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

G Justus Hofmeyr, Robert E Black*, Ewelina Rogozińska, Austin Heuer, Neff Walker, Per Ashorn, Ulla Ashorn, Nita Bhandari, Zulfiqar A Bhutta, Annariina Koivu, Somesh Kumar, Joy E Lawn, Stephen Munjanja, Pieta Näsänen-Gilmore, Doreen Ramogola-Masire, Marleen Temmerman, and the* Lancet *Small Vulnerable Newborn Steering Committee†*

A package of care for all pregnant women within eight scheduled antenatal care contacts is recommended by WHO. Some interventions for reducing and managing the outcomes for small vulnerable newborns (SVNs) exist within the WHO package and need to be more fully implemented, but additional effective measures are needed. We summarise evidence-based antenatal and intrapartum interventions (up to and including 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-income and middle-income countries, could prevent 5·202 million SVN births (sensitivity bounds 2·398–7·903) and 0·566 million stillbirths (0·208–0·754) per year. These interventions, along with two that can reduce the complications of preterm (<37 weeks' gestation) births (antenatal corticosteroids and delayed cord clamping), could avert 0·476 million neonatal deaths (0·181–0·676) per year. If further research substantiates the preventive effect of three additional interventions (supplementation with omega-3 fatty acids, calcium, and zinc) on SVN births, about 8·369 million SVN births (2·398–13·857) and 0·652 million neonatal deaths (0·181–0·917) could be avoided per year. Scaling up the eight proven interventions and two intrapartum interventions would cost about US$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 effects on SVN babies, within the context of access to family planning services and addressing social determinants of health. Attaining high effective coverage with these interventions will be necessary to achieve global targets for the reduction of low birthweight births and neonatal mortality, and long-term benefits on growth and human capital.

Published **Online**
May 8, 2023
https://doi.org/10.1016/S0140-6736(23)00355-0

See **Online/Comment**
https://doi.org/10.1016/S0140-6736(23)00721-3

This is the fourth in a **Series** of four papers about small vulnerable newborns. All papers in the Series are available at https://www.thelancet.com/series/small-vulnerable-newborns

*Joint first authors

†Collaborators listed at the end

Department of Obstetrics and Gynaecology, University of Botswana, Gaborone, Botswana (Prof D Ramogola-Masire MD, Prof G J Hofmeyr DSc); **Effective Care Research Unit, University of the Witwatersrand, Johannesburg, South Africa** (Prof G J Hofmeyr); **Department of Obstetrics and Gynaecology, Walter Sisulu University, East London, South Africa** (Prof G J Hofmeyr); **Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (Prof R E Black MD, A Heuer MSc, N Walker PhD); **Evidence-Based Medicine Consultancy, Bath, UK** (E Rogozińska PhD); **Center for Child, Adolescent, and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland** (Prof P Ashorn MD, U Ashorn PhD, A Koivu PhD, P Näsänen-Gilmore PhD); **Department of Paediatrics, Tampere University Hospital, Tampere, Finland** (Prof P Ashorn); **Centre for Health Research and Development, Society for Applied Studies,**

Introduction

Antenatal care, the routine health care provided to pregnant women and adolescent girls, was first introduced in the UK in the 1920s.[1] The original UK schedule, comprising antenatal contacts at around weeks 16, 24, and 28, followed by fortnightly contacts up to 36 weeks' gestation and then weekly contacts until childbirth, is thought to have informed antenatal care programmes worldwide.[1,2] As this schedule was not evidence based, in the 1990s, WHO did a large randomised controlled 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 than in the standard model. The statistical significance of the results for this secondary outcome was not reported in the original publication. 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 gestational weeks 12, 26, and 32, and between gestational weeks 36 and 38.

In 2013, reanalysis of WHO trial data confirmed an increase in perinatal mortality in the four-contact model compared with the eight-contact model,[5] as did a systematic review of three trials from low-income and middle-income countries (LMICs).[2] WHO reviewed its guidance on the basis of these findings and a subsequently published report from South Africa, which found an increase in third trimester stillbirths with the four-contact model.[6] In 2016, WHO antenatal care guidelines were published, recommending an integrated package of care delivered by eight scheduled antenatal contacts at gestational weeks 12, 20, 26, 30, 34, 36, 38, and 40, designed for the routine care of healthy pregnant women and adolescent girls.[7] A notable 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. Although the guidelines include a selection of interventions aimed at women in particular high-risk contexts (eg, women living in malaria-endemic areas), interventions aimed at improving outcomes among pregnant women at high risk of having a small vulnerable newborn (SVN), such

New Delhi, India (N Bhandari PhD); Centre of Excellence in Women and Child Health & Institute for Global Health & Development, Aga Khan University, Karachi, Pakistan (Prof Z A Bhutta PhD); Centre for Child Global Health, Hospital for Sick Children, Toronto, ON, Canada (Prof Z A Bhutta); Jhpiego, Baltimore, MD, USA (S Kumar PhD); MARCH Center, London School of Hygiene & Tropical Medicine, London, UK (Prof J E Lawn PhD); Department of Obstetrics and Gynaecology, University of Zimbabwe, Harare, Zimbabwe (Prof S Munjanja MD); Centre of Excellence in Women and Child Health—East Africa, Aga Khan University, Nairobi, Kenya (Prof M Temmerman PhD)

Correspondence to: Prof Robert E Black, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA rblack1@jhu.edu

See Online for appendix

Key messages

Package of proven antenatal interventions

The eight contacts recommended by WHO during pregnancy provide a means to implement quality antenatal care, including interventions to reduce the incidence of small vulnerable births and stillbirths. Proven antenatal interventions, including multiple micronutrient supplements, balanced protein and 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 supports their efficacy for reducing the incidence of small vulnerable births, omega-3 fatty acids supplements, zinc supplements (or higher doses of zinc in multiple micronutrient supplements), and calcium supplements would provide substantial additional benefits.

Effects and cost

If full coverage (90%) of eight interventions with proven efficacy is achieved in 2030 in 81 low-income and middle-income countries, more than 5 million preterm and small-for-gestational age births, over half a million stillbirths, and nearly half a million neonatal deaths could be prevented at a cost of US$1·1 billion. If three additional interventions with potential benefits are proven efficacious and added to full coverage antenatal care in 2030, more than 8 million preterm or small-for-gestational-age births, and more than half a million stillbirths and neonatal deaths could be prevented at a cost of $4·1 billion.

Accelerating progress towards targets

Implementation of proven interventions in antenatal care could bring the neonatal mortality rate in these 81 countries from 25·1 deaths per 1000 livebirths in 2023 to 20·1 deaths per 1000 livebirths in 2030, a 20% reduction, and could reduce the prevalence of low birthweight by 17·9%—more than half of the World Health Assembly's 30% reduction target for 2030. Implementation of the proven and potential interventions could reduce the neonatal mortality rate to 18·3 per 1000 livebirths, helping to achieve the Sustainable Development Goal target of 12 or fewer deaths per 1000 livebirths, and could reduce the prevalence of low birthweight by 28·6%, nearly meeting the World Health Assembly's 30% reduction target.

as women with a history of preterm birth, HIV, or a risk of pre-eclampsia, tend to be fragmented across other WHO guidelines.

The SVN term, as defined in the first paper in this Series, includes preterm newborns (born before 37 weeks' gestation), babies who are small for gestational age (SGA; birthweights below the 10th percentile for gestational age and sex), and low birthweight (LBW) babies (weighing <2500 g) who are not preterm or SGA.[8] The SVN term comprises a larger group of small babies who are preterm or SGA, but who might not all be LBW. The worldwide prevalence of SVN births in 2020 has been estimated at 26·2% of livebirths annually, including 9·9% 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 newborn babies will establish whether Sustainable Development Goal 3.2 for the reduction of neonatal and child mortality is met.

We recognise the fundamental role of social determinants of health in pregnancy, such as physical safety, food and water security, sanitation, education, employment, infrastructure, and equity. However, these determinants, and the management of medical conditions and pregnancy complications, are beyond the scope of this paper. Instead, we have focused on interventions with robust evidence of effectiveness from randomised controlled trials. We acknowledge that antenatal and intrapartum interventions exist that are widely recommended but not supported by randomised controlled trial evidence. This lack of support is due to lack of equipoise regarding their effectiveness, such as caesarean delivery for breech presentation and obstetric interventions for preterm multiple pregnancy. Avoidance of unintended pregnancy is essential to achieve improvements in every aspect of pregnancy outcomes, including SVN births. The focus of this paper is on antenatal interventions in LMICs to prevent SVN births, and peripartum and intrapartum interventions to improve SVN outcomes implemented by obstetric or midwifery providers, up to and including clamping of the umbilical cord. 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 antenatal care framework, and estimate the annual number of SVN births, stillbirths, neonatal deaths, and cases of stunting averted by scaling up the interventions in 81 LMICs, and the anticipated additional costs.

Evidence for antenatal interventions from a global review

In three major databases of medical literature (MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials), we systematically searched for papers published between Jan 1, 2000, and Oct 8, 2020, to identify systematic reviews of interventions aimed at reducing the incidence of preterm, SGA, or LBW births, and their associated poor outcomes (see appendix pp 2–19 for search details). The searches were subsequently restricted to papers published between Jan 1, 2015, and Oct 8, 2020, and were supplemented with the findings of a separate review[10,11] and input from the wider group of experts collaborating on the *Lancet* Small Vulnerable Newborn series. If 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 randomised controlled trials done only in an LMIC or if the non-Cochrane review was more current than the Cochrane one.

Identified interventions were grouped according to whether they were applicable to all pregnant women, pregnant women at increased risk of having a preterm or SGA birth, or pregnant women with imminent preterm birth. We classified interventions with a significant benefit on preterm birth, SGA, or LBW as proven, and interventions with non-significant evidence, but with an overall suggestion of benefit, as potential. These potential interventions require evidence of their effectiveness through further research. We have listed the interventions considered in the review of evidence (appendix pp 5–6) and assessed them accordingly (appendix pp 7–19). We report risk ratios (RRs) taken from the selected meta-analyses or trials. We present the interventions (classified as proven or potential) with their respective measures and information about the certainty of evidence with the Grading of Recommendations Assessment, Development, and Evaluation framework[12] (tables 1, 2).

Although no interventions show an overall increase in births, early pregnancy interventions that improve placental function might enable pregnancies that would have otherwise been lost before viability and thus not counted, to be prolonged and lost after viability, or present with growth impairment. These pregnancies could result in a spurious increase in stillbirth or SGA births, which could lead to underestimation of 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. Data generation and synthesis is a constantly evolving field[30] and it is not easy to keep abreast of new evidence. Due to the wide scope of this work, some more current systematic reviews could have been missed. Furthermore, for interventions with more than one systematic review, we have chosen the one that most closely corresponds with current WHO recommendations (such as calcium supplementation for women with low dietary calcium intake), or specifies how the intervention could be implemented in an LMIC setting.

Routine interventions for all pregnant women to prevent SVN types

We identified four interventions with evidence showing or suggesting a potential reduction in the rate of preterm or SGA births among pregnant women in LMICs (table 1). The evidence for multiple micronutrient supplementation compared with just iron and folic acid supplementation shows an effect on LBW births (RR 0·85 [95% CI 0·77–0·93]), SGA births (0·90 [0·84–0·96]), and stillbirths (0·91 [0·85–0·98]).[13] The evidence for detection and treatment of syphilis is based on a meta-analysis (Tong H, Heuer A, Walker N, unpublished) of observational studies that compared early versus late syphilis treatment, treated versus untreated syphilis, and appropriate versus inappropriate syphilis treatment. There was high consistency across the three comparisons, and we used the effect of early versus late initiation of syphilis treatment on LBW births (0·50 [0·41–0·58] and preterm births (0·48 [0·39–0·58]). The evidence for stillbirths is based on studies of pregnant women treated for syphilis.[15] Omega-3 fatty acids supplementation (without concomitant interventions) reduced preterm births before 34 weeks' gestation (0·62 [0·46–0·82]), but there was no significant effect on preterm births before 37 weeks' gestation (0·90 [0·80–1·01]).[16] Detection and treatment of asymptomatic bacteriuria in pregnancy is a WHO-recommended intervention because of its effect on LBW birth (0·63 [0·45–0·90]); the evidence comes mainly from studies done in high-income countries.[14] There was no significant effect on preterm births (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 showing or suggesting a 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 (RR 0·71 [95% CI 0·54–0·94]) and stillbirths (0·39 [0·19–0·80]).[17] Low-dose aspirin reduced preterm births (0·89 [0·81–0·98]).[18] Progesterone provided vaginally reduced preterm births before 34 weeks' gestation (0.78 [0.68–0.90]), and the effect on preterm births (0·92 [0·84–1·00]) was close to significance.[20] Psychosocial treatment for smoking cessation[22] is a WHO-recommended intervention based on its effect on LBW births (0·83 [0·72–0·94]); however, this approach did not have a significant effect on preterm births (0·93 [0·77–1·11]). The evidence for insecticide-treated bednets shows an effect on LBW births (0·77 [0·61–0·98]) and stillbirths (0·68 [0·48–0·98]), but not on preterm births (0·74 [0·42–1·31]).[23] The provision of intermittent preventive therapy with antimalarials in pregnancy has a similar effect on LBW births to that of insecticide-treated bednets.[31] The other three interventions show potential in reducing the rate of preterm or SGA births; however, more research is required to establish the effects before they can be recommended for prevention of these birth outcomes. Calcium supplementation in all women reduced preterm births before 37 weeks' gestation (0·76 [0·60–0·97]), but did not significantly reduce preterm births in women with low calcium intake

(0·81 [0·64–1·02]).[22] Zinc supplementation, which is currently recommended by WHO for additional research, did not significantly reduce preterm births before 37 weeks' gestation (0·87 [0·74–1·03]).[25]

Evidence derived from the synthesis of multiple observational studies shows that the consumption of foods fortified with folic acid at the time of conception and throughout pregnancy seems to be associated with a

	Effect measure (95% CI); certainty of evidence				Population in the trials	Evidence relevance to low-income or middle-income setting	Effect proven or potential	WHO recommendation
	Preterm birth (<37 weeks)	SGA	Low birthweight	Stillbirth				
Routine interventions for all pregnant women to prevent the incidence of small vulnerable newborns in LMICs								
Multiple micronutrient supplements*[13]	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 randomised trials were done in LMICs	Proven	Recommended in the context of research
Screening and treatment for asymptomatic bacteriuria[14]	0·57 (0·21–1·56); very low	Not reported	0·63 (0·45–0·90); low	Not reported	All pregnant women	All randomised trials were done 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 (Tong H, Heuer A, Walker N, unpublished)	Proven	Recommended[7]
Omega-3 fatty acids supplements without concomitant interventions[16]	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 randomised trials were done in upper-middle-income or high-income countries	Potential	Currently not recommended by WHO
Targeted interventions to prevent preterm and SGA births among women with specific indications or needs in LMICs								
Balanced energy and protein supplements[17]	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	Randomised trials were done primarily in LMICs	Proven	Context-specific recommendation (in undernourished populations)[7]
Low-dose aspirin[18]	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, randomised trial done in LMICs	Proven	Recommended for women at risk of pre-eclampsia (2021 WHO guideline)[19]
Progesterone (provided vaginally)[20]	<37 weeks: 0·92 (0·84–1·00); moderate; <34 weeks: 0·78 (0·68–0·90); not graded	Not reported	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 or short cervix ≤25mm, or both)	Randomised trials done across a range of settings (high-income, middle-income, and low-income countries)	Proven	Currently not recommended by WHO
Calcium supplements[21]	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 (women diagnosed with hypertensive disorders of pregnancy were excluded)	Randomised trials done across many countries	Potential	Context-specific recommendation (rigorous research)[7]
Psychosocial interventions for smokers[22]	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 randomised trials done in high-income countries	Proven	Currently not recommended by WHO

(Table 1 continues on next page)

	Effect measure (95% CI); certainty of evidence				Population in the trials	Evidence relevance to LMIC setting	Effect proven or potential	WHO recommendation
	Preterm birth (<37 weeks)	SGA	Low birthweight	Stillbirth				
(Continued from previous page)								
Insecticide-treated bednets[23]	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	Randomised trials done in low-income countries	Proven	Recommended for all pregnant women in malaria-endemic areas (2014 WHO recommendation)[24]
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 who might have had normal zinc concentrations, or who might have been, or were likely to have been, zinc deficient	Randomised trials done across many countries	Potential	Context-specific recommendation (rigorous research)[7]
Periconception food fortification or supplementation 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 done in high-income countries (the USA, the Netherlands, and Denmark) and China	Proven	Recommended by WHO for prevention of neural tube defects

SGA=small for gestational age. LMICs=low-income and middle-income countries. *Compared with iron with or without folic acid supplementation. †Crude, unadjusted risk ratio. ‡Fetal death or stillbirth. §Presented grading is as done by the authors of the original publication. The outcomes that were not included by the summary of findings were graded for completeness of presented information. ¶Fetal loss due to miscarriage or stillbirth. ||SGA and intrauterine growth restriction.

Table 1: **Evidence base of interventions aimed to reduce the incidence of preterm births, SGA births, low birthweight births, or stillbirths**

	Effect of intervention		Population	Evidence relevance to LMIC setting	Effect proven or potential	Intervention in the context of WHO guidelines
	Outcome	Effect measure (95% CI); certainty of evidence				
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 done in LMICs	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 done mainly in high-income settings	Proven	Recommended by WHO[29]

LMICs=low-income and middle-income countries.

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

reduction in preterm births (RR 0·88 [0·85–0·91]).[26] However, we did not include this intervention in our modelling as it is not provided as part of routine antenatal care.

Targeted interventions to manage a 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.[32]

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

We used the Lives Saved Tool (LiST)[33] to estimate the effect 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 subnational level. LiST incorporates coverage data for 70 interventions whose efficacy values are routinely updated to reflect current evidence. The tool includes the effect of interventions delivered before or during pregnancy on birth outcomes (such as stillbirths, preterm births, SGA births, and LBW births). When there are significant effects of interventions for preterm births or SGA births, these interventions were used in LiST. For interventions with a significant effect on LBW births, but not on preterm births or SGA births, the effects on these birth outcomes were used regardless of their significance. The effectiveness of an intervention is applied to a predefined subset of the total population that would benefit from that intervention to estimate the effect of increased coverage on specific health outcomes (LiST methods are briefly described in the appendix p 20).

Our study's analysis of proven interventions included eight interventions that are shown to prevent preterm or SGA births (appendix p 21) and from these effects we estimate their influence on the prevention of LBW births. To model the effect of these interventions, we increased coverage from 2023 national levels (appendix pp 22–25) to 90% coverage in 2024 for 81 countries (appendix pp 26–27). We also did a supplemental analysis of proven and potential interventions to model the effects of increasing the coverage of three other interventions in addition to those included in the analysis of proven interventions (appendix p 28).

Each LiST analysis estimated the change in the number of preterm births, SGA births, LBW births, and stillbirths resulting from increased intervention coverage. We used the intervention effects from selected meta-analyses (tables 1, 2, appendix p 21). To create sensitivity bounds (SB), we did the same LiST analyses with the upper and lower 95% CIs from these meta-analyses for all included interventions and outcomes.

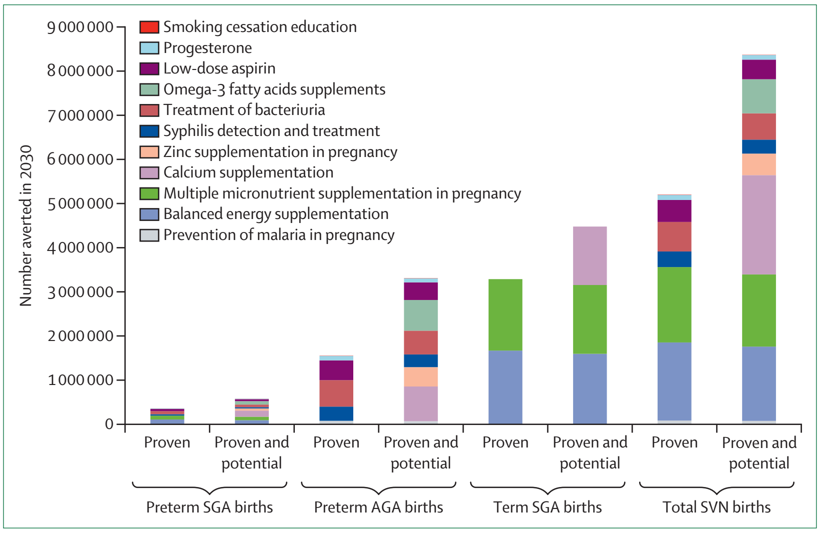

Figure 1: **Impact of interventions on SVN types in 81 low-income and middle-income countries**
AGA=appropriate for gestational age. SGA=small for gestational age. SVN=small vulnerable newborn.

On the basis of 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 combined. The assumptions for increased intervention coverage were made for 2024 and continued at that level until 2030. Results were grouped at regional levels and were also presented for all 81 countries. We estimated the costs of scaling up the proven and potential interventions with methods (appendix pp 29–30) and costs (appendix pp 31–33). All models were generated with LiST version 6.2 beta 34.

Analysis of proven interventions

After full scale-up of proven interventions, about 0·360 million (SB 0·196–0·521) combined preterm and SGA (preterm-SGA) births, 1·556 million (1·173–2·315) preterm appropriate-for-gestational-age (preterm-AGA) births, and 3·287 million (1·029–5·068) term SGA births, amounting to a total of about 5·202 million (2·398–7·903) SVN births, could be averted per year (figure 1, appendix pp 34–36). Among these SVN births would be about 2·442 million (1·131–3·694) LBW births (appendix pp 34–36).

Low-dose aspirin supplementation and the treatment of asymptomatic bacteriuria and syphilis account for 87·9% (1 367 505/1 555 630) 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. These two nutrition interventions could have the greatest effect on LBW births, accounting for 67·1% (1 638 245/2 442 040) of the total.

Among the SVN types, increased coverage of the eight interventions included in the proven interventions analysis could decrease preterm-SGA births for all 81 countries by 31·7% (SB 17·3–45·9; table 3). The overall decrease would be 17·4% (5·5–26·8) for term-SGA births, 16·9% (12·8–25·2) for preterm-AGA births, and 17·9% (8·3–27·1) for LBW births. Increased coverage of the eight interventions would reduce all types of SVN births by 17·8% (8·2–27·0), and could reduce the prevalence of LBW births from 14·2% in 2023 to 11·7% in 2030 (figure 2).

The proven interventions could avert about 0·566 million (SB 0·208–0·754) stillbirths per year (68·0% from balanced energy and protein supplementation; appendix p 36), resulting in a reduction of 31·5% of the projected 1·794 million stillbirths in 2030. About 0·476 million (0·181–0·676) neonatal deaths could be averted per year as a result of full coverage of eight proven antenatal interventions and two intrapartum interventions (appendix p 37, figure 3). Scaling up these interventions would result in a 20·0% 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

	Preterm SGA		Preterm AGA		Term SGA		Total SVN births		Low birthweight	
	Proven interventions (% decrease [SB])	Proven and potential Interventions (% decrease [SB])	Proven interventions (% decrease [SB])	Proven and potential interventions (% decrease [SB])	Proven interventions (% decrease [SB])	Proven and potential interventions (% decrease [SB])	Proven interventions (% decrease [SB])	Proven and potential interventions (% decrease [SB])	Proven interventions (% decrease [SB])	Proven and potential interventions (% decrease [SB])
All countries	31·7 (17·3–45·9)	51·0 (17·3–73·9)	16·9 (12·8–25·2)	36·0 (12·8–56·2)	17·4 (5·5–26·8)	23·7 (5·5–41·5)	17·8 (8·2–27·0)	28·6 (8·2–47·5)	17·9 (8·3–27·1)	28·6 (8·3–46·9)
Central and southern Asia	27·5 (15·4–40·8)	47·1 (15·4–70·2)	14·7 (11·0–23·0)	33·6 (11·0–53·8)	15·1 (5·0–23·4)	21·1 (5·0–37·5)	15·6 (6·7–24·1)	24·8 (6·7–42·3)	15·8 (6·7–24·4)	24·9 (6·7–42·3)
Eastern and southeastern Asia	27·1 (14·3–40·8)	50·3 (14·3–75·5)	13·8 (9·8–22·2)	34·7 (9·8–56·1)	15·3 (5·0–23·8)	23·9 (5·0–44·1)	15·14 (7·5–23·8)	29·6 (7·5–50·4)	15·2 (7·3–23·72)	29·1 (7·3–49·3)
Latin America and the Caribbean	30·6 (16·3–44·4)	49·0 (16·3–71·9)	16·8 (11·7–25·2)	34·4 (11·7–54·1)	17·4 (5·4–26·8)	23·2 (5·4–40·6)	17·6 (8·6–26·8)	29·1 (8·6–47·5)	17·6 (8·6–26·5)	28·8 (8·6–46·6)
North Africa and western Asia	29·2 (15·3–42·6)	46·9 (15·3–69·2)	15·6 (10·7–23·4)	32·6 (10·7–51·5)	16·2 (5·2–25·1)	21·4 (5·2–37·7)	16·5 (8·3–25·1)	27·9 (8·3–46·6)	16·6 (8·2–25·2)	27·5 (8·2–44·8)
Oceania	30·6 (14·3–45·1)	38·8 (14·3–57·8)	13·5 (8·9–21·2)	23·1 (8·9–38·2)	19·9 (6·0–30·6)	20·2 (6·0–31·4)	18·4 (7·1–28·3)	21·6 (7·1–34·1)	18·6 (7·0–28·5)	21·5 (7·0–33·8)
Sub-Saharan Africa	39·6 (21·1–55·3)	58·2 (21·1–80·5)	19·5 (15·1–27·8)	39·0 (15·1–59·1)	24·6 (7·0–37·6)	31·9 (7·0–54·0)	22·8 (11·5–33·6)	36·3 (11·5–57·1)	22·6 (11·7–33·2)	36·2 (11·7–56·7)

SB=sensitivity bounds. SGA=small for gestational age. AGA=appropriate for gestational age. SVN=small vulnerable newborn.

***Table 3:* Percentage decrease in adverse birth outcomes for 81 countries and by region**

births (30·3%), balanced protein and energy supplementation (17·0%), antenatal corticosteroids for preterm labour (16·9%), and multiple micronutrient supplementation (15·1%). The nutrition interventions alone could account for 32·0% (152 169/476 169) of the reduction in deaths. Increased coverage of these interventions could reduce the neonatal mortality rate from 25·1 deaths per 1000 livebirths in 2023 to 20·1 deaths per 1000 livebirths in 2030 (appendix p 38).

The number of children with stunting in the 81 countries in 2030 could be 2·9% lower because of increased coverage of the eight interventions included in the proven interventions analysis (appendix p 39). This decrease amounts to about 4·536 million fewer children with stunting globally in 2030 than in 2023, with the largest reduction in central and southern Asia (3·9%). The scale-up of proven interventions could also result in about 0·529 million additional years of schooling and about US$7·269 billion additional lifetime earnings for the first birth cohort after full coverage of interventions in 81 countries (appendix p 39).

Analysis of proven and potential interventions

After full scale-up of proven and potential interventions, about 0·579 million preterm-SGA births (SB 0·196–0·839), 3·312 million preterm-AGA births (1·173–5·166), and 4·478 million term-SGA births (1·029–7·852) could be averted per year, amounting to a total of 8·369 million SVN births (2·398–13·857), with 3·899 million LBW births (1·131–6·402; figure 1, appendix pp 34–36).

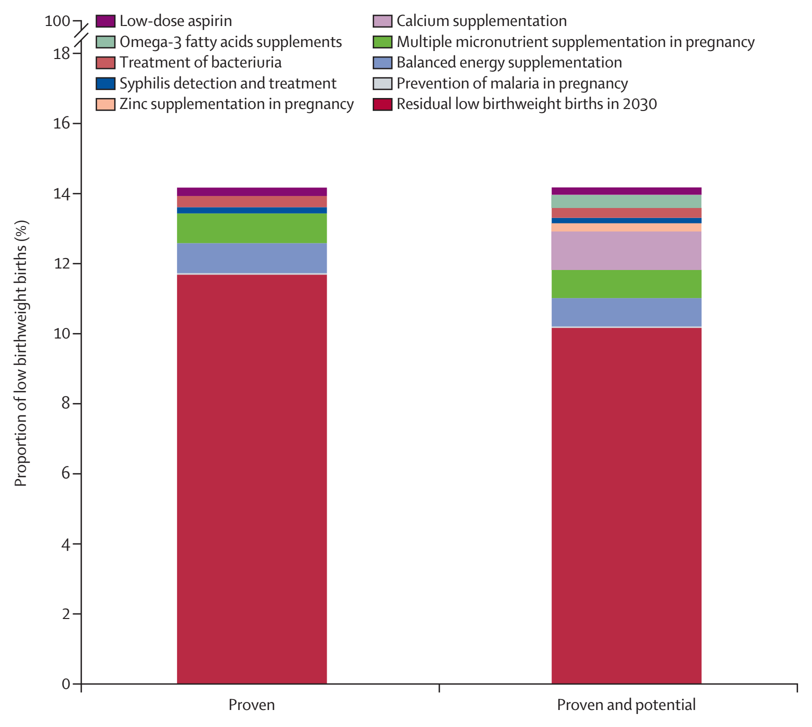

***Figure 2:* Contribution of antenatal interventions in achieving the World Health Assembly target of a 30% reduction in the prevalence of low birthweight births in 2030, in 81 low-income and middle-income countries**

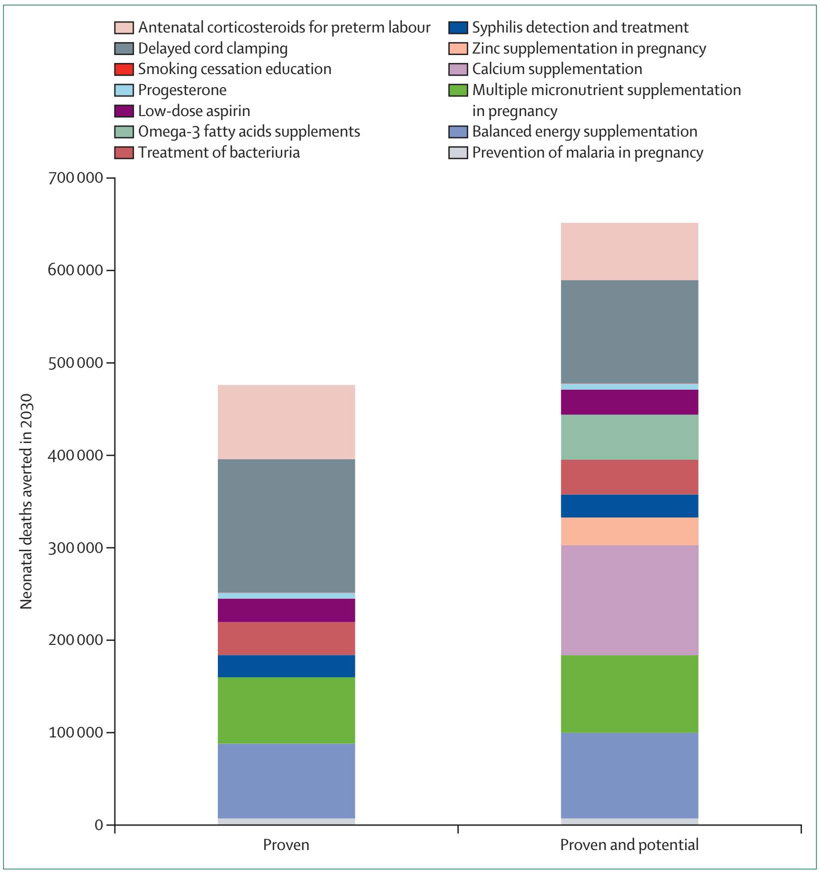

Figure 3: **Neonatal deaths averted by intervention in 2030 for 81 low-income and middle-income countries**

Increased calcium supplementation would have the largest effect on preterm-AGA births (a reduction of 23·7%), followed by omega-3 fatty acids (21·0%) and treatment of bacteriuria (16·2%; appendix pp 34–36). Balanced protein and energy supplementation, multiple micronutrient supplementation, and calcium supplementation each reduced term-SGA births by 29·6–35·6% (appendix p 35). These combined supplementations had the greatest effect on LBW births, accounting for 66·7% (2 601 781/3 898 607) of the total reduction.

The analysis of proven and potential interventions found greater possible decreases in SVN types compared with the proven interventions analysis (table 3). We estimated a 51·0% (SB 17·3–73·9) decrease in preterm-SGA births compared with the baseline scenario for all countries, and each region had decreases between 38·8% and 58·2%. The analysis of proven and potential interventions resulted in a 36·0% (12·8–56·2) reduction in preterm-AGA births, and a 23·7% (5·5–41·5) reduction in 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) for all countries. Increased coverage of the full set of interventions could reduce the rate of LBW births from 14·2% in 2023 to 10·2% in 2030, which is close to the 30% reduction target for LBW births by 2030 in these countries (figure 2).

The proven and potential interventions could also reduce stillbirths by about 0·566 million (SB 0·208–0·754), with balanced protein and energy supplementation accounting for two-thirds of this reduction (appendix p 36). Implementing these interventions would result in a 32·4% reduction of the projected 1·749 million stillbirths in 2030.

About 0·652 million neonatal deaths (SB 0·181–0·917) could be averted per year as a result of increased coverage of the proven and potential interventions (figure 3; appendix p 37). This increased coverage would result in a 27·3% reduction of projected neonatal deaths that could occur without scaling up these interventions in 2030. The interventions with the largest effect in reducing neonatal deaths 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 alone could account for 57·4% of the neonatal mortality reduction (appendix p 37). Increased coverage of the proven and potential interventions could reduce the neonatal mortality rate from 25·1 deaths per 1000 livebirths in 2023 to 18·3 deaths per 1000 livebirths in 2030 (appendix p 38).

By 2030, the number of children with stunting in these 81 countries could be 5·4% lower as a result of increased coverage of the proven and potential interventions (appendix p 39). This decrease amounts to about 8·5 million fewer children with stunting globally in 2030, with the largest reduction in central and southern Asia (7·3%). The scale-up of proven and 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 (appendix p 39).

The cost of scaling up proven and potential interventions

In LiST, we estimate the total costs for each intervention, which include drug and supply costs, labour costs, other recurrent costs (such as training, supervision, utilities, and programme management [appendix p 30]),[34] capital costs, and above-facility costs. LiST's costing methods draw on WHO's One Health model to get the definition of needs for the intervention, the supply and drug costs, and country-specific costs (details on the costs for interventions are in the appendix, pp 31–33).[35]

Scaling up the eight proven interventions from their current coverage would cost an estimated $1·126 billion per year (appendix p 40). Balanced protein and energy supplementation ($509 million) and multiple micronutrient supplementation ($371 million) have the greatest incremental costs, and account for 78·2% of the total cost. The estimated cost for scaling up the proven and potential interventions is $4·148 billion per year. Supplementation of calcium and omega-3 fatty acids 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 to meet global targets

If fully implemented, the antenatal interventions with proven efficacy in preventing preterm or SGA births could reduce LBW births by 17·9%. This reduction is about 60% of what is needed to reach the World Health Assembly's 30% reduction target by 2030.[36] If additional research supports the current evidence for interventions that can potentially reduce SVN births, their implementation could reduce LBW births by 28·6%—nearly enough to reach the target. Although there are not global targets for the reduction of preterm or SGA births, reducing these vulnerable births is highly desirable because they result in substantial morbidity and mortality. We found that implementation of proven and potential interventions resulted in the largest reduction in preterm-SGA births (by 51·0%), which is especially important because they have the highest risk of mortality of these SVN births.[37]

Integrating the proven interventions into routine antenatal care services could reduce stillbirths by 31·5% and neonatal deaths by 20·0%. If further research shows the efficacy of the potential interventions, which currently only have suggestive effects, neonatal deaths could be reduced by more than a quarter to 18·3 deaths per 1000 livebirths in 2030. This reduction would facilitate achieving the aim of Sustainable Development Goal 3.2 in reducing neonatal mortality to 12 or fewer deaths per 1000 livebirths by 2030.[38]

Implementation of SVN interventions in routine antenatal care

WHO recommendations for antenatal care include many specific clinical and laboratory assessments and services (appendix pp 41–44). Although these provisions are appropriate components of routine care, attributing SVN birth outcomes to their specific effects is not always possible. Some interventions that are recommended for other reasons could also have important effects on birth outcomes (eg, aspirin or calcium supplementation). Broadening the use of aspirin from the current WHO guidance for women with two moderate risk factors to also include all nulliparous women, which we recommend because of its beneficial effect in a trial in eight LMICs,[14] would substantially increase the effect on preterm births. Evidence also supports the provision of multiple micronutrient supplements instead of just iron and folic acid for women in LMICs.[13] Broadening WHO recommendations from the use of multiple micronutrient supplements in the context of research to use for all women in LMICs could result in substantial reductions in SGA births, stillbirths, and neonatal deaths. More research is urgently needed to establish the effect of omega-3 fatty acids, zinc supplementation (by possibly increasing the zinc dose in multiple micronutrient supplements), calcium supplementation (with 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, the feasibility of improving diets before and during pregnancy to be sufficient in calories, protein, essential fats, micronutrients, and calcium, as well as the fortification of staple foods with micronutrients and calcium, should be considered. Although these improvements are ideal, they will be difficult and slow to achieve in many LMICs and targeted nutritional supplementation might 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]).[39] Because of the uncertain benefit and scarce usage in LMICs, this technology was not included in our LiST analyses. The advent of low-cost doppler devices such as the UmbiFlow device (Council for Scientific and Industrial Research, Pretoria, South Africa), used by nurses and midwives, could make this technology feasible in LMICs in the future.[40]

The provision of corticosteroids to women at risk of premature labour[27] and delaying cord clamping for preterm births[28] could substantially reduce neonatal mortality. Delaying cord clamping has benefits for anaemia in all infants and reduces complications of prematurity, such as necrotising enterocolitis and sepsis.[41] Delayed cord clamping should not be conceptualised 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 underutilised intervention with a large effect on mortality, which could be implemented immediately with no need for additional commodities.

Increasing antenatal care contacts between pregnant women and health-care providers as a platform for specific interventions has the potential to save lives.[2] However, with coverage of the previous four-contact schedule still inadequate in many low-resource settings (54·8% for the 81 countries; appendix p 25),[42–45] implementing the eight-contact schedule will be challenging. In 2023, coverage of the first trimester contact, which is associated with a greater likelihood of regular antenatal care attendance,[42] was 24·0% in low-income countries compared with 81·9% in high-income countries.[46] Initiating antenatal care early in pregnancy is especially important for possible SVN interventions such as supplementation with multiple micronutrients, calcium, and aspirin, because enhanced benefits have been found with their initiation before 20 weeks of gestation.[19,47]

Even when a woman receives the scheduled number of contacts, there is no guarantee that she receives the recommended list of interventions, or the quality of antenatal care provided. Most studies of antenatal care coverage are crude and rely on women's recall of the number of antenatal care contacts through household surveys.[48] In addition, equipment and supplies needed for the essential components of antenatal care, such as blood pressure measurement and syphilis screening and treatment, are often not available or not used.[43,49,50] Data collected on these essential antenatal care practices are scarce, and better measurement of effective coverage of antenatal care components is needed to ensure service quality and improve accountability.[48,51–53] WHO has recommended that antenatal care indicators include the percentage of pregnant women with at least one blood pressure measurement during pregnancy, the percentage of women with at least one blood pressure measurement in their third trimester, the percentage of women whose baby's heartbeat was listened to at least once, and the percentage of pregnant women counselled about danger signs.[52]

Every effort should be made to improve access to routine and near-term contacts, particularly when screening for hypertensive disorders and impaired fetal growth in the third trimester, and when planning interventions such as labour induction or caesarean section in specific cases. However, one high-quality contact in early pregnancy could achieve most of the following interventions: screening for syphilis and HIV, estimation of gestational age and date of delivery by use of ultrasonography, 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 post-partum long-acting contraception), and malaria interventions in endemic regions. Insecticide-treated bednets are one-time interventions recommended as early in pregnancy as possible. If intermittent preventive treatment for malaria with sulfadoxine and 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 interventions to encourage healthy eating and physical activity, and counselling for intimate partner violence, and caffeine, alcohol, and substance abuse.

Clearly no single intervention in pregnancy can eliminate LBW births or its component parts of preterm births and SGA births, but combined interventions as part of antenatal care can have an effect. A randomised controlled trial in India showed that a package of interventions in pregnancy—such as treatment of asymptomatic bacteriuria and reproductive tract infections, multiple micronutrient supplementation, protein and energy supplementation for women who are underweight, calcium supplementation, and managing medical conditions—can reduce SGA births by 20%, preterm births by 15%, and LBW births by 13%, although the upper bound of the 95% CI slightly crossed 1 for preterm and LBW births.[54] These results are similar to what we predict with our analyses, and additional interventions such as aspirin can increase the effect on preterm births. In addition, the trial found that preconception interventions, including multiple micronutrient and nutritional supplements and managing medical conditions (which we do not consider in this paper), had additional effects on LBW and SGA births.

Detailed approaches to implement these recommendations are beyond the scope of this paper. Close attention should be given to strategies and delivery platforms that reach marginalised and vulnerable populations, which include community-based strategies that use health-care workers and strategies to organise participatory groups for women.[17] The relative benefit of these approaches has been underscored in fragile health-care systems and in humanitarian contexts.[55] These approaches allow community health-care workers to identify women early in their pregnancy and offer appropriate support. However, without also providing quality maternal health care and reliable transport systems, they might not greatly affect neonatal mortality.

In the past two decades there has been substantial attention on reducing neonatal mortality through improvements in labour, delivery, and postnatal care, especially in the 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 births, including both preterm and SGA births, have elevated risks of death and consequences for long-term growth, development, and adult health, should lead to enhanced efforts to prevent these vulnerable birth outcomes. At a cost of $1·1 billion for scaling up proven interventions in the 81 countries in 2030, about 0·476 million 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 0·652 million neonatal deaths at $6300 per death. Including the full benefit of averting stillbirths and SVN births with additional effects on post-neonatal mortality and, for babies 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 effects for SVN babies will be necessary to achieve global targets for the reduction of LBW births and neonatal mortality, and longer-term benefits on growth and human capital.

The Lancet Small Vulnerable Newborn Steering Committee

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Contributors

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

Declaration of interests

PA and NW report grants from the Children's Investment Fund Foundation. All other authors declare no competing interests.

Acknowledgments

The production of this manuscript was funded by a grant from the Children's Investment Fund Foundation. The funder had no role in the writing of the manuscript or the decision to submit it for publication.

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