RESEARCH PAPER

# Profile of Published Cochrane Systematic Reviews in Child Health From Low- and Middle-Income Countries

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**Objective:** Setting priorities in health research is a challenge at the global and national levels. Use of evidence-based approach is uncommon and needs to be promoted in low-and middle-income countries (LMIC). We describe profile of Cochrane systematic reviews focussing on participation from LMIC. **Methods:** We searched six Cochrane review groups producing reviews relevant to child health in low- and middle-income countries for published Cochrane systematic reviews from 1 March, 2009 till 18 March, 2015 in the Cochrane Library. **Results:** A total of 669 Cochrane systematic reviews from six review groups were found. Low proportion of lead authors from low- and middle-income countries was found in 4 out of 6 review groups. About 50% of the reviews showed inconclusive evidence. 101/669 (15%) empty reviews were found needing more primary studies. ***Conclusions:*** The proportion of Cochrane authors from low- and middle-income countries is low. Capacity-building in systematic reviews and good quality primary research in these countries is warranted.

**Keywords:** *Diarrhea, Evidence-based medicine, Health policy, Meta-analysis.*

Priority-setting in health research is a challenge at the global, national and local levels. Most low- and middle-income countries (LMIC) do not have a systematic priority setting mechanism in place; occasionally, there are disease-driven or funder-driven approaches for prioritization, but these tend to be reactionary approaches. Strategic priority-setting is essential to promote and provide direction to research and innovation in a resource-constrained environment. There is no agreed best practice for priority-setting, though the US National Institute of Health (NIH), the World Health Organization (WHO) and the Child Health and Nutrition Research Initiative (CHNRI) have proposed a methodology [1-3]. Priority-setting using an evidence-based approach is uncommon and needs to be promoted in LMIC settings as it provides information and tools to help with priority setting [4].

Systematic reviews based on a number of primary studies, are placed at the top of the evidence pyramid [5], and are considered important for policy decision-making [6,7]. The knowledge emerging from systematic reviews assist health planners to set priorities for health research, implement proven interventions, and use limited resources judiciously. However, the information about systematic reviews addressing problems of LMIC is scant. We analyzed child relevant Cochrane systematic reviews [8] to find the publication of LMIC knowledge gaps and to prepare a list of primary research questions, for potential uptake in research agenda in LMIC.

## Methods

We identified top six Cochrane Review Groups reported to have the maximum number of child-relevant systematic reviews in the Cochrane Library [6]. We used a working definition of child-relevant systematic reviews as one that intended to use children (0-18 yrs) as their populations, exclusively, or along with an adult population of both genders. An information specialist searched the databases of six Cochrane Review Groups (ranked in order of their contribution towards child-related SRs): (Acute Respiratory Infections [ARI]; Infectious Diseases; Neonatal; Cystic Fibrosis and Genetic Disorders; Airways; Developmental, Psycho-social and Learning Problems) from 1st March, 2009 till 18th March, 2015 in the Cochrane Library. We screened all systematic reviews from a LMIC perspective, noted their use of GRADE to assess the quality of evidence, and collected information on the conclusiveness of the review to find research leads for the future. We used the search strategy developed by Bow, *et al*. [6].

The records identified from the search were screened by two authors for inclusion. Any discrepancies were sorted out by discussion among authors to reach a final decision. An electronic data extraction form was developed in Microsoft Excel, pilot tested and refined for this purpose. The title, author information, objectives, methods, main results and authors' conclusions sections of the included Cochrane reviews from the six Cochrane review groups were abstracted. We used the affiliations provided in the authors' section of the review to judge whether the corresponding author belonged to a LMIC or not. Information on the country where the trials were conducted was extracted from the 'Characteristics of included studies' tables. To categorize the country of corresponding authors we referred to the human development index classification as high, medium or low as defined by the United Nations [9] and income level (high, upper-middle, lower-middle, or low income according to the World bank [10]. We used standard definitions to classify interventions as pharmacological, behavioral, physical environment-related, psychosocial, or other. Type of study design: RCTs or quazi-RCTs; number of trials in the reviews; types of intervention; total number and type of participants: children and/or adults; disease/condition being addressed, use of meta-analysis and evaluation of evidence as per GRADE was extracted from the 'Data collection and analysis section' of the reviews. Information about gap in knowledge was inferred from the 'Overall completeness and applicability of evidence' and 'Quality of the evidence' sections. If the reviews reported 'inconclusive evidence', we looked for any reasons cited.

Evidence as per Grading Recommendation Assessment Development Evaluation [11] was classified as low, moderate, or high. If GRADE was not used in a review, we examined and categorized the reviews as those that assessed allocation concealment, risk of bias, and used the Jadad scale [12].

We explored each variable separately in the data set using univariate method to summarize the range of values and also the central tendency, wherever possible. Analyses were carried out within the six Cochrane review groups individually and also overall.

## RESULTS

We identified 669 Cochrane systematic reviews addressing research questions of importance to LMICs; most (176, 26.3%) from the Airways group (***Table* I**).

Corresponding authors were from LMICs in 122 (18.2%) reviews, and 22.3% of included trials had been conducted in these countries.

**TABLE I** SUMMARY OF GENERAL INFORMATION AND CHARACTERISTICS OF INCLUDED STUDIES IN CHILD-RELEVANT SYSTEMATIC REVIEWS (*N*=669)

| *CRG name* | *Number of systematic reviews (n= 669)* | *Corresponding author from LMIC (n=122)* | *Net number[#] of systematic reviews (n=568)* | *Trials included in reviews, conducted in LMIC (n=149)* | *Children as participants in trials included in reviews (n=296)* | *Systematic reviews with Meta-Analysis (n=464)* | *GRADE used in reviews (n=210)* | *Inconclusive evidence due to not enough RCTs (n=344)* | *Inconclusive evidence due to small sample sizes(n=204)* |
|---|---|---|---|---|---|---|---|---|---|
| Airways | 176 | 9 | 158 | 0 | 51 | 148 | 45 | 122 | 51 |
| Neonatal | 155 | 15 | 129 | 35 | 129 | 105 | 24 | 64 | 58 |
| ARI | 97 | 30 | 91 | 24 | 44 | 71 | 48 | 48 | 44 |
| Cystic | 100 | 25 | 71 | 12 | 12 | 41 | 20 | 42 | 24 |
| Developmental | 78 | 15 | 60 | 22 | 48 | 44 | 26 | 55 | 19 |
| Infectious disease | 63 | 20 | 59 | 56 | 12 | 55 | 47 | 13 | 8 |

*[#]Number of Cochrane Reviews after deleting empty (without any trials) reviews; ARI: Acute respiratory infections; CRG: Cohrane Review Group; LMIC: Low- and middle-income countries; RCT: Randomized controlled trial.*

**WHAT THIS STUDY ADDS**

- There is limited involvement of authors from LMICs in generating evidence from systematic reviews.
- A list of titles registered with Cochrane that were empty reviews (101) at the time of the study is presented for researchers to take up these topics as primary research.

As expected, Neonatal group reviews (*n*=155) had 100% neonatal participants, whereas the combined proportion of pediatric participants in the remaining five groups was 32.5% (167 out of 514). Use of meta-analysis in systematic reviews was quite common (61.3%); although, use of GRADE for assessing the quality of evidence was low (31.4%) and not uniform across groups (***Table* I**). The proportion of reviews that reported evidence to be conclusive also varied widely across groups (data not shown), and overall 396 (59.2%) reviews reported the evidence as insufficient.

Systematic reviews from all the six review groups cited not having sufficient number of randomized controlled trials (51.4%) and small sample size (30.5%) in included studies as the reasons for insufficient evidence. The median number of RCTs included in the reviews was 12, 9, 8, 8, 5 and 4 in Infectious diseases, Airways, Acute respiratory infections, Developmental, Neonatal and Cystic fibrosis groups, respectively. About 15% (101 out of 669) of systematic reviews across the six review groups were 'empty reviews' (29% in the Cystic fibrosis and Genetic diseases group; <1% in the ARI group) (***Web Appendix* 1**).

## DISCUSSION

Our study showed that the proportion of Cochrane authors from LMICs is low as compared to the high-income countries; very few RCTs conducted in LMICs were included in Cochrane reviews. Use of meta-analysis was observed to be high; but the use of GRADE by different groups was variable. Our study is limited to the top six Cochrane review groups, which produce approximately 50% of reviews including children as participants [6].

Our finding of low proportion of Cochrane authors from LMICs is in agreement with other publications reporting more than half of systematic reviews being produced in high-income countries. Other authors have reported that most primary studies are conducted in the US, UK, Canada with limited application to LMICs [13,14]. The reasons for inconclusive evidence reported by authors were: lack of sufficient number of trials included in the reviews and small sample sizes in the studies included, similar to report by Willhelm, *et al.* [15], who listed the common reasons for inconclusive reviews as small number of patients, insufficient data, insufficient methodological quality, and heterogeneity of studies. Reasons for lack of studies from LMICs in Cochrane reviews could be: lack of well conducted trials in LMICs/ or poor quality of trials leading to their exclusion from the review process [16]; absence of electronic databases prior to 1980s; non-publication of negative trials; stringent regulatory mechanisms; and lack of funding. Our study findings suggest that capacity-building in methodology of systematic reviews in India and other LMIC needs to be increased in order to bridge the existing gap. Systematic reviews with conclusive evidence should be used to prevent research waste (of repeated trials with same objectives). At the same time, systematic reviews with inconclusive evidence should prompt more research to reach conclusive answers. Our study showed that reaching conclusive evidence is difficult to achieve even while synthesizing evidence in systematic reviews.

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***Web Appendix* 1** LIST OF EMPTY REVIEWS

**Cochrane Airways Group**

1. Honey and lozenges for children with non-specific cough, 2. Restriction of oral intake of water for aspiration lung disease in children, 3. Treatment of obstructive sleep apnoea for chronic cough in children, 4. Breathing exercises for dysfunctional reathing/hyperventilation syndrome in children, 5. Methylxanthines for prolonged non-specific cough in children, 6. Inhaled cromones for prolonged non-specific cough in children, 7.Indoor air modification interventions for prolonged non-specific cough in children, 8. Influenza vaccine for children and adults with bronchiectasis, 9. Oral non steroid anti-inflammatories for children and adults with bronchiectasis, 10. Singing for children and adults with bronchiectasis, 11. Feather versus non-feather bedding for asthma, 12. Short acting beta2-agonists for bronchiectasis, 13. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy, 14. Oral corticosteroids for bronchiectasis (stable and acute exacerbations), 15. Lifestyle modification for obstructive sleep apnoea, 16.Anticholinergic therapy for bronchiectasis, 17. Alexander technique for chronic asthma, 18. Long-acting beta2-agonists for bronchiectasis, 19. Written individualised management plans for asthma in children and adults, 20. Oral methylxanthines for bronchiectasis

**Cochrane Cystic Fibrosis and Genetic Disorders Group**

1. Newborn screening for homocystinuria, 2. Carnitine supplementation for inborn errors of metabolism, 3. Pneumococcal vaccines for cystic fibrosis, 4. Surgical interventions for treating pectus excavatum, 5. Vitamin A supplementation for cystic fibrosis, 6. Anti-inflammatory drugs and analgesics for managing symptoms in people with cystic fibrosis-related arthritis, 7. Disease modifying anti-rheumatic drugs in people with cystic fibrosis-related arthritis, 7. Hematopoietic stem cell transplantation for people with sickle cell disease, 8. Gene therapy for sickle cell disease, 10. Hematopoietic stem cell transplantation for Gaucher disease, 11. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis, 12. Antibiotics for treating community acquired pneumonia in people with sickle cell disease, 13. Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease,14. Topical cystic fibrosis transmembrane conductance regulator gene replacement for cystic fibrosis-related lung disease, 15. Gene therapy for haemophilia, 16. Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis, 17. Psychological therapies for thalassaemia, 18. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis, 19. Embolisation for pulmonary arteriovenous malformation, 20. Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis, 21. Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis, 22. Timing of hypertonic saline inhalation for cystic fibrosis, 23. Antibiotic treatment for Stenotrophomonas maltophilia in people with cystic fibrosis, 24. Antibiotic treatment for Burkholderia cepacia complex in people with cystic fibrosis experiencing a pulmonary exacerbation, 25. Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis, 26. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibros, 27. Vaccines for preventing invasive salmonella infections in people with sickle cell disease, 28. Blood transfusions for treating acute chest syndrome in people with sickle cell disease, 29. Desmopressin acetate (DDAVP) for preventing and treating acute bleeds during pregnancy in women with congenital bleeding disorders, 30. Hematopoietic stem cell transplantation for people with β-thalassaemia major

**Cochrane Neonatal Group**

1. Recombinant human activated protein C for severe sepsis in neonates, 2. Instruments for assessing readiness to commence suck feeds in preterm infants: effects on time to establish full oral feeding and duration of hospitalization, 3. Vasopressin and its analogues for the treatment of refractory hypotension in neonates, 4. Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation, 5. Non-nutritive sucking for gastro-oesophageal reflux disease in preterm and low birth weight infants, 6. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome, 7. Oral immunoglobulin for the treatment of rotavirus diarrhea in low birth weight infants, 8. Banked preterm versus banked term human milk to promote growth and development in very low birth weight infants, 9. Continuous versus bolus intragastric tube feeding for preterm and low birth weight infants with gastro-oesophageal reflux disease, 10. Patient isolation measures for infants with candida colonization or infection for preventing or reducing transmission of candida in neonatal units, 11. Prophylactic antibiotics to reduce morbidity and mortality in newborn infants with intercostal catheters, 12. Techniques to ascertain correct endotracheal tube placement in neonates, 13. Deep versus

shallow suction of endotracheal tubes in ventilated neonates and young infants, 14. Oral lactoferrin for the treatment of sepsis and necrotizing enterocolitis in neonates, 15. Surfactant for pulmonary haemorrhage in neonates, 16. Acupuncture for hypoxic ischemic encephalopathy in neonates, 17. Saline irrigation for the management of skin extravasation injury in neonates, 18. Early removal versus expectant management of central venous catheters in neonates with bloodstream infection, 19. Surfactant for bacterial pneumonia in late preterm and term infants, 20. Videolaryngoscopy versus direct laryngoscopy for tracheal intubation in neonates, 21. Home- versus hospital-based phototherapy for the treatment of non-haemolytic jaundice in infants at more than 37 weeks' gestation, 22. Hydralazine in infants with persistent hypoxemic respiratory failure, 23. Milrinone for persistent pulmonary hypertension of the newborn, 24. Octreotide for the treatment of chylothorax in neonates, 25. Routine neonatal circumcision for the prevention of urinary tract infections in infancy, 26. Fluid restriction and prophylactic indomethacin versus prophylactic indomethacin alone for prevention of morbidity and mortality in extremely low birth weight infants

**Cochrane Developmental, Psychosocial and Learning Problems Group**

1. Cognitive-behavioural interventions for children who have been sexually abused, 2. Acupuncture for Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents, 3. Music education for improving reading skills in children and adolescents with dyslexia, 4. Melatonin for non-respiratory sleep disorders in visually impaired children, 5. Gastrostomy feeding versus oral feeding alone for children with cerebral palsy, 6. Fundoplication versus postoperative medication for gastro-oesophageal reflux in children with neurological impairment undergoing gastrostomy, 7. Auditory-verbal therapy for promoting spoken language development in children with permanent hearing impairments, 8. Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders, 9. Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities, 10. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood, 11. Dietary interventions for RAP and IBS in childhood, 12. Psychosocial interventions for RAP and IBS in childhood, 13. Amphetamines for ADHD in adults, 14. Immediate-release methylphenidate for ADHD in adults, 15. Advocacy interventions to reduce or eliminate violence and promote the physical and psychosocial well-being of women who experience intimate partner abuse, 16. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women, 17. Psychological interventions for adults who have sexually offended or are at risk of offending, 18. Aerobic exercise training programmes for improving physical and psychosocial health in adults with Down syndrome.

**Cochrane Infectious Diseases Group**

1. Lactose avoidance for young children with acute diarrhea, 2. Vaccines for preventing rotavirus diarrhoea: vaccines in use, 3. Mass drug administration for malaria, 4. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever).

**Cochrane ARI Group**

1. Nebulized epinephrine for croup in children, 2. Heliox inhalation therapy for bronchiolitis in infants, 3. Neuraminidase inhibitors for preventing and treating influenza in adults and children, 4. Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze, 5. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children, 6. Acupuncture for mumps in children, 7. Advising patients to increase fluid intake for treating acute respiratory infections, 8. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children, 9. Chinese medicinal herbs for mumps, 10. Surfactant therapy for bronchiolitis in critically ill infants, 11. Chinese medicinal herbs for measles, 12. Decongestants and antihistamines for acute otitis media in children.