



Low birth weight, small-for-gestational age (SGA), pre-term birth, stillbirths, perinatal and neonatal mortality are important adverse outcomes of pregnancy [1]. The incidence of low birth weight in developing countries varies from 6 - 30%, and at least one-third of these are small for gestational age, especially in settings with high rates of maternal undernutrition. Small for gestational age (SGA) babies are those whose birth weight lies below the 10<sup>th</sup> percentile for a particular gestational age [2]. Vast majority of these are due to fetal growth problems that occur during pregnancy, including intrauterine growth restriction (IUGR) [3]. Full term SGA infants may not have complications related to organ immaturity like

("Mothers"[Mesh] OR "Pregnancy"[Mesh] OR mother\* OR maternal OR pregnancy) AND ("Micronutrients"[Mesh] OR "multiple micronutrient\*" OR multivitamin OR micronutrient\*) AND (supplement\*)

#### Selection (inclusion/exclusion criteria)

All prospective randomized controlled trials (RCTs) evaluating multiple micronutrient supplementation in women during pregnancy, irrespective of language or publication status, were included. Multiple micronutrients were defined as supplementation with at least 5 micronutrients including the UNIMMAP formulation [13] or those with comparable composition. These supplements were compared to maternal iron-folate supplementation. There were no limits on gestational age at the time of enrolment in the study and the duration of supplementation. Quasi-randomized trials were included as there was an adequate number of good quality RCTs available. We did not conduct sub-group analyses with respect to different dosages of iron in the multiple micronutrient supplements. Other than the assessment of SGA and neonatal mortality, we did not specifically evaluate minor adverse effects of the supplements such as nausea and vomiting among the mothers and newborns.

#### Validity assessment

The overall quality of evidence of an outcome, however, was assessed and graded according to the CHERG adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) technique [16,17] based on three components: 1) the volume and consistency of the evidence; 2) the size of the effect, or risk ratio; and 3) the strength of the statistical evidence for an association between the intervention and outcome, as reflected by the p-value [16]. The individual studies were also graded. Three categories of criteria were used to judge quality of individual study evidence in the meta-analysis: 1) study design; 2) study quality; 3) relevance to the objectives of the review [16]. The following four grades were given to individual studies: high, moderate, low or very low. Studies received an initial score of high if it was a randomized or cluster randomized trial. The grade was decreased by 0.5 to 1 for each study design limitation. In addition, studies reporting an intent-to-treat analysis or with statistically significant strong levels of association (>80% reduction) received 0.5-1 grade increases. A study with a final grade of very low was excluded on the basis of inadequate study quality. This review is shaped in large part by the needs of the LiST model. In that model, increases in coverage of an intervention result in a reduction of one or more cause-specific deaths or in reduction of a risk factor. Therefore, this review and the grade process used are designed to develop estimates of the effect of an intervention in

reducing either a risk factor or a death due to specific cause. For more details of the review methods, the adapted grade approach or the LiST model, see the CHERG method's paper [16]. For the LiST tool, we have defined SGA as an outcome rather than low birth weight as the model utilizes the former for the cohort effect. The SGA babies, belonging to the least 10<sup>th</sup> centile of the birth weight, could be at a higher risk of mortality and thus a greater effect of an intervention. Besides, in several populations used in the studies, the two terms have been used synonymously.

#### Data abstraction and study characteristics

Each study that satisfied the eligibility criteria was included in the review. Data were double abstracted into a standardized rectangular database [16] that was accessible through Excel (Additional File 1). Key variables like participants' characteristics, sample size, location, setting, blinding, allocation concealment, description of intervention and control groups (in terms of dosage and time of enrolment) and all the other outcomes of interest were recorded.

#### Quantitative data synthesis

The assessment of statistical heterogeneity among trials was done by visual inspection i.e. the overlap of the confidence intervals among the studies, and by the Chi square (P-value) of heterogeneity in the meta-analysis. A low P-value (less than 0.10) or a large chi-squared statistic relative to its degree of freedom was considered as providing evidence of heterogeneity. The I<sup>2</sup> values were also looked into, and roughly an I<sup>2</sup> greater than 50% was taken to represent substantial and high heterogeneity.

were performed according to the mean maternal body mass index (BMI). In an effort to understand the context of neonatal outcomes, we evaluated the effect of multiple micronutrient supplements on neonatal mortality by sub-group analysis according to the percentage of facility-based deliveries. Not all studies provided sufficient data to allow categorization of health system functionality for maternal health, but information on facility births or home births was available. We used an arbitrary cut off of 60%, where more than 60% facility births represented a proxy for skilled attendance.

selected for inclusion in this review. We evaluated the impact of the intervention on the following outcomes: maternal anemia, SGA and neonatal and early infant mortality.

#### Study characteristics

The baseline characteristics of all the studies including

#### Trial flow

A total of 4,187 hits were identified from our search strategy (Figure 1). After screening the titles and abstracts, 43 studies were initially considered eligible and finally, 17 studies comprising of 14 trials were

2 mg copper, 65 g selenium, 800 g RE itamin A, 1.4









