## Title

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PERSPECTIVE

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# Medical reversals in low- and middle-income countries

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## Summary

**Background:** Low- to middle-income countries (LMICs) often have limited budgets for health care, and as such, they need to prioritize health care interventions that are evidence based. However, sometimes, interventions are implemented despite a lack of supporting evidence because of a perceived biologic plausibility or because they have worked in other populations. Later, some of these interventions are shown to either lack benefit or are harmful in randomized studies, which we call a medical reversal.

**Main body:** In this paper, we discuss a variety of medical reversals in LMICs, ranging from tuberculosis to nutrition to malaria to septic shock. These practices were previously identified, but we wish to highlight those that are most relevant to LMICs.

**Conclusion:** Identifying and eliminating these practices will help in better allocation of limited health care resources and dollars in LMICs.

KEYWORDS

evidence-based medicine, health care, medical reversal, nutrition, resource allocation

## 1 | BACKGROUND

Because of often limited and fixed health care budgets, it is important that low- and middle-income countries (LMICs) prioritize effective, evidence-based care. Randomized controlled trials (RCTs) are the gold standard for informing evidence-based practice, and the number of published RCTs in LMICs increased from 32 in 2003 to 211 in 2013.[1] This increase is informative, as it reflects a growing interest in identifying interventions that work, while eliminating those practices that are wasteful.

  

Interventions in LMICs are at times implemented because they seem intuitive and there is biologic plausibility; the interventions have worked in other populations (ie, generalizability); the assumption that if an intervention improves outcomes in a severe disease state or in severe deficiency, the intervention should improve outcomes in less-severe disease states or more subtle levels of deficiency; or, if a little is beneficial, a larger dose would provide greater benefit.

Many times medical practices are deployed because of a desire to move policy ahead, despite a lack of supporting evidence. However, when these interventions are tested in well-done RCTs, the results are not always positive or beneficial and the practice ought to be deimplemented. We call such instances a medical reversal.[2-6] Here, we will discuss interventions that, while implemented in LMICs with positive intentions, have resulted in no benefit and sometimes more adverse outcomes.

These practices were recently identified through a systematic search of RCTs published in the top medical journals.[7] In total, 396 reversals were identified, and of those, 8% of the reversals came from studies conducted in LMICs.

## 2 | TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus (HIV) and tuberculosis (TB) are two of the leading causes of death in low-income countries,[8] and a number of interventions to treat and prevent these illnesses have been attempted.

### 2.1 | Prevention

An example of TB control is with efforts to prevent active cases of TB with isoniazid in high-risk populations in South Africa, which is increasingly being used for this purpose, especially in countries with a high HIV burden.[9] The World Health Organization (WHO) created a broad recommendation for isoniazid preventive therapy in HIV-positive individuals on the basis of early studies.[10] When this was tested in a randomized trial of both HIV-infected and HIV-uninfected infants, the incidence of TB infection, disease, or death was no different between infants prophylactically treated with isoniazid or placebo in either HIV-uninfected or -infected infants.[11]

Because people working in mines are at higher risk of developing TB, isoniazid has been recommended by the South African government for these individuals with concomitant HIV, in an attempt to control comorbidity.[12] In a randomized trial of 15 geographically discrete mining clusters (78 744 miners), screening for TB and treatment with isoniazid to miners without active TB did not reduce the prevalence or the incidence of TB in individuals working in mines.[13] The results of these studies suggest that broad recommendations to prophylactically treat all individuals in high-risk populations do not always lead to better health outcomes and that further studies should better define the subpopulations who will actually benefit from these types interventions before recommendations are made.

The issue of determining which population benefits from prevention strategies has arisen with other TB interventions. Such is the case with the BCG revaccination to prevent TB. The benefit of a one-time BCG vaccination has been controversial because of its inconsistent effectiveness, but there has been enough evidence of its benefit that many countries have adopted recommendations for BCG vaccination.[14] In efforts to boost the benefit of this vaccine, many countries have adopted the practice of BCG revaccination, even though there is a lack of evidence for this.[15] In a cluster-randomized trial of BCG revaccination in school-aged children in Brazil, the incidence of TB was no different between schools assigned to revaccination and those assigned to no revaccination.[15] The idea that if some is good, more must be better is clearly not applicable in the case of BCG revaccinations to prevent TB.

## 2.2 | Treatment of complications

TB and HIV lead to numerous complications such as pericarditis and meningitis, in which inflammatory pathways are thought to contribute significantly to the morbidity caused by these diseases. Corticosteroids decrease inflammation and therefore have been widely used, particularly in Asia, as a mainstay of treatment. However, corticosteroids are nonspecific in the biologic processes they affect, and in some conditions, specifically those that are infectious in nature, there is a need for balance between the anti-inflammatory and immunosuppressive actions of cortisone.[16]

In the case of cryptococcal meningitis, often a sequelae of inadequately treated HIV, corticosteroids are widely used[17] in order to suppress the inflammatory response and control cerebral edema.[18] Moreover, corticosteroids are suggested by the Ministry of Health Myanmar as a treatment option for patients with cryptococcal meningitis.[19] In a randomized trial of patients with cryptococcal meningitis who were HIV positive and resided in several Asian or Ugandan countries, patients randomized to dexamethasone treatment not only had no improvement in mortality compared with those taking placebo but had higher rates of disability.[17]

Steroids for the treatment of tuberculous pericarditis have also been regularly used by clinicians for the treatment of tuberculous pericarditis[20] and recommended jointly by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America.[21] Similarly, in an RCT of patients with HIV and tuberculous pericarditis residing in eight African countries and who were assigned to prednisolone, the composite outcome of death, cardiac tamponade, or constrictive pericarditis was no lower than patients assigned to placebo.[22]

# 3 | NUTRITION

## 3.1 | Vitamins and supplements

Micronutrients are essential for human growth and biologic functioning. Overt deficiencies can be serious, and they are more common in LMICs than in other parts of the world. Vitamin A deficiency, for example, ranges between 6% for east and southeast Asia to as high as 48% in sub-Saharan Africa.[23] Micronutrient deficiencies are likely an indication of a larger and more serious condition of overall malnutrition. In these cases, supplementation with a single nutrient is unlikely to improve the health of these individuals. Programs to add iodine to salt have been successful, but many other programs to add micronutrient supplements to the diets of people residing in countries with a high prevalence of malnutrition have largely failed to show meaningful benefit.[24-26]

Vitamin A programs have been ongoing for several decades now, and billions of vitamin A supplements have been donated to these programs—The United Nations Children's Fund has received almost four billion capsules by the Canadian International Development alone.[27] In light of high prevalence of vitamin A deficiency in some countries and with the understanding that vitamin A is essential for the growth of the fetus and for the mother's own tissues and for promoting healthy mucosal barriers to prevent the infection of pathogens,[28] vitamin A supplementation has been targeted as an intervention for reducing morbidity and mortality in at-risk populations. Early RCTs showing that vitamin A supplementation could reduce mortality in children prompted widespread implementation of vitamin A supplementation programs.[29] However, several subsequent and larger RCTs of vitamin A supplementation were performed on women and infants in several sub-Saharan African countries. In two related trials, 22 955 newborn infants (ages 2 h to 2 d) from Ghana[30] and 31 999 newborn infants from Tanzania[31] were randomized to a single 50 000 IU vitamin A dose or placebo. Vitamin A supplementation did not improve survival in either Ghana or Tanzania. Similarly, in a trial in Ghana where 104 484 women of reproductive age were given 25 000 IU retinol equivalents and 103 297 women were given placebo, neither pregnancy-related death, overall death, or live births was any better in those receiving vitamin A supplementation.[24]

Zinc is another micronutrient that has been associated with not only improved survival but also better immune function, and less diarrhea and pneumonia, which are both associated with higher mortality.[25] Zinc supplementation is recommended mainly for the treatment of diarrhea to reduce childhood mortality,[32] and some have advocated prophylactic supplementation in high-risk populations.[33,34] In an RCT in Zanzibar, 42 546 children (1-36 months of age) were randomized to iron, folic acid, and zinc; iron and folic acid; zinc; or placebo daily.[25] Because of an increase in hospital admissions and possibly mortality from iron supplementation, the study was temporarily halted and participants taking iron were switched to either zinc or placebo.[35] These early findings contradict international guidelines supporting iron and folic acid in young children with a high prevalence of anemia.[36] In the end, there were no differences in overall mortality, malaria-related deaths, or diarrhea-related deaths between those with zinc supplementation and those without. Another trial with a similar study design also randomized children in Nepal to iron, folic acid, and zinc; iron and folic acid; zinc; or placebo daily. It too was halted early, and groups with iron were switched to either zinc or placebo. Again, there was no difference in mortality nor were there differences in diarrhea, dysentery, or acute lower respiratory infections.[26]

A noteworthy point from these studies is the harm that can come from the routine supplementation of iron. As previously mentioned, for children residing in Zanzibar, death or treatment in a hospital was 12% higher in children who received iron supplementation than in those who did not, and hospitalization was 11% higher in these children.[35] Many children in east Africa are anemic, and international guidelines recommended that iron supplements be routinely provided to children residing in areas with a high prevalence of anemia.[36] The concern that iron supplementation in individuals with malaria would exacerbate the burden and transmission of malaria was considered secondary to the benefits of treating and preventing anemia in these populations.[37] Once again, results from the study in Zanzibar demonstrated the harms that come from generalizing results to a broad population without adequate data.

There is a great need to find effective interventions for the treatment of malnutrition, and results from these trials highlight the fact that malnutrition, although common in low-income countries, is not a condition that can be simply treated with a single-approach intervention. This lesson is demonstrated repeatedly in trials that have focused on other single-parameter nutritional interventions.

## 4 | OTHER REVERSALS

Malaria is another health condition that contributes to the morbidity in some LMICs. The implementation of several preventive measures, notably long-lasting insecticidal nets and indoor residual spraying, has helped greatly reduce the incidence of malaria.[38] These two interventions have successfully been used independently, but because there are still millions of cases of malaria that occur each year, the combination of these two interventions has also been used in an attempt to further reduce transmission, even though there has been little evidence to support the practice.[39] In a randomized trial, 70 community clusters that included 7845 children, the incidence of clinical malaria was no different between those who received the combination of indoor residual spraying and long-lasting insecticidal nets and those who received only long-lasting insecticidal nets.[38] Again, this is another case of more is not necessarily better, particularly when there is additional expenditure with no evidence of benefit.

Chagas disease often results in cardiomyopathy. Treatment has focused on drugs that would clear the parasite in order to prevent more serious complications, and because benznidazole's action is to do just that, it has been the most common treatment for Chagas disease.[40] Benznidazole is most beneficial in patients who are newly diagnosed with Chagas disease. The WHO has recommended antiparasitic treatment even for patients with a chronic-phase infection even though there is not clinical evidence for its effectiveness.[41] In a large RCT that included patients with established Chagas cardiomyopathy residing in several South and Central American countries, benznidazole was tested against placebo.[42] In spite of a reduced serum parasite detection in the benznidazole group, those in the intervention arm did not have reduced cardiac clinical deterioration after 5 years of follow-up, when compared with those

on placebo. This is an example of extrapolating effectiveness data from acute to chronic infection, which unfortunately is not corroborated in clinical trials that include chronically infected populations.

Corticosteroids are regularly used in treating women in preterm labor, and their use results in a reduction of neonatal mortality by 31% in high-income countries.[43] The benefit of these common drugs is so established that several national and international health organizations have recommended their use.[44,45] In spite of these recommendations and the demonstrated efficacy of these drugs, access to these drugs by women in low-income countries is low, compared with high-income countries.[46] When an antenatal scale-up program was implemented in low-income countries (including 101 randomized clusters with approximately 100 000 live births), 28-day neonatal mortality in preterm infants was not decreased and, in fact, was higher among those in the intervention arm compared with standard care.[46] Moreover, suspected maternal infection was higher in the intervention arm. This trial effectively illustrates the harms that can come from generalizing the results of studies showing beneficial interventions to all populations.

The implementation of an early resuscitation protocol in patients with sepsis is also an example where effectiveness of an intervention in high-income countries has been generalized to LMICs. In 2001, results from an RCT were published showing the benefit of an early resuscitation protocol in sepsis,[47] and this practice became widely used in the United States and later became incorporated into Surviving Sepsis guidelines.[48] When this practice was tested in Zambia, with the randomization of adults with sepsis and hypotension to either an early resuscitation protocol for sepsis or usual care, more people in the early sepsis protocol group had in-hospital mortality, compared with the usual care group.[49] The authors postulate that differences in health status (the trial in Zambia had a high number of individuals who were malnourished, which could have predisposed them to pulmonary edema and respiratory failure with the rapid administration of intravenous fluid boluses) and use of mechanical ventilation contributed to the differences in study outcomes.

Similarly, the early administration of isotonic fluid is recommended for children who are in shock.[50] This practice is widely practiced throughout the world, but because of limited resources, children experiencing shock in low-income countries often do not receive this intervention unless their case is very serious. In the FEAST study, children residing in Uganda, Kenya, or Tanzania with severe febrile illness were randomized to either an albumin bolus group, a saline-bolus group, or no bolus.[51] Treatment with either albumin or saline bolus in children with severe febrile illness led to higher 48-hour mortality and mortality after 4 weeks when compared with no bolus. As for why this intervention failed to show benefit, the authors point to the disagreement in treating children with malaria with isotonic fluid, and because the clinical cause of severe illness is not known upon hospital admission, a broad recommendation of early administration of isotonic fluid may be contraindicated for populations with a high prevalence of malaria.

Together, these miscellaneous examples show that a variety of interventions, of broadly different putative mechanism of action, and different rationale, all have failed when tested in rigorous randomized studies.

## 5 | CONCLUSION

Public health measures to reduce mortality in LMICs are vital, but money spent on these measures and programs, because it is limited, should be spent on interventions that are evidence based and not implemented merely because they seem logical or because they have worked in other populations with different cultural or health care practices. We have presented here a list of interventions that, while on the basis of biological plausibility and/or effective used in other settings, have not produced positive outcomes and in some cases have caused more harm than doing nothing. Identifying and eliminating ineffective interventions will help in more optimal program planning and policy development. Some fraction of expenditures on ongoing interventions may be better directed to conducting robust studies to determine if the interventions truly work as intended.

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## AUTHOR CONTRIBUTIONS

All authors reviewed data used for this review. A.H. drafted the manuscript, and C.L. and V.P. were involved with the editing and revision of the writing. All authors read and approved the final manuscript.

## AVAILABILITY OF DATA AND MATERIALS

All studies for this review are publicly available, and the full methodology for identifying included studies can be found at https://elifesciences.org/articles/45183 doi: 10.7554/eLife.45183.

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