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Evidence-based antenatal interventions to reduce the incidence of small vulnerable newborns and their associated poor outcomes

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Summary

World Health Organization (WHO) recommends a package of care for all pregnant women within eight scheduled antenatal care (ANC) contacts. Some interventions for reducing and managing these small vulnerable newborn (SVN) outcomes exist within the WHO package and need to be more fully implemented, but additional effective measures are needed. We summarize evidence-based antenatal and intrapartum interventions (up to clamping the umbilical cord) to prevent vulnerable births or improve outcomes, informed by systematic reviews. We estimate, using the Lives Saved Tool, that eight proven preventive interventions (multiple micronutrient supplementation, balanced protein and energy supplementation, low dose aspirin, progesterone provided vaginally, education for smoking cessation, malaria prevention, treatment of asymptomatic bacteriuria, and treatment of syphilis), if fully implemented in 81 low-and middle-income countries, could prevent 5·202 (2·398-7·903) million SVN births and 0·566 (0·208-0·754) million stillbirths per year. These interventions, along with two that can reduce the complications of preterm births (antenatal corticosteroids and delayed cord clamping) could avert 0·476 (0·181-0·676) million neonatal deaths per year. If further research confirms the impact of three additional preventive interventions (omega-3 fatty acids supplementation, calcium supplementation, and zinc supplementation) on SVN births, the impact could increase to prevention of about 8·369 (2·398-13·857) million SVN births and 0·652 (0·181-0·917) million neonatal deaths per year. Scaling up the eight proven interventions would cost about $1·1 billion in 2030 and the potential interventions would cost an additional $3·0 billion. Implementation of antenatal care recommendations is urgent and should include all interventions that have proven impact on small vulnerable newborns, within the context of access to family planning services and addressing social health determinants of health. Achieving high effective coverage with these interventions will be necessary to achieve global targets for reduction of low birth weight and neonatal mortality, as well as longer-term benefits on growth and human capital.

Key Messages

- ***Package of proven antenatal interventions***: WHO-recommended 8 contacts during pregnancy provide a means to implement quality antenatal care, including interventions to reduce small vulnerable births and stillbirths. Proven antenatal interventions, including multiple micronutrient supplements, balanced protein energy supplements, aspirin, treatment of syphilis, education for smoking cessation, prevention of malaria in pregnancy, treatment of asymptomatic bacteriuria, and progesterone provided vaginally could reduce preterm births and small for gestational age births and should be scaled-up. Antenatal corticosteroids and delayed cord clamping can reduce the complications of preterm births and associated mortality.
- ***Potential interventions***: If additional research confirms their efficacy for reducing small vulnerable births, omega-3 fatty acid supplements, zinc supplements (or higher doses of zinc in multiple micronutrient supplements), and calcium supplements would provide substantial additional benefits.
- ***Impact and cost***: If full coverage of eight interventions with proven efficacy is achieved in 2030 in 81 low- and middle-income countries, 5·202 (2·398-7·903) million preterm or small for gestational age births, 0·566 (0·208-0·754) million stillbirths and 0·476 (0·181-0·676) million neonatal deaths could be prevented at a cost of $1·1 billion. If three additional interventions with potential benefits are proven efficacious and added to full coverage antenatal care in 2030, 8·369 (2·398-13·857) million preterm or small for gestational age births, 0·566 (0·208-0·754) million stillbirths and 0·652 (0·181-0·917) million neonatal deaths could be prevented at a cost of $4·1 billion.
- ***Accelerating progress towards target***: Implementation of proven interventions in antenatal care could bring the neonatal mortality rate in these 81 countries from 25·1 per 1000 live births in 2023 to 20·1, a 20% reduction, and reduce the prevalence of low birth weight by 17·9%, more than half of the World Health Assembly target of 30% reduction for 2030. Implementation of the proven and potential interventions could reduce the neonatal mortality rate to 18·3 per 1000 live births, helping achieve the Sustainable Development Goal target of less than 12 per 1000 live births, and reduce the prevalence of low birth weight by 28·6%, nearly meeting the World Health Assembly of 30% reduction target.

Antenatal care (ANC), the routine health care provided to women and adolescent girls during pregnancy, was first introduced in the United Kingdom (UK) in the 1920's.[1] The original UK schedule, comprising antenatal contacts at around 16, 24 and 28 weeks of pregnancy, followed by two-weekly contacts up to 36 weeks' gestation and then weekly contacts until childbirth, is thought to have informed ANC programs around the world.[1,2] As this schedule was not evidence-based, in the 1990's, World Health Organization (WHO) conducted a large randomized trial comparing a four-contact antenatal care model with the 'standard' contact model consisting of a median of eight contacts.[3] Stillbirths were more common in the four-contact arm of the trial compared with the standard model. The statistical significance of the results for this secondary outcome was not reported in the original publication. Thus, in 2002, WHO recommended a four-contact antenatal care package for women with uncomplicated pregnancies.[4] Antenatal contacts with this four-contact model, known as focused or basic antenatal care were scheduled at 12, 26, 32 and 36–38 weeks of gestation.

In 2013, re-analysis of WHO trial data confirmed an increase in perinatal mortality in the four-contact model in comparison to the eight-contact model[5] as did a systematic review of three trials from low- and middle-income countries (LMIC).[2] Based on these findings and a subsequently published report from South Africa, which found an increase in third trimester stillbirths with the four-contact model[6], WHO reviewed its guidance. In 2016, WHO antenatal care guidelines were published, recommending an integrated package of care delivered by eight scheduled antenatal contacts at 12, 20, 26, 30, 34, 36, 38, and 40 weeks' gestation and designed for the routine care of healthy pregnant women and adolescent girls.[7] A significant addition to WHO's recommended package of care was the introduction of a routine early ultrasound examination before 24 weeks of gestation to improve estimation of gestational age. While the guidelines include a selection of interventions aimed at women in certain high-risk contexts, (e.g., those living in malaria-endemic areas), interventions aimed at improving outcomes among pregnant women at high risk of having a small vulnerable newborn (e.g., women with a history of preterm birth, living with HIV, or at risk of pre-eclampsia) tend to be fragmented across other WHO guidelines.

The term 'small vulnerable newborn' (SVN), as defined in paper 1 in this series, includes preterm newborns (born before 37 weeks' gestation) and those born small for gestational age (SGA, weight less than the 10th percentile for gestational age and sex) and low birth weight (LBW) newborns (weighing less than 2500g) who are not preterm or SGA.[8] The SVN term comprises a larger group of small babies defined by any group of preterm, or SGA, but who may not all be LBW. The worldwide prevalence for SVN births for 2020 has been estimated at 26·2% of live births annually including 9·8% for preterm births and 17·4% for SGA births.[9] More than half (55·4%) of neonatal deaths (deaths in the first 28 days after birth) have been attributed to SVN births.[9] Strategies targeting this vulnerable group of fetuses will determine whether or not Sustainable Development Goal (SDG) 3·2 for reduction of neonatal and child mortality is met.

We recognize the fundamental role of social determinants of health such as physical safety, food security, water security, sanitation, education, employment, infrastructure, and equity, which are beyond the scope of this paper, as is the management of medical conditions and pregnancy complications. We have focused on interventions with robust evidence of effectiveness from randomized trials. We acknowledge that there exist antenatal and intrapartum interventions which are widely recommended, but not supported by randomized trial evidence, due to lack of equipoise regarding their effectiveness, such as caesarean delivery for very low birthweight breech presentation and obstetric interventions for preterm multiple pregnancy. Empowerment of women to avoid unintended pregnancy is critical to achieve improvements in every aspect of pregnancy outcome, including SVN. The focus of this paper is on antenatal interventions in LMIC to prevent SVN births and peripartum and intrapartum interventions to improve SVN outcomes implemented by obstetric/midwifery providers up to and including the clamping of the umbilical cord, but not neonatal care. We provide an overview of the evidence base supporting the interventions applicable to preventing SVN births and their consequences. We also recommend ways to deliver the interventions identified, with reference to WHO's ANC framework, and estimate the annual number of SVN births, stillbirths, neonatal deaths, and cases of stunting averted by scaling up the interventions in 81 LMIC and the anticipated additional costs.

Evidence for antenatal interventions from a global review

In three major databases of medical literature (Medline, Embase, and Cochrane Central Register of Controlled Trials), we carried out a systematic search from 2000 to October 2020 (subsequently limited to 2015-2020) to identify systematic reviews of interventions aimed to reduce the incidence of preterm, SGA, or LBW births and their associated poor outcomes (see Webappendix Panel 1 for search details). The searches were supplemented with the findings of the CIFFTAU overview review[10,11] and input from the wider group of experts collaborating on the Lancet Small Vulnerable Newborn series. Where there was more than one review on a topic, we used the Cochrane review in the first instance unless there was a non-Cochrane review of randomized trials conducted only in the LMIC or the non-Cochrane review was more current than the Cochrane one.

Identified interventions were grouped according to whether they were applicable to 1) all pregnant women, 2) pregnant women at increased risk of having a preterm or SGA birth or 3) pregnant women with imminent preterm birth. We classified interventions with a statistically significant benefit on preterm birth, SGA or LBW as 'proven', and those with non-significant evidence, but the overall direction suggesting benefit as 'potential', requiring confirmation of their effectiveness through further research. Interventions considered in the review of evidence are listed in Webappendix Table 1and the reviews assessed in Webappendix Table 2. We report risk ratios (RR) taken from the selected meta-analyses or trials. In Table 1 and Table 2, we present the interventions classified as 'proven' or 'potential' with their respective measures and information about the certainty of evidence using GRADE framework.[12]

Though no interventions show an overall increase in SVN births, it is possible that early pregnancy interventions that improve placental function might enable pregnancies which would have been lost before viability and thus not counted, to be prolonged and lost after viability or presenting with growth impairment, resulting in a spurious increase in stillbirth or SGA births and thus under-estimating the beneficial effect of the intervention.

Our work is underpinned by a wide and systematic search for evidence supplemented with input from subject-area experts, but is not without limitations. Evidence generation and synthesis is a constantly evolving field[13] and it is not easy to stay current. Due to the wide scope of this work, it is possible that some more current systematic reviews could have been missed. Furthermore, some interventions have more than one recent systematic review and we have chosen the one that most closely corresponded to current WHO recommendations, e.g., calcium supplementation for women with low dietary calcium intake, or how the intervention could be implemented in a LMIC setting.

Routine interventions for all pregnant women to prevent SVN types

We identified four interventions with evidence demonstrating or suggesting potential reduction in the rate of preterm or SGA births among pregnant women in LMIC (Table 1). The evidence for multiple micronutrient supplementation in comparison to iron and folic acid shows an effect on LBW, SGA births and stillbirths (RR 0·85 [95% CI 0·77-0·93], RR 0·90 [0·84-0·96] and 0·91 [0·85-0·98], respectively).[14] The evidence for detection and treatment of syphilis is based on a meta-analysis (unpublished data; Tong H, Heuer A, Walker N) of observational studies that compared early versus late treatment, treated versus untreated and appropriate versus inappropriate treatment. There was high consistency across the three comparisons, and we used the effect of early versus late initiation of the treatment on LBW (0·50 [0·41-0·58) and preterm birth (0·48 [0·39-0·58]). The evidence for stillbirths is based on studies of pregnant women treated for syphilis.[15] The evidence for omega-3 fatty acid supplementation (without concomitant interventions) suggests an effect on preterm births less than 37 weeks' gestation (0·90 [0·80-1·01]) and an effect on preterm births less than 34 weeks' gestation (0·62 [0·46-0·82]).[16] Detection and treatment of asymptomatic bacteriuria in pregnancy is a WHO recommended intervention based on its effect on LBW birth (0·63 [0·45-0·90]); the evidence comes mainly from studies conducted in high-income countries.[17] The effect on preterm births is 0·57 (0·21-1·56).

Targeted interventions to prevent SVN types among women with specific indications or needs

We identified eight interventions with evidence demonstrating or suggesting potential reduction in the prevalence of SVN types for pregnant women with specific indications or needs (Table 1). The evidence for balanced protein and energy supplements shows an effect on SGA births and stillbirths (RR 0·71 [0·54-0·94] and 0·39 [0·19-0·80], respectively).[18] The evidence for low dose aspirin and progesterone (provided vaginally) shows effects on preterm births (RR 0·89 [0·81-0·98])[19] and (0·92 [0·84-1·00]), respectively.[20] Psychosocial intervention for smoking cessation[21] is a WHO recommended interventions based on evidence of an effect on LBW (RR 0·83 [0·72-0·94] may have an effect on preterm births (RR 0·93 [0·77-1·11]). The evidence for insecticide-treated bed nets shows an effect on LBW (0·77 [0·61-0·98] and stillbirths (RR 0·68 [0·48-0·98]), as well as a possible effect on preterm births (RR 0·74 [0·42-1·31].[22] The provision of intermittent preventive therapy with antimalarials in pregnancy has a similar effect on LBW to that of insecticide-treated nets.[23] The other three interventions show potential to reduce the rate of preterm or SGA births; however, more research is required to confirm the effects before they can be recommended for prevention of these birth outcomes. High dose calcium supplementation is recommended by WHO for prevention of pre-eclampsia, but may also reduce both preterm births (RR 0·81 [0·64-1·02]) and SGA births (RR 0·85 [0·60-1·21]) in women with low calcium intake.[24] Zinc supplementation, currently recommended by WHO in the context of rigorous research, may potentially have an effect on preterm births (RR 0·87 [0·74-1·03]).[25]

Consumption of foods fortified with folic acid at the time of conception and after seems to be associated with reduction in preterm births (RR 0·88 [0·85-0·91])[26]; evidence derived from synthesis of multiple observational studies. Because this is not an intervention provided as part of antenatal care it was not included in modeling the impact of interventions.

Targeted interventions to manage the fetus at risk of death from being born preterm,

We identified two interventions that reduce mortality for preterm births (Table 2): antenatal corticosteroids for women at risk of preterm birth with an effect on neonatal mortality due to complications of prematurity (0·85[0·77-0·93])[27], and delayed cord clamping with an effect on neonatal mortality (0·73 [0·54-0·98]).[28] Both interventions are recommended by WHO.[29]

Estimation of reductions in SVN types and lives saved if antenatal interventions are scaled up

We used the Lives Saved Tool (*LiST*)[30] to estimate the impact on birth outcomes, neonatal and child mortality, nutritional status, and other health effects of increased maternal and child health intervention coverage at the national and sub-national level. *LiST* incorporates coverage data for 70 interventions whose efficacy values are routinely updated to reflect current evidence. The tool includes the impact of interventions delivered before or during pregnancy on birth outcomes (stillbirths, preterm births, SGA births and LBW births). The effectiveness of an intervention is applied to a predefined subset of the total population that would benefit from that intervention to estimate the impact of increased coverage of the intervention on specific health outcomes. The *LiST* methods are briefly described in Webappendix Panel 2.

This study's primary analysis (Proven Interventions) included eight interventions proven to prevent preterm or SGA births (Webappendix Table 3) and from these effects we estimate the impact on prevention of LBW births. To model the impact of these interventions, we increased coverage from 2023 national levels (Webappendix Table 4) to 90% coverage in 2024 for 81 countries (listed in Webappendix Table 5). We also performed a supplemental analysis (Proven & Potential Interventions) to model the effects of increasing the coverage of three additional interventions, as well as those included in the primary analysis (Webappendix Table 6).

Each *LiST* analysis estimated the change in the number of preterm, SGA and LBW births and stillbirths resulting from increased intervention coverage. We used the intervention effects from selected meta-analyses (Tables 1 and 2 and Webappendix Table 3). To create sensitivity bounds we did the same *LiST* analyses using the upper and lower 95% Confidence Intervals from these meta-analyses for all included interventions and outcomes.

Based on the increased risk of mortality and childhood growth faltering for these birth outcomes, we also calculated the deaths and cases of stunting that could be averted by each intervention and the total for all interventions. The assumptions for increased intervention coverage were made for 2024 and continued at that level to 2030. Results were grouped at regional levels, as well as presented for all 81 countries. Estimates of the costs of scaling up Proven and Potential Interventions were done using the methods in Webappendix Panel 3 and the costs in Webappendix Table 7. All models were generated using *LiST* version 6·2 beta 34.

Primary Analysis (Proven Interventions)

After full scale-up of Proven Interventions, 360,000 (196,000-521,000) combined preterm and SGA (preterm-SGA), 1·556 million (1·173-2·315 million) preterm-appropriate-for-gestational age (preterm-AGA), and 3·287 million (1·029-5·068 million) term-SGA, amounting to a total of about 5·202 million (2·398-7·903 million) SVN births, could be averted per year (Webappendix Table 8, Figure 1). Among these would be 2·442 million (1·131-3·694 million) LBW births (Webappendix Table 8).

Treatment of asymptomatic bacteriuria and syphilis and low dose aspirin account for 88·0% (1367505/1555630) of the total effect on preterm-AGA births. Balanced protein and energy supplementation and multiple micronutrient supplementation are the only interventions that have proven evidence of a protective effect for term-SGA births. Calcium supplementation, balanced protein and energy supplementation and multiple micronutrient supplementation could have the greatest impact on LBW births, accounting for 66·7% (2601781/3898607) of the total.

Among the SVN types, increased coverage of the eight interventions included in the Proven Interventions analysis could have the largest relative impact on decreasing preterm-SGA births, a

31·7% (17·3%-45·9%) decrease for all 81 countries (Table 3). The overall decrease in term-SGA, preterm-AGA and LBW births would be 17·4% (5·5%-26·8%), 16·9% (12·8%-25·2%), and 17·9% (8·3%-27·1%) for each, respectively. For all SVN types the reduction would be 17·8% (8·2%-27·0%). Increased coverage of the eight interventions could reduce the prevalence of LBW births from 14·2% in 2023 to 11·7% in 2030 (Figure 2).

The Proven Interventions could avert 566,000 (208,000-754,000) stillbirths per year (68·0% from balanced energy and protein supplementation) **(**Webappendix Table 9). This would result in a reduction of 32.4% of the projected 1·794 million stillbirths in 2030.

About 476,000 (181,000-676,000) neonatal deaths could be averted per year as the result of full coverage of Proven Interventions (Webappendix Table 10, Figure 3). This would result in a 20·1% reduction in the projected 2·382 million neonatal deaths without intervention in 2030. The interventions with the largest relative effect would be delayed cord clamping for preterm births (30·3%), balanced protein energy supplementation (17·0%), antenatal corticosteroids for preterm labor (16·9%), and multiple micronutrients (15·1%); the nutrition interventions could account for 32·1% (152169/476169) of the reduction in deaths. Increased coverage of the Proven Interventions could reduce the neonatal mortality rate from 25·1 per 1,000 live births in 2023 to 20·1 per 1,000 live births in 2030 (Webappendix Figure 1).

The number of stunted children in the 81 countries in 2030 could be 2·9% lower as a result of increased coverage of the eight interventions included in the Proven Interventions analysis (Webappendix Table 11). This decrease amounts to about 4·536 million fewer stunted children globally in 2030 than in 2023. The number of stunted children could decrease the most in Central and Southern Asia (3·9%).

Scale up of Proven Interventions could result in about 529,000 additional years of schooling and $7·269 billion additional lifetime earnings for the first birth cohort after full coverage of interventions in 81 countries (Webappendix Table 12).

Supplemental Analysis (Proven & Potential Interventions)
After full scale-up of Proven & Potential Interventions, 579,000 (196,000-839,000) preterm-SGA, 3·312 million (1·173-5·165 million) preterm-AGA, 4·478 million (1·029-7·852 million) term-SGA, amounting to a total of 8·369 million (2·398-13·857 million) SVN births, could be averted per year. Among these would be 3·899 million (1,131-6,402 million) LBW births. (Webappendix Table 8, Figure 1).

Increased calcium supplementation would have the largest effect on preterm-AGA births (23·7%), followed by omega 3 fatty acids (21·0%) and treatment of bacteriuria (16·2%). For term-SGA births balanced protein and energy supplementation, multiple micronutrient supplementation, and calcium supplementation each had substantial effects (29·6-35·6%). Calcium supplementation, balanced protein and energy supplementation, and multiple micronutrient supplementation had the greatest impact on LBW births accounting for 66·5% (2601781/3898607) of the total.

The Proven & Potential Interventions analysis found markedly greater possible decreases in SVN types compared to the Proven Interventions analysis (Table 3). We estimated a 51·0% (17·3%-73·9%) decrease in preterm-SGA births compared to the baseline scenario for all countries, while each region had decreases of a third to half. The Proven & Potential Interventions analysis resulted in 36·0% (12·8%-25·2%) and 23·7% (5·5%-41·5%) decreases in preterm-AGA and term-SGA births for all countries. Sub-Saharan Africa would have the greatest decrease in each adverse birth outcome. For all SVN births the reduction was 28·6% (8·2%-47·5%). Increased coverage of the full set of interventions could reduce the rate of LBW births from 14·2% in 2023 to 10·2%, near the LBW target of 30% reduction for these countries in 2030 (Figure 2).

The Proven & Potential Interventions could reduce stillbirths by 566,000 (208,000-754,000), two-thirds from balanced protein and energy supplementation (Webappendix Table 9). This would result in a reduction of 32·4% of the projected 1·749 million stillbirths in 2030.

About 652,000 (181,000,917,000) neonatal deaths could be averted per year as the result of increased coverage of the Proven & Potential Interventions (Webappendix Table 10, Figure 3). This would result in a 27·3% reduction of projected neonatal deaths that may occur without scaling up these interventions in 2030. The interventions with the largest effect would be calcium supplementation (18·3%), delayed cord clamping (17·1%), balanced protein and energy supplementation (14·2%), and multiple micronutrient supplementation (12·9%); nutrition interventions could account for 57·4% of the neonatal mortality reduction (Webappendix Table 10). Increased coverage of the Proven & Potential Interventions could reduce the neonatal mortality rate from 25·1 per 1,000 live births in 2023 to 18·3 per 1,000 live births in 2030 (Webappendix Figure 1).

The number of stunted children in these countries in 2030 could be 5·4% lower as a result of increased coverage of the interventions included in the Proven & Potential Interventions analysis (Webappendix Table 11). This decrease amounts to about 8·5 million fewer stunted children globally in 2030. The number of stunted children could decrease the most in Central & Southern Asia (7·3%).

Scale up of Proven & Potential Interventions could result in about 939,000 additional years of schooling and $12·976 billion additional lifetime earnings for the first birth cohort after full intervention coverage is achieved in 81 countries (Webappendix Table 12).

Cost of Scaling Up Proven Interventions and Proven & Potential Interventions

In *LiST* we estimate the total costs for each intervention which includes drug and supply costs, labor costs, other recurrent costs, capital costs, and above-facility costs. *LiST* costing methods draw on WHO's OneHealth model to get both definition of needs for the intervention, as well as costs for supply and drug costs and country-specific costs. Details on the costs for interventions are in Webappendix Table 13.[31]

Scaling up the eight interventions included in the Proven Interventions analysis from their current coverage would cost an estimated $1·126 billion per year (Webappendix Table 13). Balanced energy supplementation and multiple micronutrient supplementation have the greatest incremental costs ($509 million and $371 million, respectively) and account for 78·2% of the total cost. Among the Proven & Potential interventions, the estimated cost is $4·148 billion per year. Calcium supplementation and omega-3 fatty acid supplementation have the greatest incremental costs and account for 61·5% of the total cost. These costs would be very substantial increases from what is currently spent on these interventions annually, but far smaller than the gains in lifetime earnings if the interventions are implemented.

SVN interventions help achieve global targets

The antenatal interventions with proven evidence of efficacy to prevent preterm or SGA births, if fully implemented, could reduce LBW births by 17·9%, about 60% of what is needed to reach the World Health Assembly target of 30% reduction by 2030.[32] If additional research confirms the effects suggested by current evidence for interventions with potential impact on SVN births, their implementation could reduce LBW births nearly enough (28·6 %) to reach the target. There are not global targets for reduction of preterm or SGA births, but reduction of these vulnerable births is highly desirable because they result in substantial morbidity and mortality. We found the largest reduction with proven and potential intervention, by one half, in the preterm-SGA births, which is especially important because they have the highest risk of mortality of these SVN births.[33]

Integrating the Proven Interventions into routine antenatal care services could reduce stillbirths by nearly a third and neonatal deaths by one-fifth. If further research demonstrates the efficacy of the additional interventions that currently have suggestive effects, neonatal deaths could be reduced by more than a quarter to 18·3 per 1000 live births in 2030. This would facilitate achieving the SDG 3·2 aims of reducing neonatal mortality to 12 or less per 1000 live births by 2030.[34]

Implementation of SVN interventions in routine antenatal care

WHO recommendations for antenatal care include many specific clinical and laboratory assessments and services (Webappendix Table 14). While these are appropriate components of routine care, it is not always possible to attribute specific effects on SVN birth outcomes. Some interventions are recommended for other reasons, but may also have important effects on birth outcomes e.g., aspirin or calcium supplementation. Broadening the use of aspirin from the current WHO recommendation for women with two moderate risk factors to also include all nulliparous women, shown to benefit in a trial in eight LMIC,[17] as we recommend, would substantially increase the impact on preterm births. Evidence supports the provision of multiple micronutrient supplements instead of only iron and folic acid for women in LMIC[14]; broadening WHO recommendation from use of multiple micronutrient supplements in the context of research to use for all women in LMIC could result in substantial reductions in SGA births, as well as in stillbirths and neonatal deaths. More research is urgently needed to determine the impact of omega-3 fatty acids, zinc supplementation (possibly increasing the zinc dose in multiple micronutrient supplements), calcium supplementation, including a lower dose than currently recommended, or fortification of food with calcium, and folic acid fortification on SVN birth outcomes. Confirmation of the possible effects of these interventions could spur efforts for their implementation. Because the evidence supporting nutritional interventions is strong and growing, it is important to consider the feasibility of improving diets before and during pregnancy to be sufficient in calories, protein, essential fats, micronutrients, and calcium, as well as fortification of staple foods with micronutrients and calcium. While this would be ideal, it will be difficult and slow to achieve in many LMIC and targeted nutritional supplementation may be necessary.

The evidence for use of doppler ultrasound to identify fetuses with poor prognosis showed an effect on perinatal mortality RR 0·71 (0·52-0·98), but non-significant effects on stillbirths and neonatal deaths.[35] Because of the uncertain benefit and very limited experience in LMIC this was not included in our *LiST* analyses. The advent of low-cost doppler devices such as the umbiflow device, implemented by nurses and midwives, may make this technology feasible in LMIC in the future.[36]

Provision of corticosteroids to women at risk of premature labor[27] and delaying cord clamping for preterm births[28] could substantially reduce neonatal mortality. Delaying cord clamping has benefits for anemia in all infants and reduces complication of prematurity, such as necrotizing enterocolitis and sepsis.[37] Later cord clamping should not be conceptualized as an intervention, but rather returning to a normal birth process, instead of the medical practice of early clamping, which has no scientific basis. Delayed cord clamping is of particular importance because it is a neglected and underutilized intervention with a large effect on mortality, which could be implemented immediately with no need for additional commodities.

More antenatal care contacts between pregnant women and health providers as a platform for specific interventions has the potential to save lives.[2] However, with coverage of the previous four-contact schedule in many low resource settings still inadequate (54·8% for the 81 countries, Webappendix Table 4),[38-41] implementing the eight-contact schedule will be challenging. Coverage of the first trimester contact, which is associated with a greater likelihood of regular ANC attendance,[38] was 24·0% in low-income countries compared with 81·9% in high-income countries in 2013.[42] Initiating ANC early in pregnancy is especially important for possible SVN interventions, such as multiple micronutrients, calcium and aspirin, because enhanced benefits have been found with their initiation before 20 weeks of gestation.

Even when a woman receives the scheduled number of contacts, there is no guarantee that she receives the recommended list of interventions, or of the quality of ANC provided. Most studies of ANC coverage are crude and rely on women's recall of the number of ANC contacts through household surveys.[43] In addition, equipment and supplies needed for the essential components of ANC, e.g. blood pressure (BP) measurement and syphilis screening and treatment, are often not available or not utilized.[39,44,45] Data collected on these essential ANC practices are limited and it is increasingly acknowledged that better measurement of effective coverage of the components of ANC is needed to ensure service quality and improve accountability.[43,46-48] WHO has recommended that ANC indicators include the percentage of pregnant women with at least one BP measurement, the percentage of pregnant women with at least one BP measurement in the third trimester, the percentage of women whose baby's heartbeat was listened to at least once, and the percentage of women counselled about danger signs.[47]

Every effort must be made to improve access to repeat routine contacts, particularly in the third trimester for screening for hypertensive disorders and impaired fetal growth, and a contact near term for planning interventions such as labor induction or caesarean section in specific cases However, most of the interventions recommended here could be achieved with a single high quality contact in early pregnancy including: screening for syphilis and HIV, estimation of gestational age and expected date of delivery, including ultrasound, provision of supplements for the whole pregnancy, dietary and lifestyle advice, enquiry for obstetric history suggesting cervical insufficiency, counselling for self-care during pregnancy including danger signs in later pregnancy, contraceptive counselling including postpartum long-acting contraception; and in endemic regions malaria interventions. Insecticide-treated bed nets are one-time interventions (as early in pregnancy as possible). If intermittent preventive treatment for malaria with sulphadoxine/pyrimethamine is indicated, at least three doses should be taken during pregnancy. Psychological interventions for smoking cessation are best initiated in early pregnancy as part of existing counselling interventions, such as healthy eating, physical activity, caffeine, alcohol, substance abuse and intimate partner violence.

Clearly no single intervention in pregnancy can eliminate LBW or its component parts, but combined interventions as part of antenatal care can have an impact. A randomized trial in India demonstrated that a package of interventions in pregnancy, including those we recommend, such as treatment of asymptomatic bacteriuria and reproductive tract infections, multiple micronutrients, protein and energy supplements for underweight women, calcium, and managing medical conditions can reduce SGA by 20%, preterm births by 15% and LBW by13%, although the upper bound of the confidence interval slightly crossed 1 for the latter two outcomes.[49] These results are similar to what we predict with our analyses, and additional interventions e.g., aspirin can increase the impact on preterm births. In addition, the trial found that preconception interventions including multiple micronutrients and nutritional supplements and managing medical conditions that we do not consider in this paper, had additional effects on LBW and SGA.

Detailed approaches to implement these recommendations are beyond the scope of this paper, Close attention must be given to strategies and delivery platforms that reach marginalized and vulnerable populations. These include community-based strategies employing community health workers as well as strategies to organize participatory women groups.[18] The relative benefit of these approaches has been underscored in fragile health systems and humanitarian contexts.[50] These approaches the opportunity for including early identification of pregnancy to the repertoire of work by community health workers, but may by themselves, not substantially impact mortality without addressing timely transport systems and quality maternity care in facilities.

In the last two decades there has been substantial attention to reducing neonatal mortality through improvements in labor and delivery and post-natal care, especially management of asphyxia, sepsis, and complications of preterm birth. These efforts have had some success and remain crucial for further reduction of neonatal deaths. The recognition that SVN, including both preterm and SGA births, have elevated risks of death and for those who survive long-term, consequences for growth, development and adult health should lead to enhanced attention to prevention of these vulnerable birth outcomes. At a cost of $1·1 billion for scaling up proven interventions in the 81 countries in 2030 about 476,000 neonatal deaths could be averted at about $2400 per death. For scaling up proven and potential interventions $4·1 billion per year would be needed to avert about 652,000 neonatal deaths at $6300 per death. Including the full benefit of averting stillbirths and the small vulnerable newborn births with additional effects on post-neonatal mortality and, for those who survive, long-term health consequences would make these interventions even more cost-effective. Implementation with high effective coverage of all interventions that have proven impact on small vulnerable newborns will be necessary to achieve global targets for reduction of LBW and neonatal mortality, as well as longer-term benefits on growth and human capital.

Contributors

GJH, REB and PA conceived the paper. ER conducted the mapping of evidence. NW, REB and AH conducted the *LiST* analysis. RB and GJH wrote the first draft. All authors contributed to the writing and revision of the paper and approved the final version.

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Declarations of interests

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Table 1. Evidence-base of interventions aimed to reduce the incidence of preterm, small for gestational age, low birth weight births or stillbirths.

Intervention	Effect measure: Risk Ratio (95% Confidence Interval) CERTAINTY OF EVIDENCE				Population in the trials	Evidence relevance to low or middle income setting	Effect proven or potential	World Health Organization (WHO) recommendation
	Preterm birth (< 37 weeks)	Small for Gestational Age	Low birthweight	Stillbirth				
Routine interventions for all pregnant women to prevent small vulnerable newborns in LMIC								
Multiple micronutrient supplements† [14]	0·96 (0·91-1·01) **MODERATE**	0·90 (0·84-0·96) **LOW**	0·85 (0·77-0·93) **HIGH**	0·91 (0·85-0·98) **MODERATE**	All pregnant women	All randomized trials were conducted in lower and middle-income countries.	Proven	Recommended in the context of robust research
Screening and treatment for asymptomatic bacteriuria[17]	0·57 (0·21-1.56) **VERY LOW**	Not reported	0·63 (0·45-0·90) **LOW**	Not reported	All pregnant women	All randomized trials conducted in high-income countries.	Proven	Recommended[7]
Screening and treatment for syphilis[15]	0·48 (0·39-0·58)§ Not graded	Not reported	0·50 (0·41-0·58)§ Not graded	0·21 (0·12-0·35)§ Not graded	All pregnant women	Systematic review and meta-analysis of observational studies (unpublished data; Tong H, Heuer A, Walker N)	Proven	Recommended[7]
Omega-3 fatty acid supplements without	0·90 (0·80-1·01) **MODERATE**	1·05 (0·93-1·20) **MODERATE**	0·96 (0·86-1·07) **LOW**	0·92 (0·60-1·42) **LOW**	All pregnant women	Most randomized trials were conducted in upper-middle or	Potential	Currently not recommended by WHO

concomitant interventions[16]						high-income countries.		
Targeted interventions to prevent preterm and SGA births among women with specific indications or needs in LMIC								
Balanced energy and protein dietary supplements[18]	0·86 (0·50-1·46) **VERY LOW**	0·71 (0·54-0·94) **LOW**	0·60 (0·41-0·86) **LOW**	0·39 (0·19-0·80) **LOW**	**Review inclusion**: All pregnant women with no systemic illness.	The randomized trials were conducted primarily in lower and middle-income countries.	Proven	Context-specific recommendation (in undernourished populations)[7]
Low dose aspirin[19]	0·89 (0·81-0·98) **HIGH**	0·95 (0·90-1·01) **HIGH**	0·94 (0·87-1·01) **HIGH**	0·85 (0·68-1·06) **HIGH**	**Trial inclusion**: Nulliparous women with a singleton pregnancy	Highly relevant, randomized trial conducted in in lower and middle-income countries.	Proven	Recommended for women at risk of pre-eclampsia (WHO guideline 2021)
Progesterone (provided vaginally)[20]	0·92 (0·84-1·00) **MODERATE** **< 34 weeks** 0·78 (0·68-0·90) **Not graded**	NR	0·82 (0·74-0·91) **MODERATE**	0·94 (0·53-1·65)** **LOW**	**Review inclusion:** Women with singleton pregnancy at risk of preterm birth (history of preterm birth and/or short cervix ≤25mm)	Randomized Trials conducted across range of settings (high-, middle- and low-income)	Proven	Currently not recommended by WHO

High dose calcium supplements[24]	All women 0·76 (0·60-0·97) **LOW**[††] Women with low Ca intake 0·81 (0·64-1·02) **LOW**	All women 1·05 (0·86-1·29) **MODERATE** Women with low Ca intake 0·85 (0·60-1·21) **MODERATE**	All women 0·85 (0·72-1·01) **MODERATE** Women with low Ca intake 0·95 (0·85-1·05) **MODERATE**	All women 0·90 (0·74-1·09) **MODERATE** Women with low Ca intake 0·86 (0·70-1·07) **MODERATE**	**Review inclusion**: Pregnant women, regardless of the risk of hypertensive disorders of pregnancy (excluded women with diagnosed hypertensive disorders of pregnancy)	Randomized trials conducted across the spectrum of countries.	Potential	Context-specific recommendation (rigorous research)[7]
Psychosocial interventions for smokers[21]	0·93 (0·77-1·11) **HIGH**	Not reported	0·83 (0·72-0·94) **HIGH**	1·20 (0·76-1·90) **HIGH**	**Review inclusion**: Women who are currently smoking or have recently quit smoking and are pregnant, in any care setting.	All randomized trials conducted in high-income countries.	Proven	Currently not recommended by WHO
Insecticide-treated bed nets[22]	0·74 (0·42-1·31) **MODERATE**	Not reported	0·77 (0·61-0.98) **MODERATE**	0·68*** (0·48-0·98) **MODERATE**	**Review inclusion**: Pregnant women in malaria endemic areas.	Randomized trials conducted in low-income countries.	Proven	Recommended for all pregnant women in malaria endemic areas (WHO recommendations for achieving universal coverage with long-lasting insecticidal nets in malaria control 2014)

Zinc supplements[25]	0·87 (0·74-1·03) **LOW**	1·02* (0·92-1·12) **MODERATE**	0·94 (0·79-1·13) **MODERATE**	1·22 (0·80-1·88) **LOW**	**Review inclusion**: Pregnant women with no systemic illness. Women may have had normal zinc levels, or they may have been, or were likely to have been, zinc-deficient.	Randomized trials conducted across the spectrum of countries.	Potential	Context-specific recommendation (rigorous research)[7]
Peri-conception food fortification or supplements with folic acid[26]	0·88 (0·85-0·91)§ Not graded	Not reported	Not reported	Not reported	Women with folate deficiency or needing additional folate	Observational studies conducted in high income countries (US, The Netherlands & Denmark) and China	Proven	Recommended by WHO for prevention of neural tube defect

†Compared with iron with or without folic acid supplementation
††Presented grading is as done by the authors of the original publication. The outcomes that were not included by Summary of Findings were graded for completeness of presented information. For details see Webappendix 1.
**Small for gestational age and intrauterine growth restriction*
***Fetal death/stillbirth*
****Fetal loss – miscarriage or stillbirth*
§Crude, unadjusted risk ratio

Table 2. Targeted interventions to manage pregnancies identified as at risk of preterm delivery or with preterm delivery or ruptured membranes

Intervention (Source of evidence)	Effect of intervention		Population	Evidence relevance to LMIC setting	Effect proven or potential	Intervention in the context of WHO guidelines
	Outcome	Effect RR (95%CI)				
Antenatal corticosteroid[27]	**Neonatal deaths from preterm birth**	0·85 (0·77-0·93) **MODERATE**	Women at risk of preterm delivery	Half of the included trials (10/20) were conducted in low and middle-income setting.	Proven	Recommended by WHO for women at risk of premature delivery
Delayed cord clamping[28]	**Neonatal deaths from preterm birth**	0·73 (0·54-0·98) **MODERATE**	Women with preterm delivery	The trials were conducted mainly in high income setting.	Proven	Recommended (Intrapartum WHO guideline 2018) recommendation has been integrated from WHO Guideline: delayed cord clamping for improved maternal and infant health & nutrition outcomes

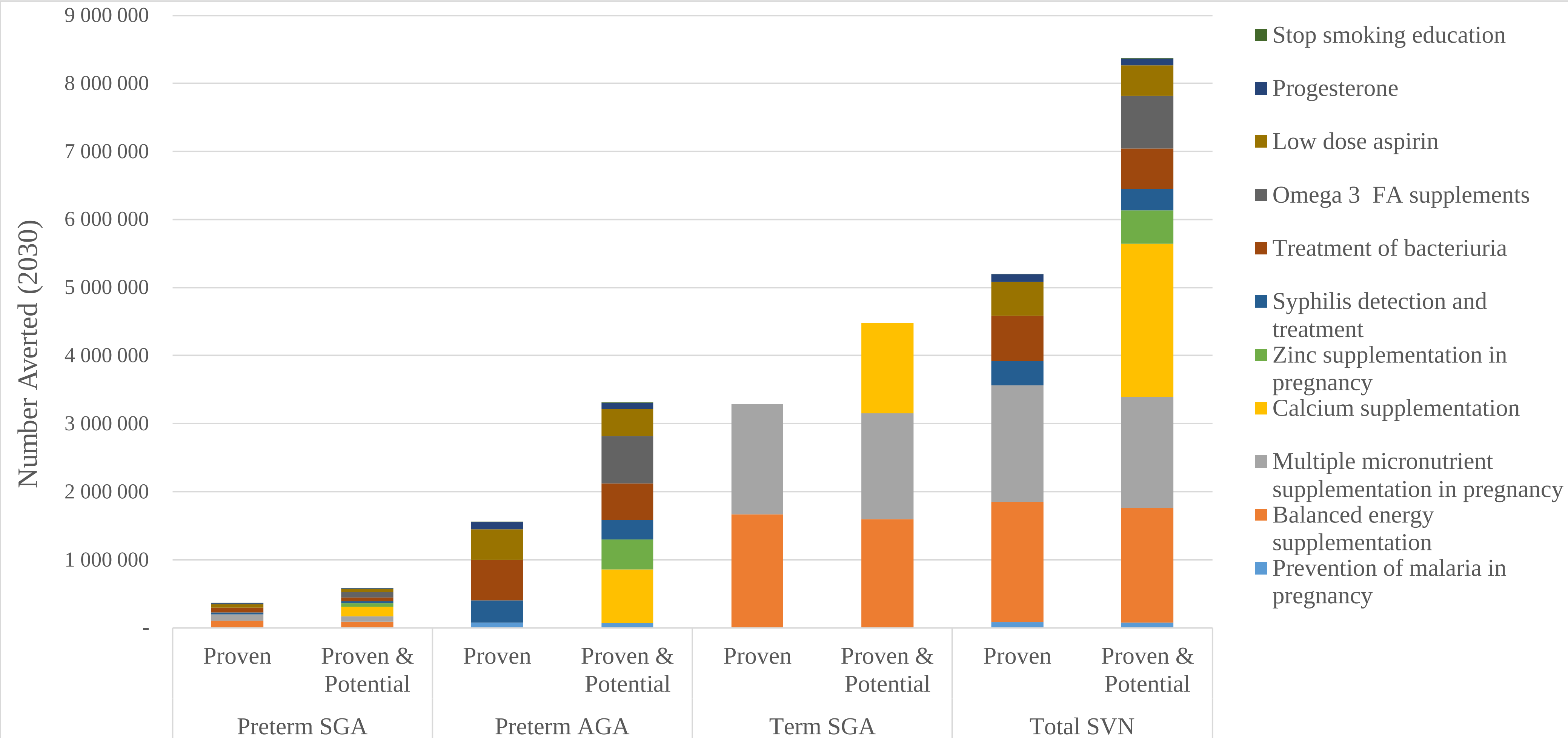

Figure 1. Impact of interventions on small vulnerable newborn types in 81 low- and middle-income countries

Table 3. Percent Decrease in Adverse Birth Outcomes for 81 Countries and by Region

	Preterm SGA		Preterm AGA		Term SGA		Total SVN		Low birthweight	
	Proven Interventions	***Proven & Potential Interventions***	***Proven Interventions***	***Proven & Potential Interventions***	***Proven Interventions***	***Proven & Potential Interventions***	***Proven Interventions***	***Proven & Potential Interventions***	***Proven Interventions***	***Proven & Potential Interventions***
All Countries										
	31·7 (17·3 - 45·87)	51·02 (17·3 - 73·89)	16·92 (12·76 - 25·18)	36·02 (12·76 - 56·17)	17·39 (5·45 - 26·81)	23·69 (5·45 - 41·54)	17·8 (8·21 - 27·04)	28·63 (8·21 - 47·47)	17·88 (8·28 - 27·05)	28·55 (8·28 - 46·87)
By Region										
Central & Southern Asia	27·51 (15·4 - 40·84)	47·07 (15·4 - 70·17)	14·74 (11·01 - 23)	33·6 (11·01 - 53·83)	15·14 (4·95 - 23·44)	21·05 (4·95 - 37·51)	15·61 (6·66 - 24·11)	24·77 (6·66 - 42·25)	15·83 (6·7 - 24·4)	24·88 (6·7- 42·27)
Eastern & South-Eastern Asia	27·08 (14·29 - 40·81)	50·3 (14·29 - 75·46)	13·76 (9·76 - 22·19)	34·67 (9·76 - 56·14)	15·34 (5 - 23·77)	23·87 (5 - 44·09)	15·14 (7·47 - 23·75)	29·61 (7·47 - 5·36)	15·17 (7·3 - 23·72)	29·05 (7·3- 49·27)
Latin America & Caribbean	30·6 (16·3 - 44·43)	49·02 (16·3 - 71·94)	16·83 (11·66 - 25·24)	34·42 (11·66- 54·05)	17·35 (5·43 - 26·83)	23·2 (5·43 - 40·62)	17·63 (8·62 - 26·76)	29·11 (8·62 - 47·5)	17·55 (8·6 - 26·54)	28·81 (8·6- 46·62)
North Africa & Western Asia	29·22 (15·3 - 42·56)	46·93 (15·3 - 69·23)	15·59 (10·68- 23·39)	32·6 (10·68 - 51·48)	16·19 (5·18 - 25·08)	21·35 (5·18 - 37·68)	16·53 (8·31 - 25·09)	27·92 (8·31 - 46·61)	16·61 (8·15 - 25·17)	27·47 (8·15- 44·75)
Oceania	30·6 (14·34 - 45·14)	38·76 (14·34 - 57·79)	13·52 (8·91 - 21·16)	23·11 (8·91 - 38·24)	19·86 (5·98 - 30·58)	20·2 (5·98 - 31·39)	18·35 (7·08 - 28·27)	21·57 (7·08 - 34·07)	18·55 (7·03 - 28·52)	21·53 (7·03- 33·84)
Sub-Saharan Africa	39·55 (21·1 - 55·27)	58·23 (21·1 - 80·49)	19·54 (15·09 - 27·82)	38·97 (15·09 - 59·05)	24·56 (7·01 - 37·56)	31·92 (7·01- 53·9)	22·8 (11·48 - 33·61)	36·29 (11·48 - 57·11)	22·63 (11·7 - 33·17)	36·2 (11·7- 56·73)

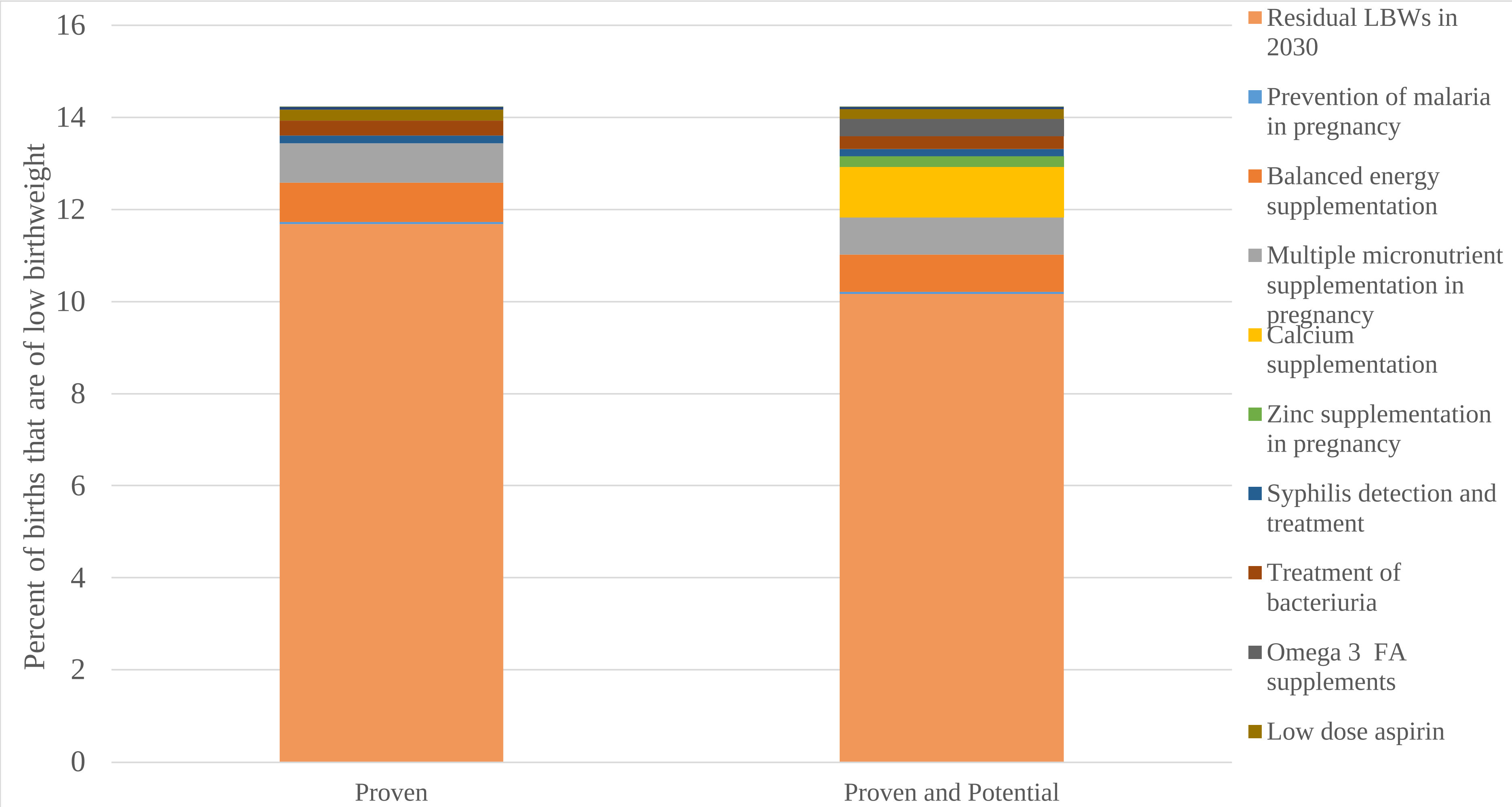

Figure 2. Contribution of antenatal interventions to achieving the World Health Assembly target for 30% reduction in the prevalence of low birth weight births in 2030 in 81 low- and middle-income countries.

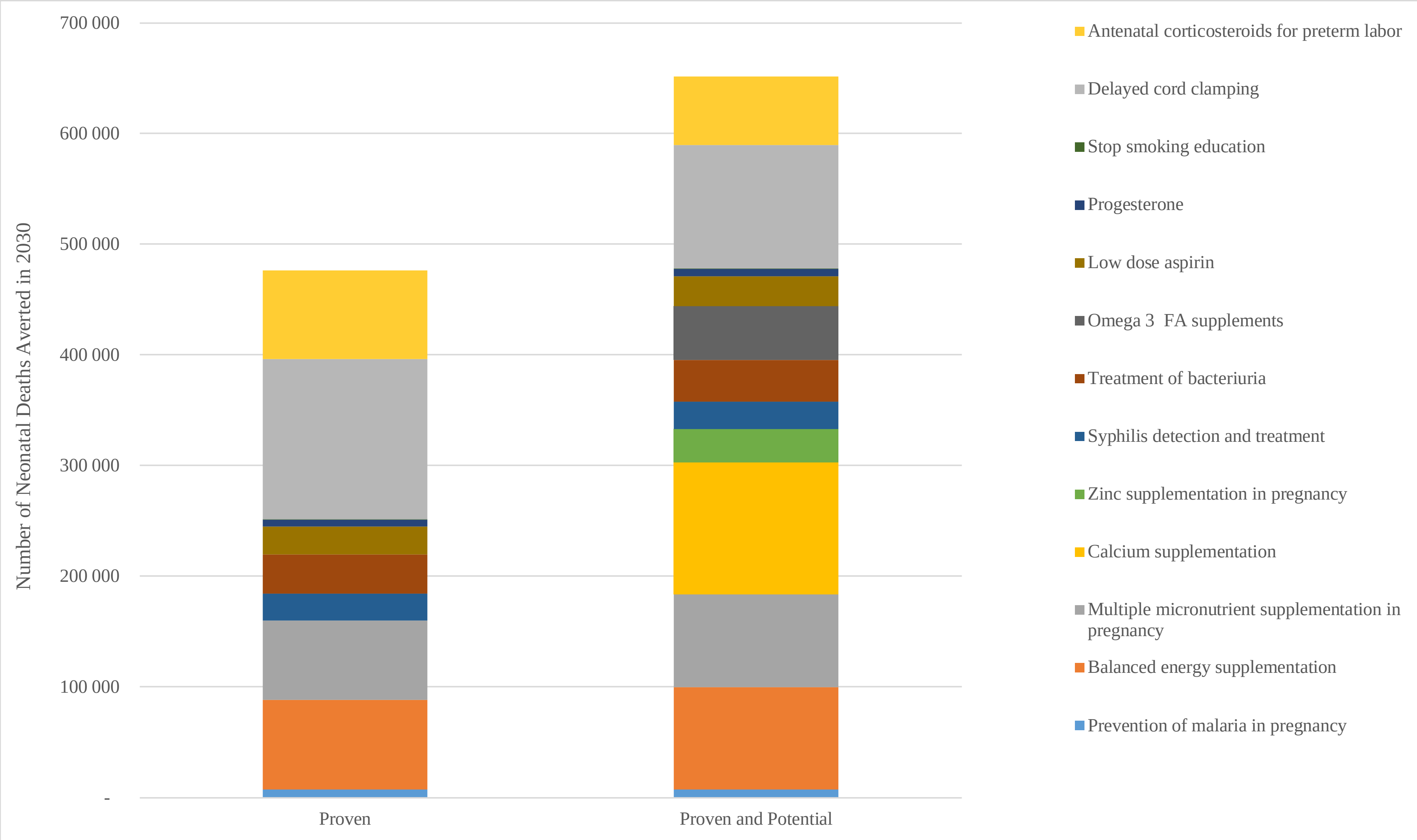

Figure 3. Neonatal Deaths Averted by Intervention in 2030 for 81 low- and middle-income countries