bill Silverman, Sinclair and co-editor Michael Bracken 'came to the rescue of beleaguered neonatologists and bewildered parents by organizing this remarkable volume at a time when it is sorely needed'.<sup>3</sup> Following Iain Chalmers' establishment of The Oxford Database of Perinatal Trials, and in the tradition of *Effective Care in Pregnancy and Childbirth*,<sup>7</sup> the textbook focused on evidence of effectiveness and safety derived from randomized trials. As well as synthesizing evidence in a format useful to clinicians, the book sought to identify gaps in knowledge in order to stimulate future research endeavours.

The book was unusual in that it had its own 'methods section', describing not only the statistical methods used to combine trials and present data but the search strategy undertaken to locate all relevant studies and the criteria by

which validity of primary studies was assessed. The methods used in *Effective care* formed the basis of those used in the neonatal module of the Cochrane Library. In summary, these are as follows.

- All relevant trials should be included, i.e., the search strategy should be as broad as possible; searching for trials that have not been published in full through the proceedings of conferences and hand-searching journals supplement the usual MEDLINE search.
- Validity of studies should be assessed. Attention is given to blinding of the randomization process, blinding of the intervention, completeness of follow-up, and blinding of the outcome measurement. The key criterion used for trial inclusion is blinding of randomization.
- When appropriate, the results of individual trials should be combined to produce a point estimate of treatment effect along with a measure of the uncertainty surrounding this point estimate, the 95% confidence interval. Thus for categorical outcomes relative risk, risk difference and number needed to treat are used, and for continuous outcomes weighted mean differences are calculated.

With the advent of the Cochrane Library, an additional level of quality control was added. Prior to undertaking a review, authors are required to publish a protocol for that review. In the protocol, the reviewer specifies the objectives of the review as an explicit, focused research question identifying the population, the intervention, and the outcomes (both beneficial and harmful) of interest. The reviewer also sets out not only a main objective but also secondary objectives: for example, subgroup analyses or analyses of sources of variation in the results of the primary studies. In this way methods-driven Cochrane reviews were set apart from results-driven conventional reviews.

### The present

'Look not mournfully into the past. It comes not back again. Wisely improve the present. It is thine. Go forth to meet the shadowy future, without fear.' Henry Wadsworth Longfellow.

The Cochrane Collaboration was founded in 1993, and the Neonatal Review Group was registered in the same year. The founding editors Jack Sinclair, Michael Bracken, Roger Soll and Jeffrey Horbar are supported by the review group coordinator, Diane Haughton. Four regional coordinators have been added to the review group to enhance recruitment and training of reviewers in Europe and Australasia. The Neonatal Review Group is generously supported by the National Institute of Child Health and Human Development.<sup>a</sup> The Australasian Co-ordinating Network for The Cochrane Neonatal Review Group is supported by a grant from the Australian Department of Health and Aging.

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The Cochrane Library is published four times a year on CD and on the internet. Residents of several countries – including Australia, Denmark, England, Ireland, Norway, Sweden and Wales – can access the Library free through a 'national provision'. Several initiatives provide free access in Latin America, the Caribbean and low-income countries.<sup>8</sup> The Cochrane neonatal reviews can also be accessed on a website maintained by the NICHD.<sup>9</sup>

From a small base, the number of protocols, reviews and updates published by the Neonatal Review Group has grown steadily over the past 8 years (Fig. 1). Reassuringly, the growth of each has advanced in parallel, i.e., in general there is timely conversion of protocols to reviews and updating of existing reviews. The continued growth in the number of protocols means that new questions continue to be asked and reviewers have not yet exhausted the topics to be addressed.

Recruitment of reviewers has predominantly occurred in Australia, North America and the United Kingdom (Table 1). However, the geographic base is broadening and now includes 288 reviewers from 18 countries, including Africa and Asia.

Review of progress in 2003 noted that the distribution of review topics strongly favoured topics relating to therapy for respiratory disorders, and neglected such common issues as jaundice and parental attachment.<sup>10</sup> This disparity continues in 2005. In Disk Issue 3 2005, of the 263 reviews and protocols, 33 relate to mechanical ventilation, and 15 to respiratory distress syndrome, whereas there are only single reviews for developmental care and promoting parental attachment. The majority (145/263) of topics specifically focus on preterm infants, and many of the remainder also deal with management in the neonatal intensive care unit.

## The future

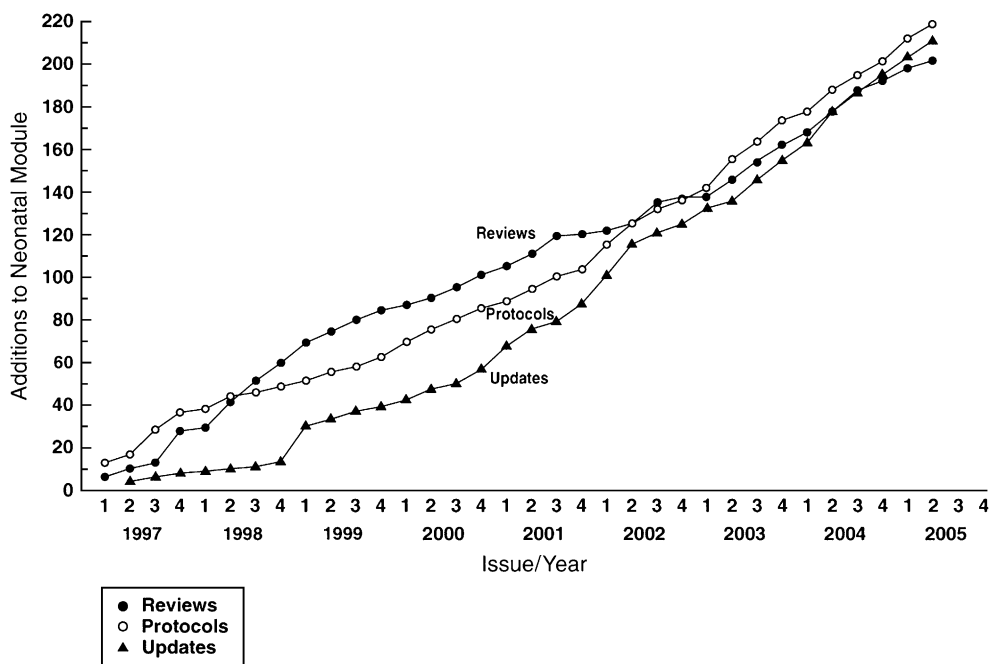
When you make a mistake, don't look back at it long. Take the reason of the thing into your mind and then look forward. Mistakes are lessons of wisdom. The past cannot be changed. The future is yet in your power.  
Hugh White (US politician, 1773–1840)

The field of neonatology is comparatively young but one in which important 'mistakes' have been made. Response to these mistakes drives the neonatal review group. The mistakes are of two types: first, that exemplified by the oxygen toxicity story related earlier – the error of widespread acceptance of an uncritically evaluated treatment which ultimately proved harmful; and second, the error illustrated by the Cochrane logo, the delayed implementation of an effective therapy (antenatal corticosteroids for the prevention of respiratory distress syndrome). The challenge for the future is to avoid these errors, obvious in hindsight but much less easy to identify in the hurley-burley of day-to-day clinical practice.

## Maintenance of existing material

### Volume of work

Reviews are useful only if they are both accurate and up-to-date. An advantage of the Cochrane Library's structure is that errors in reviews can be corrected and new data included in the regular 3-monthly updates. However, this process is time-consuming for both reviewers and editors, and the demands will only increase in the future. Although some salary support is provided for the coordinating editors, co-editors, review group coordinators and other staff, none is provided for reviewers or regional



**Figure 1** Growth in output of the Neonatal Review Group of the Cochrane Collaboration. Cumulative numbers of new protocols for reviews, new reviews, and updates of existing reviews, by Cochrane Library disk issue and year from 1997 to Issue 3, 2005.

**Table 1** Nationalities of neonatal review group reviewers

Australia	96
Canada	44
France	1
Germany	1
Hungary	1
India	1
Ireland	3
Israel	1
Italy	2
Malaysia	5
Netherlands	4
Nigeria	2
Spain	3
Sweden	1
Switzerland	6
UK	66
Uruguay	6
USA	46
<i>In addition, new reviewers with assigned titles from:</i>	
China	
Saudi Arabia	
Pakistan	
Brazil	

coordinators. Contributions are made on a voluntary basis, presumably driven by the contributor's sense of the importance of the work. Most reviews are performed by clinicians and are fitted in between clinical duties. Formal recognition of the worth of reviews has been slow in developing. In the past, systematic reviews were seen as lesser publications rather than hypothesis-driven research projects with well-developed methodology and clinically important conclusions. It is no coincidence that the country with the most neonatal reviewers, Australia, has formalized recognition of Cochrane reviews in at least two areas. First, the subcommittee on neonatal/perinatal training within the Royal Australasian College of Paediatrics recommends that at least one of three required projects for specialist recognition be a Cochrane review. This is mutually beneficial; the trainee gains experience in a structured, high-quality research project and a quality publication, and the Cochrane neonatal group gains a (young) reviewer capable of maintaining the review for many years! Second, within Australian universities, Cochrane reviews are now recognized as publications of equal value, for the purposes of academic advancement, as other original research published in high-quality hard-copy journals. A concerted effort has been made to involve every neonatal intensive care unit in Australia. This has largely been achieved, with 18 of 22 units having at least one reviewer on site.

#### Aging reviewers and editors

More than a decade into its existence, the Cochrane Collaboration faces the first generational change in its reviewers and editors. As retirements occur it is vital that individual reviews continue to be maintained either by other members of the original authorship team or recruitment of new reviewers to that team. How the review groups handle this recurring problem in its first iteration

will determine the pace of expansion and the quality of the Cochrane Library in the future.

### Enhancing and expanding the neonatal module

#### More reviews

The list of topics and the way in which they are organized are based on the structure used more than a decade ago in *Effective Care of the Newborn Infant*.<sup>6</sup> This structure has served the neonatal module well, but inevitably must change as new interventions are tested and old interventions are used for different indications and in new combinations. For example, nasal continuous airway pressure (NCPAP) has re-emerged as a primary mode of respiratory support and a potential alternative to endotracheal intubation. Combinations of NCPAP with early surfactant and nitric oxide have been tested. Different devices delivering NCPAP have been developed and compared. Many subtly different modes of triggering and targeting ventilation parameters have emerged and will continue to proliferate as clinicians try to reduce the damage caused by ventilating fragile premature lungs. At present new titles are determined largely by potential reviewers themselves who locate gaps in the module's coverage. Until now there has been no attempt to systematically identify new topics by surveying the basic science literature and presentations at scientific meetings. By doing so the neonatal module could anticipate developments in the field and structure the topics accordingly. The fundamental benefit of formulating a protocol before evidence is published would strengthen reviews and guide researchers planning further trials in the area.

#### Setting the research agenda

The role of the Cochrane Library in synthesizing existing evidence for clinicians is matched in importance by its less obvious role in identifying gaps in existing knowledge and thereby guiding researchers to important questions. It is common for young reviewers to be disappointed at the end of the review process when the conclusion 'more evidence is required' is reached. This may be seen in a positive light: after surveying the existing evidence a reviewer is in an ideal position to identify important characteristics of future trials, particularly focusing on outcome measures that will be important to clinicians considering a novel therapy, or an existing therapy that remains to be fully evaluated.

#### Making reviews more user-friendly

Whenever a new topic is considered, a question is posed; should the topic be broad or narrow? There are advocates for both approaches, resulting in two camps, 'lumpers' and 'splitters'. A narrow review has the advantages that it is both easier to prepare and easier to read. However, when this approach is followed multiple reviews are required, sometimes duplicating effort and resulting in less informative reviews. Lumping aspects of a topic into a single review adds to the complexity of the review for the authors and readers but may provide a more comprehensive overview. In most cases the neonatal review group has chosen the simplicity of multiple, narrow reviews. Thus there are individual reviews on each permutation of aspects of surfactant treatment; prophylaxis and treatment, natural and synthetic formulations, multiple and single doses.

While simpler from a scientific point of view, busy clinicians are left with considerable work to do to determine best practice for their patients in this field. Similar issues exist in the areas of postnatal corticosteroids, methyxanthine therapy, and therapy for a patent ductus arteriosus. The concept of 'bridging reviews' has been advocated in order to bring together information on a particular disease process or specific therapy in a user-friendly fashion.

## Extending the scope of the collaboration

### Diagnostic tests

To date, the Cochrane Collaboration in general, and the neonatal review group in particular, have confined their reviews to topics of controlled trials of therapies. Since therapy should follow diagnosis, and as misclassification of patients may lead to inappropriate therapy, it is vital that diagnostic tests are as rigorously scrutinized as interventions. The first protocol for a review of diagnostic utility with health outcomes – routine screening by echocardiography to reduce morbidity and mortality from congenital heart disease in neonates with Down syndrome – was published in Issue 3, 2005, of the Cochrane Library.<sup>11</sup> There are many diagnostic tests in modern neonatology that demand similar evaluation. It seems logical to begin with commonly performed tests such as clinical examination to determine correct endotracheal tube position, clinical and echocardiographic diagnosis of patent ductus arteriosus, new (cytokines) and old (full blood examination) tests for detecting sepsis, and new (MRI) and old (ultrasound) brain imaging techniques. Eager reviewers will be kept fully occupied for many years to come!

### Prospective meta-analysis

Conventional systematic reviews are by nature retrospective. They include trials that have been completed and usually published. In spite of the protection afforded by the protocol phase of a review, it is possible that knowledge of the results of individual trials may influence the framing of questions, the subjects included, and the outcomes assessed. Prospective meta-analysis (PMA) is a meta-analysis, usually of randomized controlled trials, which were identified, evaluated and determined to be eligible before the results of those trials became known.<sup>12</sup> It is a technique that has already been used in cardiovascular medicine<sup>13</sup> and oncology<sup>14</sup> to achieve sufficient power to answer important questions when single large-scale trials are not feasible. It is highly appropriate, given the history of oxygen therapy, that the first prospective meta-analysis in the field of neonatology is to be directed at defining the optimum oxygen levels in preterm infants. Projects have been planned and in some cases funded in North America, Europe, Australia and New Zealand.<sup>15</sup> With the agreement of the steering committees of the four proposed trials, individual patient data will be entered into a prospective meta-analysis. The combined sample size of around 5000 will provide the power to resolve the uncertainty surrounding oxygen targeting by focusing on the clinically important primary outcomes of death and neurodevelopmental impairment, as well as addressing important secondary outcomes such as retinopathy of prematurity and bronchopulmonary dysplasia. Once completed, this PMA should act as a template for future attempts to address the 'big' questions still facing neonatology.

## Addressing the global burden of disease

Archie Cochrane's initial challenge had two components: the identification of effective therapies and distribution of these interventions equitably.<sup>1</sup> If substantial headway has been made towards the first component, much remains to be done with respect to the second.

Survival at the margins of viability (23–26 weeks) has improved markedly in Western settings.<sup>16</sup> Hart's inverse care law states that 'the availability of good medical care tends to vary inversely with the need of it in the population served'.<sup>17</sup> This law holds at least as well today as it did when it was formulated in 1971. Deaths in less well developed countries account for 98% of the four million deaths worldwide in the first 28 days of life.<sup>18</sup> Indeed, the proportion of all childhood deaths that occurs in the first 4 weeks is rising and stands at 38% of those <5 years of age.<sup>19</sup> Child survival programmes in the developing world have reduced the mortality rates beyond the first month of life through attention to pneumonia, diarrhoea, malaria and vaccine-preventable conditions. In contrast, deaths in the first week of life have risen from 23% in 1980 to 28% in 2000.<sup>19</sup>

Regional studies suggest that most neonatal deaths result from combinations of prematurity or in utero growth restriction, with co-morbidities such as infections, asphyxia, hypothermia, and feeding problems.<sup>20,21</sup> Lawn et al.<sup>19</sup> attempted to delineate the characteristics of global neonatal mortality. They found that two thirds of neonatal deaths occur in the African and southeast Asian regions of WHO. More than a quarter of deaths occur in the first 24 hours of life and three quarters in the first week. Although data collection is erratic in these regions, it appears that low birth weight – either from prematurity or in-utero growth restriction – indirectly contributes to most deaths, which may be attributable to infection or asphyxia. The authors of this report suggest that the solutions to these problems do not require complex technology but attention to warmth, feeding and prevention and early treatment of infections.

The role of the Neonatal Review Group is twofold. First, it can continue the work of collating the evidence relevant to neonatal care in the developing world. As noted above (Table 1) the vast majority of reviewers come from Western countries. Recruitment of reviewers from Asia has already begun, but expansion of this base is essential if the focus of the Neonatal Review Group is to broaden to include issues most relevant to the developing world. Second, translation of evidence into practice is something that developed countries have struggled with.<sup>22</sup> There is some evidence to suggest that active strategies for the dissemination of evidence are superior to passive dissemination of consensus statements or practice guidelines through journal articles and professional societies' recommendations.<sup>23,24</sup>

## Conclusions

The science of systematic reviews and meta-analysis is young and still rapidly evolving. It is likely that when this period of the Cochrane Library's history is reviewed from a vantage point decades in the future, the methods used now will seem primitive, clumsy, and perhaps in some cases wrong. However, in a relatively short time much has been accomplished in collating and disseminating high-quality

evidence relevant to the care of newborn infants. Silverman frequently used the term 'subversive' to describe trials and reviews that challenged existing wisdom. As the Cochrane Library moves from the periphery to the mainstream of medical life, the Collaboration needs to guard against the complacency that Cochrane, Silverman and Sinclair challenged in the old order of expert-led practice. With very few material resources, the Library's most valuable asset is its band of 'enthusiastic volunteers' who find time in the midst of their busy day jobs to pose and answer the questions that will lead to better outcomes for babies everywhere.

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