## Stillbirths 3

# Stillbirths: what difference can we make and at what cost?

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**Worldwide, 2·65 million (uncertainty range 2·08 million to 3·79 million) stillbirths occur yearly, of which 98% occur in countries of low and middle income. Despite the fact that more than 45% of the global burden of stillbirths occur intrapartum, the perception is that little is known about effective interventions, especially those that can be implemented in low-resource settings. We undertook a systematic review of randomised trials and observational studies of interventions which could reduce the burden of stillbirths, particularly in low-income and middle-income countries. We identified several interventions with sufficient evidence to recommend implementation in health systems, including periconceptional folic acid supplementation or fortification, prevention of malaria, and improved detection and management of syphilis during pregnancy in endemic areas. Basic and comprehensive emergency obstetric care were identified as key effective interventions to reduce intrapartum stillbirths. Broad-scale implementation of intervention packages across 68 countries listed as priorities in the Countdown to 2015 report could avert up to 45% of stillbirths according to a model generated from the Lives Saved Tool. The overall costs for these interventions are within the general estimates of cost-effective interventions for maternal care, especially in view of the effects on outcomes across maternal, fetal, and neonatal health.**

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This is the third in a Series of six papers about stillbirths

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## Introduction

As indicated in the second paper of *The Lancet*'s Stillbirths Series,[1] stillbirths are one of the most important, yet most poorly understood and recognised adverse outcomes of pregnancy. Global estimates indicate that in 2008, at least 2·65 million (uncertainty range 2·08 million to 3·79 million) stillbirths occurred in the last trimester of pregnancy, with more than 45% in the intrapartum period. The vast majority (98%) of these stillbirths occurred in low-income and middle-income countries.[1,2] This figure approximates the total number of early neonatal deaths and is almost equal to the number of deaths in children aged 1–5 years (3·2 million).[3] Despite having enormous social and health implications for both parents, stillbirths have been invisible in policies and programmes worldwide, with little recognition of potential strategies for intervention. Stillbirths are not included in tracking of the Millennium Development Goals. Moreover, most countries do not include stillbirths in their vital statistics reporting systems and, even in the countries that do, stillbirths are generally under-reported.

A major reason for stillbirths not being included in the worldwide policy agenda is the notion that little can be done at scale in developing countries. Although efforts have focused attention on the problem in its various dimensions, not much energy has been devoted to systematically assessing whether interventions work and, importantly, whether they are affordable and implementable in low-income and middle-income countries. We undertook a systematic review of evidence for the reduction in stillbirths with a range of potential interventions, and estimated the potential effects and costs if such interventions were implemented at scale in countries with the highest burden. Finally, we used the methods developed by the Child Health and Nutrition Research Initiative (CHNRI) to draw up a list of research priorities with respect to interventions to prevent stillbirths.

## Systematic review of potential interventions to address stillbirths

### Methods

We systematically updated our previous reviews[4–6] of evidence related to interventions that could reduce the

### Key messages

- 98% of the world's 2·65 million stillbirths occur in countries of low and middle income. The five major causes are childbirth complications, maternal infections in pregnancy (eg, syphilis), maternal disorders, especially hypertension, maternal undernutrition and fetal growth restriction, and congenital abnormalities.
- We reviewed 35 potential interventions, of which we strongly recommend ten for implementation: periconceptional folic acid fortification, insecticide-treated bednets or intermittent preventive treatment for malaria prevention, syphilis detection and treatment, detection and management of hypertensive disease of pregnancy, detection and management of diabetes of pregnancy, detection and management of fetal growth restriction, routine induction to prevent post-term pregnancies, skilled care at birth, basic emergency obstetric care, and comprehensive emergency obstetric care.
- Estimates modelled with the Lives Saved Tool indicate that 99% coverage with these ten interventions could prevent 45% of stillbirths at a cost of US$9·6 billion.
- Childbirth care, particularly emergency obstetric care including caesarean section, reduces the highest number of stillbirths, and should be the first priority, especially because of the additional benefits to women and neonates. Antenatal care is low cost and highly effective against stillbirths related to infection and undernutrition, and can be provided through outreach workers and services.
- Analysis of the effect of interventions is severely hampered by the lack of data collected on stillbirths—eg, intrapartum versus antepartum and gestational age. Stillbirth measurements should be included in all existing surveillance sites, and instruments developed to allow tracking of gestational age for stillbirths.

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burden of stillbirths by comprehensively updating our search for published reports to incorporate new relevant studies, and application of stringent literature review criteria developed by the Child Health and Epidemiology Reference Group (CHERG).[7] Detailed search strategies for individual interventions and packages are available from the authors on request.

Interventions of interest were selected on the basis of clear or potential evidence of benefit across pregnancy and childbirth,[4,6] and additional interventions were included on the basis of plausibility and relevance to public health policy. Standard meta-analysis methods were used to derive pooled estimates of effects of interventions. Disaggregated effects of interventions on antepartum or intrapartum stillbirths were not available for many interventions, and information was largely available from observational studies.

To further estimate the effectiveness of selected interventions, we also undertook a Delphi process. 20 global experts and practitioners were selected to participate on the basis of subject expertise and geographical representation. Two composite Delphi sheets were prepared containing background information about the exercise, summary of the specific interventions, and relevant meta-analyses or information. One Delphi sheet (webappendix pp 1–5) assessed the potential effect of the interventions related to childbirth care and the second (webappendix pp 6–10) dealt with the interventions related to antenatal care. Responses from the experts were compiled and the median (IQR) of responses was used as a point estimate to assess reduction in stillbirths. Further details for methods are available in reports by Yakoob[8] and Syed[9] and their colleagues.

## Salient findings by intervention

### *Provision of skilled attendants during childbirth*

Most intrapartum stillbirths are associated with complications that arise during labour and are potentially preventable with appropriate care.[10,11] In high-income countries where most women receive fairly high-quality intrapartum care, the proportion of intrapartum stillbirths is less than 10% of all stillbirths.[12] In low-income and middle-income countries, an estimated 46% of women give birth at home without the benefit of a skilled birth attendant (doctor, midwife, nurse, or nurse aide).[13] Our systematic review revealed that provision of a skilled attendant at birth could reduce intrapartum stillbirths by about 23% (table 1). The Delphi consultation ascribed a median reduction in stillbirths in facility settings of 25% (IQR 20–40) to provision of skilled birth attendance.

### *Provision of basic and comprehensive emergency obstetric care in facilities*

Skilled birth attendance alone cannot address complications during childbirth that necessitate facility-based interventions to expedite delivery such as augmentation of labour, instrumental delivery, and emergency caesarean section. Much evidence supporting the benefit of basic and comprehensive emergency obstetric care for maternal and fetal outcomes is derived from fairly low-quality historical and ecological studies. Pooled analysis is not possible because of the heterogeneity of these studies, and randomised controlled trials on this subject are not feasible. From observational and time trend data in 51 countries, Goldenberg and colleagues[15] assessed the effects of both basic and comprehensive emergency obstetric care and neonatal care, and estimated a decrease of 1·61 intrapartum stillbirths per 1000 births for each 1% increase in the proportion of caesarean section births from 0% to 8% (table 1). The decrease in the rate of intrapartum stillbirths was much smaller as the proportion of caesarean sections rose above 8%, and the frequency of intrapartum stillbirths was not related to the rate of caesarean sections in developed countries with 15% or more births by caesarean section. In an expanded review of data from 188 countries, McClure and colleagues[26] showed that, in developing countries, a strong reduction in the frequency of stillbirths occurred as the proportion of births by caesarean section increased from 0% to about 10%, with little relation thereafter. However, no relation was noted between the proportion of births by caesarean section and the frequency of stillbirths in developed countries. Excess neonatal mortality and maternal morbidity are associated with increased rates of caesarean delivery.[27]

Although the quality of studies in this area is admittedly low, time trends and the reported elimination of intrapartum stillbirths from many developed and middle-income countries in tandem with increased availability of skilled care and basic and comprehensive emergency obstetric care suggest that these interventions are essential for reduction of intrapartum stillbirths. The Delphi consultation ascribed median reductions in stillbirths in facility settings of 45% (IQR 30–70) to basic emergency obstetric care, and 75% (50–85) to comprehensive emergency obstetric care.[8]

Tackling of high-risk pregnancies and complications during childbirth, with interventions to improve skilled care at birth and delivery within facilities, is key to the reduction of intrapartum stillbirths. The quality of such care is highly important: training of community health workers without adequate triage and referral is unlikely to reduce the burden of stillbirths and early neonatal mortality.[28] The fact that no differences were noted for stillbirths and perinatal deaths between facility-based and community-based births in one urban setting in Pakistan[29] underscores the importance of staff training and high quality of care.

### *Screening and intervention for high-risk pregnancies and fetal compromise*

A range of interventions have been developed to recognise problems during pregnancy associated with fetal compromise, especially impaired growth and distress.[30] These interventions include detection of intrauterine

| | Comparison | Number of studies | Effect estimates |
|---|---|---|---|
| **Care just before and during childbirth** | | | |
| Skilled birth attendance (doctor, midwife, nurse, nurse aide) | Skilled birth attendance *vs* unattended deliveries[8] | Two before–after studies | RR 0·77 (95% CI 0·69–0·85) for effect on stillbirth |
| Trained traditional birth attendance | Trained *vs* untrained traditional birth attendants[14] | One randomised trial of stillbirth, and one randomised trial of perinatal death | Adjusted OR 0·69 (95% CI 0·57–0·83; fixed model) for effect on stillbirth, and 0·70 (0·59–0·83; fixed model) for effect on perinatal death |
| Basic and comprehensive emergency obstetric care | Relation between proportion of caesarean section births and intrapartum stillbirth[15] | Regression model of data for stillbirth and caesarean section rates from 51 countries | As the proportion of caesarean section births increased from 0% to 8%, for each 1% increase, intrapartum stillbirths decreased by 1·61 per 1000 births |
| Identification and induction of mothers with ≥41 weeks of gestation | Induction of labour *vs* expectant management[16] | 13 randomised trials of stillbirth, and 13 randomised trials of perinatal death | RR 0·29 (95% CI 0·06–1·38; fixed model) for effect on stillbirth, and 0·31 (0·11–0·88; fixed model) for effect on perinatal death |
| **Antenatal care: fetal monitoring** | | | |
| Doppler velocimetry (umbilical artery) for high-risk pregnancy | Doppler ultrasound *vs* no doppler ultrasound[17] | 15 randomised trials of stillbirth, and 16 randomised trials of perinatal death | RR 0·65 (95% CI 0·41–1·04; fixed model) for effect on stillbirth, and 0·71 (0·52–0·98) for effect on perinatal death |
| **Antenatal care: improved nutrition** | | | |
| Periconceptional folic acid supplementation | Folic acid supplementation *vs* control[18] | One randomised trial and three cohort studies for primary prevention, and three randomised trials for secondary prevention of neural tube defects | RR 0·38 (95% CI 0·29–0·51) for primary prevention, and 0·30 (0·14–0·65) for secondary prevention of neural tube defects |
| Periconceptional folic acid fortification | Folic acid fortification before pregnancy[19] | 11 before–after intervention studies | RR 0·59 (95% CI 0·52–0·68) for effect on neural tube defects |
| Balanced protein-energy supplementation | Balanced protein energy *vs* controls[19] | Four randomised trials | RR 0·55 (95% CI 0·31–0·97; fixed model) for effect on stillbirth |
| **Antenatal care: prevention of infection** | | | |
| Syphilis detection and treatment | Effect of penicillin on stillbirth in pregnant women with active syphilis[20] | Eight observational studies | RR 0·20 (95% CI 0·12–0·34) for effect on stillbirth |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention | Insecticide-treated bednets and intermittent preventive treatment *vs* no bednets and placebo[21] | Seven randomised trials | RR 0·78 (95% CI 0·59–1·03) for effect on stillbirth |
| **Antenatal care: improved detection and management of morbidity** | | | |
| Prevention of hypertensive disease of pregnancy with calcium | Calcium use in women with low calcium intake *vs* placebo[22] | Three randomised trials | No significant effect on risk of stillbirth or death before discharge from hospital (RR 0·90, 95% CI 0·74–1·09) |
| Prevention of hypertensive disease of pregnancy with calcium | Calcium use in women with low calcium intake *vs* placebo[23] | Three randomised trials | RR 0·81 (95% CI 0·63–1·03) for effect on stillbirth |
| Management of hypertensive disease of pregnancy with antihypertensive agents | Any antihypertensive drug *vs* no drug for mild to moderate hypertension[24] | 18 randomised trials of stillbirth, and 20 randomised trials of perinatal death | RR 1·14 (95% CI 0·60–2·17) for effect on stillbirth, and 0·96 (0·60–1·54) for effect on perinatal death |
| Management of hypertensive disease of pregnancy with magnesium sulphate for pre-eclampsia or eclampsia | Magnesium sulphate *vs* no drug or placebo[23] | Three randomised trials of stillbirth, and two randomised trials of perinatal death | RR 0·99 (95% CI 0·87–1·12) for effect on stillbirth, and 0·98 (0·88–1·10) for effect on perinatal death |
| Detection and management of diabetes of pregnancy | Any specific treatment for gestational diabetes *vs* routine antenatal care[9,25] | One randomised trial of stillbirth | No significant effect on stillbirth (RR 0·09, 95% CI 0·01–1·70), but, in one trial, the composite outcome of perinatal morbidity (death, shoulder dystocia, bone fracture, and nerve palsy) was significantly reduced with intensive treatment for mild gestational diabetes compared with routine antenatal care (0·32, 0·14–0·73) |
| Detection and management of diabetes of pregnancy | Optimal control of serum blood glucose *vs* suboptimal control[9] | Two observational studies of stillbirth, and three observational studies of perinatal death | RR 0·51 (95% CI 0·14–1·88) for effect on stillbirth, and 0·40 (0·25–0·63) for effect on perinatal death |
| Detection and management of diabetes of pregnancy | Care before conception *vs* no care[9] | Three observational studies | RR 0·29 (95% CI 0·14–0·60) for effect on perinatal death |
| Detection and management of diabetes of pregnancy | Intensive management of gestational diabetes *vs* conventional management[9] | Three randomised trials | RR 0·20 (95% CI 0·03–1·10) for effect on stillbirth |

RR=relative risk. OR=odds ratio.

***Table 1:*** **Effect of interventions estimated by use of a model based on the Lives Saved Tool**

***Panel 1:*** **Potential interventions according to timing of care**

**Care before conception**
Target risk factors of female genital mutilation*, indoor air pollution*, smoking*, and smokeless tobacco*; birth spacing*; periconceptional folic acid supplementation or fortificaton*

**Antenatal care: improved nutrition**
Iron or iron-folate supplementation; multiple micronutrient supplementation*; vitamin A or betacarotene supplementation; magnesium supplementation for deficient states; balanced protein-energy supplementation*; zinc supplementation; supplementation with long-chain polyunsaturated fatty acids

**Antenatal care: prevention and management of infection**
Syphilis screening and treatment*; antibiotics and antisepsis for high-risk pregnancies (asymptomatic bacteriuria, bacterial vaginosis, and group B streptococcus colonisation); antibiotics for premature rupture of membranes or preterm premature rupture of membranes; anthelmintic drugs; use of antimalarial drugs and insecticide-treated bednets for prevention of malaria*; prevention of mother-to-child transmission of HIV infection; periodontal care

**Antenatal care: detection and management of morbidity**
Calcium for prevention of hypertensive disorders*; management of hypertension with antihypertensive drugs*; antiplatelet agents for high-risk pregnancy; use of heparin and other anticoagulants; antioxidants; cervical cerclage; management of intrahepatic cholestasis; maternal plasma exchange; diabetes screening and management*

**Antenatal care: fetal monitoring**
Fetal movement counting*; screening for intrauterine growth restriction including symphysis to fundal height measurement and ultrasound scanning*; doppler velocimetry*; pregnancy risk screening; pelvimetry

**Care close to the time of childbirth**
Community mobilisation and education strategies for promotion of appropriate care seeking; antepartum cardiotocography*; fetal biophysical test scoring in high-risk pregnancy; vibroacoustic stimulation; amniotic fluid volume assessment; home versus hospital-based bed rest and monitoring; in-hospital fetal surveillance unit; magnesium sulphate for prevention of preterm labour; maternal hyperoxygenation for suspected impaired fetal growth; financial incentives for care seeking*

**Care during childbirth**
Skilled birth attendants (doctors, midwives, nurses, or nurse aides)*, perinatal audit*; training of traditional birth attendants*; training of health professionals in neonatal resuscitation*; partogram use*; intrapartum cardiotocography with or without pulse oximetry*; basic and comprehensive emergency obstetric care*; induction of labour in post-term pregnancies*; magnesium sulphate for treatment of pre-eclampsia or eclampsia*; amnioinfusion; maternity waiting homes; instrumental delivery; drugs for cervical ripening and induction of labour; planned caesarean for breech presentation*; emergency loan and insurance funds for emergency obstetric care; training of community health workers*; obstetric drills; public-private partnerships to provide emergency obstetric care; home or home-like births versus hospital births*

*Interventions have been assessed in depth in our report.

growth restriction through clinical examination (such as fundal height measurement) or ultrasound screening, and formal assessment of fetal movement by mothers. Fetal movement counting is one of the oldest methods of monitoring fetal wellbeing and is based on the premise that fetal movements are an indication of CNS integrity. Fetal hypoxia or compromise can lead to reduction in fetal movements, which, when identified by the mother, can trigger prompt care seeking and further assessment. The Cochrane review by Mangesi and Hofmeyr[31] assessed three randomised trials[32–34] of routine kick counting for reduction of stillbirth, but variation in study comparisons precluded outcome pooling. Few formal well designed studies have assessed such interventions—eg, fetal movement monitoring, or training of health-care providers in measurement of fundal height for early detection of intrauterine growth restriction—in developing countries.

Sophisticated technologies have been developed to detect umbilical vascular flow patterns such as doppler velocimetry, which measures blood flow dynamics in uterine, umbilical, and fetal arteries, and is regarded as an objective method to assess pregnancies at risk of intrauterine growth restriction and other adverse perinatal outcomes.[30,35,36] In a meta-analysis of 16 studies in developed countries, doppler velocimetry of umbilical and fetal arteries in high-risk pregnancies was associated with a 29% reduction in perinatal mortality, but the specific effect on stillbirths was not significant (table 1).[17] Ultrasound examinations are now readily available in many developing countries and, although the misuse of technology for female feticide has caused much concern,[37] with appropriate use and training, ultrasound and doppler examinations could be useful adjunctive health technologies in some middle-income countries.

Timely onset of labour and delivery is an important determinant of pregnancy outcome. A post-term pregnancy (gestational age ≥42 weeks) occurs in about 5–10% of all pregnancies, and is associated with increased risk of stillbirth, macrosomia, birth injury, and meconium aspiration syndrome.[38,39] Management of post-term pregnancy, either by induction or expectant management, is a subject of some debate.[40] In an updated meta-analysis of elective induction of labour versus expectant management from 13 randomised trials, five of which were in developing countries, the interventions had uncertain effects on stillbirths, but elective induction significantly reduced perinatal mortality (table 1).[16] We believe that these findings are sufficient to recommend elective induction of labour in low-risk pregnancies at or beyond 41 weeks of gestation in settings with adequate gestational age dating and appropriate care during childbirth in facilities.

*Nutritional interventions before and during pregnancy*

A range of nutritional interventions could be implemented during the periods before and during pregnancy,[19,41] but we have focused on periconceptional folic acid, balanced energy-protein, and micronutrient supplements in pregnancy, and the potential role of calcium. Neural tube defects are associated with maternal folic acid deficiency and can be alleviated by supplementation in the

periconceptional period.[42] Folic acid supplementation or fortification periconceptionally—ie, before pregnancy and during the first 2 months of pregnancy—reduces the risk of neural tube defects (table 1),[18] which account for a small proportion of stillbirths. Furthermore, food fortification with folic acid, a more practical intervention before conception, would be the preferred intervention and could reduce the occurrence of neural tube defects by 41% (table 1).[19]

In the world's poorest countries, maternal undernutrition is a major problem and a substantial proportion of women have a body-mass index of less than 18·5 kg/m².[43] Energy intake in pregnancy is positively associated with fetal growth,[44] and balanced energy-protein intake, defined as a diet that provides up to 25% of the total energy content in the form of protein, improves fetal growth and reduces the risk of fetal and neonatal death in populations with high rates of food insecurity and maternal undernutrition. In an analysis of four trials of undernourished women in developing countries, balanced energy-protein supplementation in pregnancy was associated with a 45% reduction in stillbirths (table 1) and a smaller reduction in neonatal mortality (RR 0·62, 95% CI 0·37–1·05),[19] which confirmed the findings of an earlier meta-analysis.[45] Despite questions related to feasibility, delivery strategies, and cost-effectiveness, balanced energy-protein supplementation or alternative strategies promoting food intake should be recommended as a potentially effective intervention in malnourished pregnant women in food insecure households to reduce fetal loss and intrauterine growth restriction.[46]

For prophylaxis of gestational hypertensive disorders in pregnancy, calcium supplementation is largely effective in populations with low intake of calcium, and hence there is no evidence of benefit in developed countries with adequate intake.[47] In assessment of 13 good quality trials comprising 15730 women, Hofmeyr and colleagues[22] showed that calcium supplementation significantly reduced the risk of high blood pressure (RR 0·65, 95% CI 0·53–0·81), and reduced the risk of pre-eclampsia overall (0·45, 0·31–0·65) and in high-risk women (0·22, 0·12–0·42). Calcium supplementation also reduced the average risk of preterm birth (0·76, 0·60–0·97), but had no overall effect on the risk of stillbirth or death before discharge from hospital (table 1). In a subsequent meta-analysis using CHERG methods, calcium supplementation during pregnancy was associated with an estimated 45% reduction in the risk of gestational hypertension (0·55, 0·36–0·85) and 59% in the risk of pre-eclampsia (0·41, 0·24–0·69).[23,48] Information on stillbirth outcomes was limited, but stillbirth has a known association with hypertensive disease of pregnancy and pre-eclampsia,[49] and therefore calcium supplementation in women with low baseline calcium intake was estimated to reduce the risk of stillbirth by 19%, although the reduction was not significant (table 1).[23]

**_Panel 2:_ Description of interventions modelled by the Lives Saved Tool to address stillbirths**

**Periconceptional folic acid fortification**
Fortification of staple commodities (eg, wheat flour fortified with folic acid)

**Prevention of malaria with insecticide-treated bednets or intermittent preventive treatment with antimalarials**
Pregnant women living in malaria endemic areas who received more than two doses of sulfadoxine plus pyrimethamine during pregnancy, or who slept under an insecticide-treated bednet the previous night (whichever had the higher coverage)

**Syphilis detection and treatment**
Pregnant women screened for syphilis with the rapid plasma reagent test, and treated with 2·4 mIU benzathine benzylpenicillin if needed

**Detection and management of hypertensive disease of pregnancy**
Identification of hypertensive disease by blood pressure measurement and ancillary investigations as needed, and treatment with an effective antihypertensive agent, including magnesium sulphate and caesarean section if needed

**Detection and management of diabetes of pregnancy**
Screening with the glucose challenge test to identify women with undiagnosed pre-existing diabetes or pregnancy-induced diabetes, and optimal management with dietary advice and insulin as needed

**Detection and management of fetal growth restriction (including caesarean section or induction, if needed)**
Detection of fetal growth restriction from clinical criteria (suboptimal fundal height for gestation), poor growth on ultrasound examination, and doppler examination of umbilical artery flow, with caesarean section or induction of labour as needed

**Identification and induction of mothers with 41 weeks of gestation or more**
Reliable identification of gestational age (usually with ultrasound dating), and induction of labour at 41 weeks' gestation or later with appropriate technology (misoprostol and amniotomy as indicated)

**Skilled care at birth and immediate care for neonates**
Monitoring of progress of labour with a partograph, detection of complications, and infection control, with episiotomy if needed; and routine care practices for the neonate, including immediate drying, skin-to-skin contact or immediate wrapping for thermal care, and clean cord cutting

**Basic emergency obstetric care**
Care includes, but is not limited to, intravenous and intramuscular drug treatment (eg, antibiotics, oxytocin, and anticonvulsants), assisted vaginal delivery, manual removal of placenta, manual removal of retained products of an abortion or miscarriage, and stabilisation and referral of obstetric emergencies not managed at the basic level

**Comprehensive emergency obstetric care**
Delivery is managed at a hospital, and care includes case management of direct obstetric complications, such as antepartum haemorrhage, prolonged or obstructed labour, post-partum haemorrhage, and severe infection, in addition to all interventions included in basic emergency obstetric care, induction of labour, blood transfusion, caesarean section, symphysiotomy, and hysterectomy, if indicated

*Interventions to address stillbirths associated with infection (situational)*

Syphilis during pregnancy is common in many low-income and middle-income countries, with prevalence

| | Antepartum stillbirth effect | Intrapartum stillbirth effect | Affected fraction |
|---|---|---|---|
| **Before pregnancy and basic antenatal care** | | | |
| Periconceptional folic acid fortification | 41·0% | 41·0% | Prevalence of folic acid deficiency × increased risk of stillbirths associated with folic acid deficiency[18] |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy | 22% | NA | Prevalence of placental malaria (21·8%)[71] × increased risk of stillbirths associated with placental malaria[72] |
| Syphilis screening and treatment | 80% | NA | Prevalence of syphilis × increased risk of stillbirths associated with syphilis[73] |
| **Advanced antenatal care** | | | |
| Detection and management of hypertensive disease of pregnancy | 20% | 20% | Prevalence of hypertensive disease × increased risk of stillbirths associated with hypertension[74] |
| Detection and management of diabetes of pregnancy | 10% | 10% | Prevalence of diabetes × increased risk of stillbirths associated with diabetes[75] |
| Detection and management of fetal growth restriction | 20% | 20% | Prevalence of intrauterine growth restriction[76] × increased risk of stillbirths associated with fetal growth restriction[77] |
| Identification and induction of mothers with ≥41 weeks of gestation | 69% | 69% | Prevalence of post-term pregnancies (7·5%)[78] × increased risk of stillbirths associated with post-term pregnancy[39] |
| **Obstetric care** | | | |
| Skilled care at birth and immediate care for neonates | NA | 23% | 100%[8] |
| Basic emergency obstetric care | NA | 45% | 100%[8] |
| Comprehensive emergency obstetric care | NA | 75% | 100%[8] |

NA=not applicable.

*Table 2:* **Modelled interventions, data sources, and effect estimates used for analysis**

varying from less than 1% to 10% or higher, and is associated with a high risk of fetal and neonatal mortality.[50] Screening and treatment for syphilis is an essential component of all antenatal programmes in endemic countries. Although a Cochrane review of antibiotic treatment of syphilis in pregnancy did not identify any eligible studies,[51] randomised trials of screening and treatment for syphilis would be unethical, so appropriate observational studies should be used to establish the effectiveness of treatment. Findings of a random-effect meta-analysis of eight observational studies,[52–59] six from low-income and middle-income countries, showed a significant 80% reduction in stillbirths in infected women receiving treatment compared with those receiving no treatment (table 1).[20] We strongly recommend identification and treatment of maternal syphilis to reduce congenital syphilis and stillbirth.

The other major infection associated with stillbirth is malaria. About 10% of the world's population is exposed to clinical or subclinical malaria, and about 1 million deaths occur for every 500 million new infections yearly.[60] Every year, about 50 million pregnant women are exposed to malaria in endemic areas such as sub-Saharan Africa, parts of Latin America, and Asia.[61] Prevention strategies include prophylactic antimalarial drugs through intermittent preventive treatment, and use of insecticide-treated bednets. In two Cochrane reviews of studies in low-income and middle-income countries, intermittent preventive treatment had no significant effect on stillbirths in women in their first or second pregnancy (RR 0·96, 95% CI 0·62–1·50),[62] whereas bednet use reduced fetal loss by 32% (0·68, 0·48–0·98).[63] Bednets also had a significant effect for women in their first or second pregnancy (0·67, 0·47–0·97), but had no effect for fifth or greater pregnancies (1·02, 0·17–6·23).[63] In practical terms, however, both interventions are used in combination in endemic populations, which reduces the risk of stillbirths in women in their first or second pregnancy by an estimated 22% (table 1).[21]

### *Prevention and management of hypertensive disease of pregnancy*

In view of the association of hypertensive disease of pregnancy with maternal morbidity and mortality,[64] strategies are needed to improve prevention, detection, and antihypertensive treatment. Use of antihypertensive agents in pregnancies complicated by hypertensive disease leads to a small but insignificant reduction in the risk of perinatal mortality (table 1).[24]

Progression of pre-eclampsia to eclampsia is an obstetrical emergency. In the past decade, magnesium sulphate has replaced the use of other anticonvulsants as the drug of choice in the prophylaxis and treatment of eclampsia and is superior to the often used lytic cocktail.[65] Data for use of magnesium sulphate in pregnancy are limited by the fact that not all trials report data on fetal outcomes, and we identified no data separated by type of stillbirth (antepartum and intrapartum). From the information available, use of magnesium sulphate had no effect on stillbirths and

perinatal mortality (table 1), but reduced neonatal deaths (RR 0·37, 95% CI 0·14–1·00).[23,65]

We undertook a specific Delphi consultation to assess the potential effect of a package of interventions on stillbirths associated with maternal hypertension. The package of interventions included screening for hypertension, treatment with antihypertensive drugs, use of magnesium sulphate as needed, and induction of labour or use of caesarean section. The experts suggested a 20% median reduction in each of antepartum stillbirths (IQR 10–30) and intrapartum stillbirths (10–40) from introduction of these interventions.[23]

*Screening and optimising management of diabetes in pregnancy*

Maternal diabetes and its three categories, gestational, type 1, and type 2 diabetes, are associated with substantial risk of complications for the mother, fetus, and neonate. Complications range from variations in birthweight to fetal malformations and potentially excess perinatal mortality. Reduction in perinatal mortality is associated with any specific treatment for gestational diabetes versus routine antenatal care,[25] and with care of maternal diabetes before conception versus no care[9] (table 1). Moreover, intensive management of gestational diabetes (including specialised dietary advice, increased monitoring, and tailored dietary therapy) versus conventional management (dietary advice and insulin as needed) is associated with a reduction in the risk of stillbirth (table 1).[9,25] Findings of meta-analysis[9] of the few observational studies available suggest that optimal control of serum glucose versus suboptimal control during pregnancy was also associated with a significant decrease in the risk of perinatal mortality, but not stillbirths (table 1). In view of this insufficient information, we did a Delphi-based assessment, showing that optimum identification and management of diabetes in pregnancy could reduce each of antepartum and intrapartum stillbirths associated with maternal or gestational diabetes by a median of 10% (IQR 5–30 for antepartum stillbirths, 4–25 for intrapartum stillbirths).[9]

*Other general supportive interventions*

We assessed a range of other potential interventions with known risk factors, but for which information from robust intervention studies was not available, including birth spacing and family planning, reduction in indoor air pollution, reduction in tobacco use during pregnancy, and reduction of female genital mutilation. A discussion of the potential reduction in stillbirths in at-risk populations with these interventions is provided in webappendix pp 11–12.

The list of risk factors for stillbirth, and hence the number of potential interventions, continues to grow,[66–69] and includes environmental and genetic factors. Although some of these factors are of little public health relevance at present, they are potentially highly important for our future understanding of the pathogenesis and risks associated with stillbirth.

| | ≥25 per 1000 births | 15–24·9 per 1000 births | 5–14·9 per 1000 births |
|---|---|---|---|
| Periconceptional folic acid supplementation or fortification | No | No | Yes |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy | Yes (situational) | Yes | Yes |
| Syphilis detection and treatment | Yes (situational) | Yes | Yes |
| Detection and management of hypertensive disease of pregnancy | No | Yes | Yes |
| Detection and management of diabetes of pregnancy | No | No | Yes |
| Detection and management of fetal growth restriction | No | No | Yes |
| Identification and induction of mothers with ≥41 weeks of gestation | No | No | Yes |
| Skilled care at birth and immediate care for neonates | Yes | Yes | Yes |
| Basic emergency obstetric care | Yes | Yes | Yes |
| Comprehensive emergency obstetric care | Yes | Yes | Yes |

"Yes" refers to inclusion of that intervention in the combination of interventions for that particular stillbirth rate. "No" refers to non-inclusion.

*Table 3:* **Interventions modelled at various stillbirth rates**

## Selection of interventions for potential modelling of effects on stillbirths

### Methods

We selected a set of interventions from the range reviewed for potential assessment of effect on antenatal or intrapartum stillbirths in developing countries (panel 1). Several selected interventions are already part of the existing set of recommended intervention packages for addressing maternal and neonatal outcomes, including periconceptional folic acid supplementation, screening and management of syphilis, prevention and treatment of malaria during pregnancy in endemic areas, skilled care at birth, and basic and comprehensive emergency obstetric care in facilities. We included other interventions with potential for reduction of stillbirth because these interventions were already part of standard practice in some settings, usually in the private sector, and could feasibly be introduced and scaled up in relevant health systems. These interventions included expanded antenatal care packages for improved detection and management of hypertensive disease and diabetes in pregnancy, improved screening for high-risk pregnancies and fetal compromise, and elective induction of labour after 41 weeks' gestation.

Ten interventions were selected for modelling and effect assessment across several categories of stillbirth burden in 68 countries listed as priorities in the Countdown to 2015 report[70] (panel 2). Table 2 summarises the interventions and effect sizes modelled, and the population attributable fractions to which these effect sizes were applied.[18,73–76,79] We then considered three different combinations of these interventions that we felt could feasibly be included and scaled up by 2015: one for areas with 25 stillbirths per 1000 births or more, one for

### *Panel 3*: Background to LiST

**Modelling software**

Spectrum is a widely used demographic software package developed and refined in the past 20 years for projection of population trends by age and sex, based on UN estimates. It also includes modules to estimate the effect of interventions for family planning and AIDS developed with UNAIDS.[80,81] LiST is a new module in Spectrum based on *The Lancet*'s Series on Child Survival, Neonatal Survival, and Maternal and Child Undernutrition. LiST automatically uploads national data for health status, intervention coverage, and mortality. Users can change coverage for selected interventions by year with 2010 as the baseline. The program links user-selected coverage changes by year (up to 2015 for this report) to cause-specific mortality estimates by standard effect sizes, resulting in estimates of lives saved per year by intervention and cause for a specific country. The model was modified to specifically include information on stillbirths and interventions to prevent stillbirths.

**Baseline data and effect on mortality by intervention**

The most recent estimated causes and rates of maternal, neonatal, and child deaths,[3,82] by country, were used for this report. Coverage data is available for many interventions in populous low-income and middle-income countries through Demographic and Health Surveys. However, population-based coverage data are lacking for some interventions (eg, rates of neonatal resuscitation) so estimates were made based on other known coverage indicators, as described in the LiST manual.

LiST includes a wide range of interventions for maternal, neonatal, and child health, each recommended after application of the GRADE criteria,[83] and specific reviews to derive point estimates and confidence limits. The linked mortality effect estimates were based on a consistent review process, with use of an adapted version of GRADE to review the quality and level of evidence. Effectiveness values for each intervention were derived from a standardised review process developed by CHERG with UN partners, and with use of the GRADE criteria to establish which interventions to include and to assess the level of evidence.[7,83] The detailed review process to estimate effect sizes of cause-specific mortality,[84] and the modelling assumptions in LiST and many specific reviews have been published.[85] Modifications for the stillbirth calculations were similar to those done for previous estimates, and are undergoing vetting and inclusion in the system by use of the CHERG review and consultation process.

**Modelling methods**

Estimates of lives saved are modelled such that lives cannot be saved twice by linked interventions—eg, prevention of pneumonia by pneumococcal vaccine plus prevention of the death by case management with antibiotics. Additionally, the cohort-based approach allows an individual whose death was averted in the neonatal period to be at risk of death from other causes later in life.

LiST=Lives Saved Tool. CHERG=Child Health Epidemiology Reference Group. UNAIDS=Joint UN Programme on HIV/AIDS.

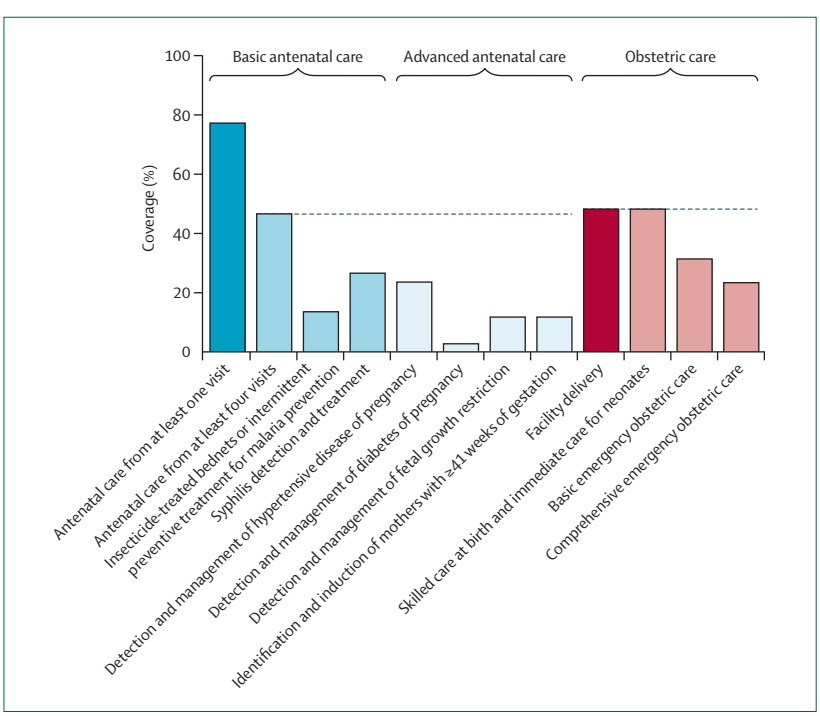


***Figure 1:*** **Average coverage of interventions for stillbirths in 68 Countdown countries**
Data are not available for periconceptional folic acid fortification.

areas with 15–24·9 stillbirths per 1000 births, and one for areas with 5–14·9 stillbirths per 1000 births (table 3).[70]

We modelled the potential effect of interventions on reduction of stillbirth with the Lives Saved Tool (LiST, version 4.23 beta 14; panel 3) at three levels of coverage: 60%, 90%, or 99% to represent universal coverage. LiST models the effect of increasing coverage of individual interventions on the reduction of deaths by specific cause of death for mothers, neonates, and children. It is based on modelling of lives saved in *The Lancet*'s Series on Child Survival, Neonatal Survival, and Maternal and Child Undernutrition, and is now built into a widely accepted demographic software package Spectrum. Coverage levels for each intervention were assessed from the latest estimates from the Countdown to 2015 report[70] or best available epidemiological information (figure 1). Effect sizes for reduction of stillbirths were entered into the model and applied to an affected fraction, representing a combination of the prevalence of the risk factor and the increased risk of stillbirth associated with that factor (webappendix p 13). LiST uses national mortality rates, categories of stillbirth (antepartum and intrapartum), and effectiveness of interventions to estimate the number of stillbirths that could be averted (panel 3). We then predicted the number of stillbirths that would be saved at coverage levels of 60%, 90%, and

| | 60% coverage | | 90% coverage | | 99% coverage | |
|---|---|---|---|---|---|---|
| | Number of stillbirths | Reduction in stillbirths | Number of stillbirths | Reduction in stillbirths | Number of stillbirths | Reduction in stillbirths |
| Baseline estimate for 2015 | 2 499 000 | .. | 2 499 000 | .. | 2 499 000 | .. |
| Periconceptional folic acid fortification | 2 481 000 | 0·7% | 2 472 000 | 1·1% | 2 470 000 | 1·2% |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy | 2 457 000 | 1·7% | 2 433 000 | 2·7% | 2 425 000 | 3·0% |
| Syphilis detection and treatment | 2 425 000 | 3·0% | 2 396 000 | 4·1% | 2 350 000 | 6·0% |
| Detection and management of hypertensive disease of pregnancy | 2 463 000 | 1·5% | 2 472 000 | 1·1% | 2 430 000 | 2·8% |
| Detection and management of diabetes of pregnancy | 2 484 000 | 0·6% | 2 475 000 | 1·0% | 2 473 000 | 1·1% |
| Detection and management of fetal growth restriction | 2 430 000 | 2·8% | 2 391 000 | 4·3% | 2 380 000 | 4·8% |
| Identification and induction of mothers with ≥41 weeks of gestation | 2 467 000 | 1·3% | 2 448 000 | 2·1% | 2 442 000 | 2·3% |
| Skilled care at birth and immediate care for neonates | 2 443 000 | 2·3% | 2 355 000 | 5·8% | 2 326 000 | 7·0% |
| Basic emergency obstetric care | 2 313 000 | 7·4% | 2 147 000 | 14·1% | 2 088 000 | 16·5% |
| Comprehensive emergency obstetric care | 2 146 000 | 14·1% | 1 824 000 | 27·0% | 1 723 000 | 31·1% |

Numbers of stillbirths have been rounded to the nearest thousand, but percentages of stillbirths averted were based on actual numbers.

***Table 4:*** **Estimated effects of individual interventions on stillbirths according to coverage level in 2015**

| | 60% coverage | | 90% coverage | | 99% coverage | |
|---|---|---|---|---|---|---|
| | Number of stillbirths averted* | Reduction in stillbirths | Number of stillbirths averted* | Reduction in stillbirths | Number of stillbirths averted* | Reduction in stillbirths |
| Periconceptional folic acid fortification | 17 000 | 0·7% | 25 000 | 1·0% | 27 000 | 1·1% |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy | 20 000 | 0·8% | 32 000 | 1·3% | 35 000 | 1·4% |
| Syphilis detection and treatment | 72 000 | 2·9% | 121 000 | 4·8% | 136 000 | 5·4% |
| Detection and management of hypertensive disease of pregnancy | 34 000 | 1·4% | 50 000 | 2·0% | 57 000 | 2·3% |
| Detection and management of diabetes of pregnancy | 15 000 | 0·6% | 22 000 | 0·9% | 24 000 | 1·0% |
| Detection and management of fetal growth restriction | 65 000 | 2·6% | 98 000 | 3·9% | 107 000 | 4·3% |
| Identification and induction of mothers with ≥41 weeks of gestation | 31 000 | 1·2% | 47 000 | 1·9% | 52 000 | 2·1% |
| Comprehensive emergency obstetric care | 361 000 | 14·5% | 622 000 | 24·9% | 696 000 | 27·9% |
| Total stillbirths averted | 615 000 | 24·6% | 1 017 000 | 40·7% | 1 134 000 | 45·4% |

Numbers of stillbirths averted have been rounded to the nearest thousand, but percentages were based on actual numbers. *Calculated on the basis of a baseline estimate of 2 499 000 stillbirths in 2015.

***Table 5:*** **Estimated effects of intervention combinations on stillbirths according to coverage level in 2015**

For more on **LiST** see http://www.jhsph.edu/dept/ih/IIP/list/index.html

99% by use of formulae equivalent to those shown in the LiST manual.

We calculated the projected effect of individual interventions (table 4) and of intervention combinations appropriate to the three levels of stillbirth rate noted above (table 5) on reduction of stillbirths, according to the three levels of coverage.

## Findings

Even at 60% coverage, the model predicted that combination of all interventions modelled could reduce stillbirths from existing baseline numbers by 25%, a proportion which could increase to nearly 45% at universal coverage (table 5). Many new interventions—such as identification and management of hypertensive disease of pregnancy, diabetes, and fetal growth restriction or compromise—are promising in terms of effects, but, as expected, the maximum reductions in stillbirths are from facility-based basic and comprehensive emergency obstetric care (figure 2).

We did not model the effect of other nutritional interventions, such as calcium and balanced energy-protein supplementation, on reduction of stillbirths. According to preliminary estimates modelled in LiST, addition of these two interventions at universal coverage could avert a further 13% of all stillbirths. However, the huge challenges with delivery strategies and costs preclude recommendation for high-scale provision of these interventions at present. Treatment of women with substantial malnutrition and food insecurity is, however, an ethical and moral imperative. In all such circumstances, strategies to provide adequate social safety nets and to address female poverty and household food insecurity should be prioritised.

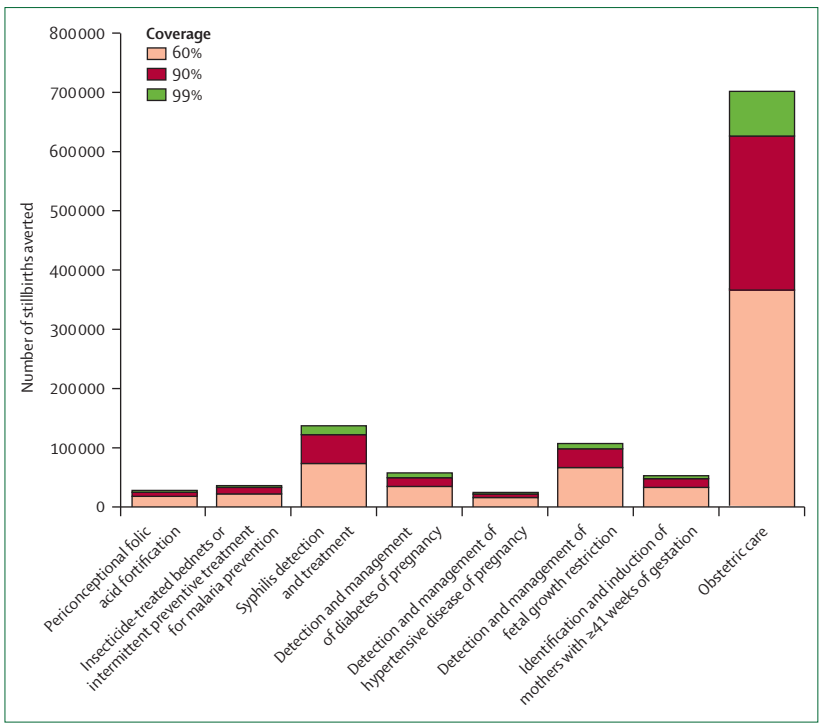


*Figure 2:* **Effect of combinations of interventions on stillbirths in 68 Countdown countries according to level of coverage**

## Modelling costs of interventions

### Methods

We estimated total costs of the interventions individually and in combination. First, detailed lists were drawn up of the type and amount of drugs, supplies, and personnel time needed for each intervention, based on standard WHO protocols and expert opinion. The cost of these items was then estimated from international drug prices (supplied by the UNICEF supply catalogue,[86] and the Management Sciences for Health international drug price indicator[87]) and country-specific salary data from the WHO-CHOICE (CHOosing Interventions that are Cost Effective) database,[88] and used to calculate average direct costs per pregnant woman. Additionally, facility and overhead costs were included for facility-based interventions, specifying the amount of time an average pregnant woman would spend at a facility (defined as minutes of an outpatient visit or days spent as an inpatient). The cost of these time estimates was calculated from country-specific estimates for the cost of an outpatient visit at a clinic or an overnight stay at a hospital, and the WHO-CHOICE database. Cost per use of equipment needed for specific interventions was calculated by dividing the cost of the equipment by the expected number of uses of the item during its lifetime. Last, an estimated percentage value was added to account for expenses from additional training,

| | Number of stillbirths | | | Marginal number of stillbirths averted* | | | Additional costs (US$ million) | | | | Proportion of total cost of interventions (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≥25 per 1000 births | 15–24·9 per 1000 births | 5–14·9 per 1000 births | ≥25 per 1000 births | 15–24·9 per 1000 births | 5–14·9 per 1000 births | ≥25 per 1000 births | 15–24·9 per 1000 births | 5–14·9 per 1000 births | Total† | |
| Baseline | 1 188 000 | 989 000 | 322 000 | .. | .. | .. | .. | .. | .. | .. | .. |
| Skilled care at birth and immediate care for neonates | 1 088 000 | 918 000 | 320 000 | 100 000 | 72 000 | 2000 | 986 | 396 | 272 | 1654 | Not modelled‡ |
| Basic emergency obstetric care | 963 000 | 813 000 | 312 000 | 125 000 | 104 000 | 8000 | 1575 | 680 | 419 | 2674 | Not modelled‡ |
| Comprehensive emergency obstetric care | 774 000 | 650 000 | 299 000 | 189 000 | 163 000 | 13 000 | 2298 | 1080 | 573 | 3951 | 40% |
| Syphilis detection and treatment | 696 000 | 590 000 | 287 000 | 78 000 | 60 000 | 11 000 | 338 | 134 | 113 | 585 | 6% |
| Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy | 663 000 | 561 000 | 285 000 | 33 000 | 29 000 | 3000 | 180 | 86 | 10 | 276 | 3% |
| Detection and management of hypertensive disease of pregnancy | NA | 544 000 | 280 000 | NA | 17 000 | 5000 | 322 | 129 | 63 | 513 | 5% |
| Periconceptional folic acid fortification | NA | NA | 271 000 | NA | NA | 9000 | 0 | 0 | 0 | 0 | 0% |
| Detection and management of diabetes of pregnancy | NA | NA | 268 000 | NA | NA | 3000 | 1463 | 692 | 984 | 3138 | 32% |
| Detection and management of fetal growth restriction | NA | NA | 264 000 | NA | NA | 4000 | 511 | 229 | 239 | 978 | 10% |
| Identification and induction of mothers with ≥41 weeks of gestation | NA | NA | 260 000 | NA | NA | 5000 | 56 | 32 | 45 | 132 | 1% |

Numbers of stillbirths and stillbirths averted have been rounded to the nearest thousand, and additional costs have been rounded to the nearest million. NA=not calculated. *Marginal stillbirths are stillbirths averted by a package in addition to those prevented by the package in the row above. †The total cost of all ten interventions is US$9.6 billion; note that this total does not include the individual costs for skilled care at birth and immediate care for neonates and basic emergency obstetric care because the costs of these interventions are included in the cost of comprehensive emergency obstetric care. ‡Proportion not calculated because 99% coverage with comprehensive emergency obstetric care was assumed.

*Table 6:* **Total additional costs of interventions at 99% coverage across the 68 Countdown countries at various stillbirth rates in 2015**

supervision, monitoring, and evaluation related to scale-up of interventions.

To account for the fact that average costs differ dependent on coverage levels, costs were adjusted based on data from the WHO-CHOICE database. For the regions covered in this report, costs of visits were estimated to be about 9% higher in regions with 80–95% coverage, and 24% higher in regions with more than 95% coverage, than were visits in regions with coverage of less than 80%. The same percentage adjustments were made to costs of overnight hospital stays. We calculated the costs of various interventions, alone or in combination, at different levels of coverage (data not shown) across the three strata of stillbirth rates and the costs of interventions by components. Detailed calculation of these estimates is provided in webappendix pp 14–21.

### Findings

As expected, the major costs of packages for saving stillbirths at universal coverage (US$9·6 billion) are largely determined by facility-based basic and emergency obstetric care and the advanced packages of antenatal care that include detection and management of pregnancy-induced hypertensive disease, diabetes, and fetal growth restriction (table 6, figure 3). These costs, however, cover gains that are spread across the full range of maternal, fetal, and neonatal outcomes.

## Identification of research gaps for future development of interventions

In view of the lack of interest and investment in research on interventions to reduce stillbirths, we aimed to identify the highest priority areas of research with the method developed by CHNRI[89] and expansion of a preliminary exercise undertaken during meetings of the Global Alliance for Prevention of Prematurity and Stillbirths (GAPPS) in 2009.[6] In the CHNRI method, experts are canvassed and consulted, and their opinions are used to give priority ratings to several research questions that could represent priority areas. Proposed research questions on interventions to prevent stillbirths were identified from several sources[4,90–92] and review of the pregnancy and childbirth database of Cochrane systematic reviews. Separate lists for countries of low income (n=52 research questions) and middle income (n=45) were then compiled by consensus among the authors of this Series. Some questions were common to both low-income and middle-income countries. From networks of researchers and professionals with an interest in stillbirths in low-income and middle-income countries, we chose experts and contacted them by email to score the questions. The research questions were divided into categories of delivery (health policy and systems) and development (improvements and applications of known interventions). Table 7 summarises the key research questions to help develop interventions and address knowledge gaps, and the corresponding questionnaires used to establish research priorities are provided in webappendix pp 22–23 for low-income countries and in webappendix pp 24–25 for middle-income countries.

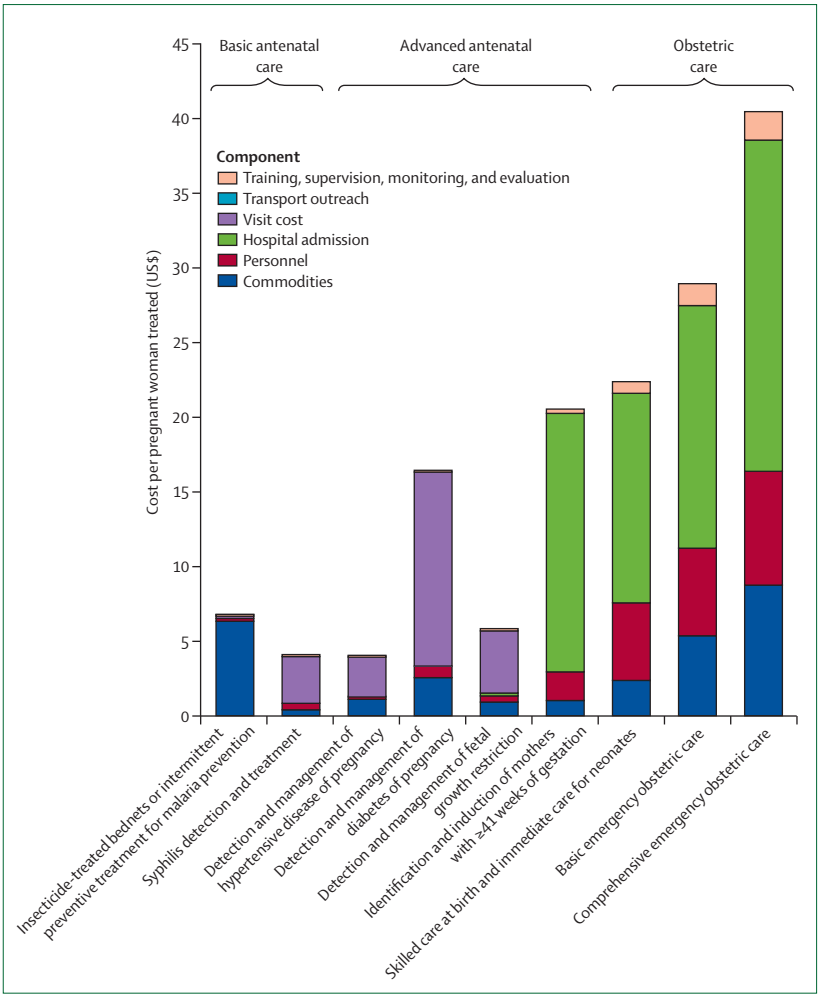


***Figure 3:*** **Costs of components of interventions per pregnant woman treated**
Public sector costs were not estimated for periconceptional folic acid fortification because implementation was assumed to be through the private sector.

## Discussion

We identified few studies in which interventions clearly reduced stillbirths. In particular, almost no studies reported disaggregated data for antepartum or intrapartum stillbirths, and only one study was an effectiveness trial.[93] These limitations impede definitive judgment of the effectiveness of interventions that benefit both mothers and neonates. For several interventions, especially those that relate to serious maternal and neonatal complications and comprehensive emergency obstetric care, the scarcity of information on stillbirth outcomes points to the need for targeted research to fill these evidence gaps. A major recommendation of this report, and of preceding reviews,[4–6] is for stillbirth measurements to be included

| | Low-income countries (n=27) | Middle-income countries (n=31) |
|---|---|---|
| How effective is a simplified partograph with an easily applied management protocol for identification of problems during labour and prevention of intrapartum-related stillbirth? | 1 | 1 |
| What is the optimum management, including drugs, follow-up, admission, and timing of delivery, for pregnancy-induced hypertension and chronic hypertension? | 2 | 5 |
| With dosing and dose-ranging studies, what are the safety profiles of oral and vaginal misoprostol for induction of labour? | NA | 2 |
| What are the safest, most acceptable, and most cost-effective methods for detection of intrapartum fetal distress in resource-poor settings? | 3 | NA |
| Does screening and treatment for urinary-tract and lower-genital-tract infections in pregnancy reduce the risk of stillbirth? | NA | 3 |
| What is the optimal management for prelabour rupture of membranes, and for suspected amniotic fluid infection? | 5 | 4 |
| What are effective approaches to promote spacing of pregnancies to at least 24 months, and what is the effect on the stillbirth rate? | 4 | NA |
| How feasible, safe, and effective is oral misoprostol for induction of labour in resource-poor settings? | 6 | NA |
| Does use of insecticide-treated bednets reduce the stillbirth rate in areas with low transmission of malaria or areas in which *Plasmodium vivax* is the most dominant pathogenic parasite? | NA | 6 |
| How safe, acceptable, and effective is routine membrane sweeping at 40 weeks' gestation to prevent continuation of pregnancies to post term? | 7 | 10 |
| How might optimum glycaemic control be achieved in diabetic pregnancy? | NA | 7 |
| Are regimens of micronutrient, vitamin, and protein-energy supplementation safe and effective in reduction of the risk of stillbirth in nutritionally deficient populations? | 8 | NA |
| Does calcium supplementation in high-risk pregnancies reduce the risk of stillbirth? | NA | 8 |
| Does serial routine serial measurement of symphysis to fundal height reduce the risk of stillbirth? | 9 | 11 |
| How can screening for diabetes be done most cost effectively? | 13 | 9 |
| How safe and effective is intracervical insertion of a Foley catheter for cervical ripening before induction? | 10 | NA |

The first ten ranked research questions in each country category are shown. n=number of questions on development of interventions. NA=not applicable because the research question was not included as an option in the list for scorers.

***Table 7:*** **Ranking of research priorities for development of interventions to reduce stillbirths in low-income and middle-income countries**

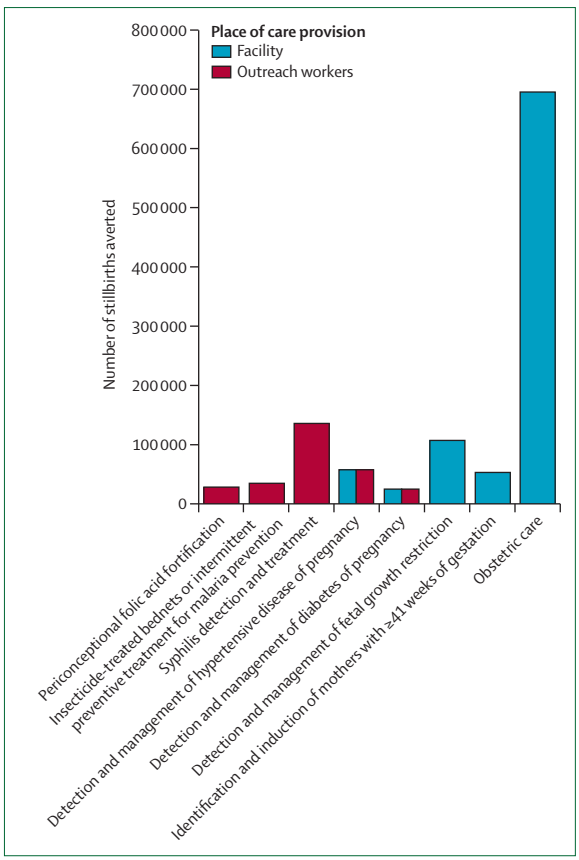


***Figure 4:*** **Effect of intervention packages on stillbirths in 68 Countdown countries by place of care provision**

in all existing surveillance sites with pregnancy detection and outcome tracking. Furthermore, instruments such as those for verbal autopsy, need to be urgently developed to allow accurate tracking of gestational age for stillbirths. Characterisation of stillbirths into antepartum and intrapartum needs to be improved to better assess the effect of interventions.

Despite the paucity of information, our report provides evidence that several interventions effectively reduce stillbirths, especially those that relate to the intrapartum period, and can be implemented within health systems. Our report also points out the need to consider additional interventions for inclusion during antenatal care in health systems as capacity for implementation increases. Some of these interventions are already available to rich people in developing countries, frequently through the private sector. The key challenge is to provide access to the poor and those residing in distant rural populations, noting that 59% of global stillbirths occur in rural families.[1] Such access might be made possible through innovative outreach models of care employing community health workers[94–96] and removal of financial and transport barriers to access skilled care.

The findings from our review of published reports and the LiST outputs strongly support the crucial part played by facility-based births and basic and comprehensive emergency obstetric care in reduction of intrapartum stillbirths. This result is not surprising. Although the total cost estimates generated by the model seem high in relation to stillbirths averted, these interventions also affect maternal and neonatal deaths, and hence need to be considered in relation to cost-benefit ratios for fetal, maternal, and neonatal deaths averted. We recognise that provision of facility-based care for all births is a lofty and distant goal for many countries with huge challenges in access and human resources. However, according to studies investigating removal of financial barriers to facility-based births[97,98] and innovations such as public-private partnerships for comprehensive emergency obstetric care,[99] this goal is at least possible in south Asian settings. Referrals to facilities alone will not improve

outcomes. Improvement of staff training and attention to quality of care is key and needs to be linked to some form of institutional assessment of staff quality and training in relation to birth outcomes and perinatal audits.[100–102] Such assessment is particularly important because excess maternal morbidity is associated with inappropriate interventions and operative deliveries in facilities.[103]

In settings with substantial shortage of skilled attendants, training of midwives and linkage of health facilities to trained traditional birth attendants could provide a short-term solution, but should not detract from long-term investments and approaches to care. In reviews of community-based packages and delivery strategies, such approaches improved birth outcomes, and reduced stillbirths and maternal morbidity.[95,96] However, a high proportion of the effect of such community platforms, including women's support groups,[104] is through preventive care and improved care seeking rather than from direct domiciliary care for maternal and neonatal complications. Indeed, community-based trials of training community health workers and traditional birth attendants in neonatal resuscitation[93,105,106] and care of neonates with very low birthweight[28] have underscored the limitations of training for such care providers. Hence, wherever deployed and feasible, outreach workers should be linked to functional facilities.

Our assessment provides strong support for scale-up of simple interventions, mostly preventive, such as improvement of nutrition, and prevention and treatment of syphilis and malaria in endemic countries. Although we did not recommend food and calcium supplements in pregnancy because of high cost and uncertain delivery strategies, these are important interventions for the future as they can improve maternal health, and reduce serious morbidity and intrauterine growth restriction. Notably, no large efficacy trial of maternal balanced energy-protein supplementation has been done since a study in Gambia more than 15 years ago.[107] Large-scale projects are needed to assess the feasibility and effect of balanced energy-protein supplementation, and develop alternative methods to address food insecurity in household settings—eg, conditional cash transfers versus food supplements, and delivery of calcium through food fortification. Consonant with the recorded reduction in maternal mortality with the development of midwifery services, often ambulatory,[108] findings of our report suggest that a substantial proportion of interventions can be delivered through outreach workers and ambulatory services. A conservative estimate suggests that such delivery could avert about 280 000 stillbirths (11%; figure 4).

This report presents the first results from use of the LiST model to assess the benefit of interventions for maternal, fetal, and neonatal mortality, including stillbirths, at a population level. Our findings underscore the need for development of models that include potential interventions to address morbidity and incorporate dimensions of interest to long-term outcomes—eg, post-asphyxial encephalopathy. Despite little information from published reports, findings of our review and modelling exercise support the contention that the global burden of stillbirths is not intransigent to change, and shows that incremental gains are possible with a combination of outreach and facility-based interventions. In countries with the highest burden of stillbirths, a large proportion of which are intrapartum stillbirths, interventions can substantially reduce stillbirths and could also improve maternal and neonatal outcomes. In fact we believe that our projected estimates of lives saved by interventions are conservative because we used the most conservative estimates for effectiveness of interventions, as per CHERG methods,[7] and the baseline coverage data for many interventions[13] was indirectly estimated and might be overestimated in many cases. The estimated 41–45% reduction in stillbirths at 90–99% coverage by the suggested interventions is probably an underestimate because most high-income and some middle-income countries have been able to reduce intrapartum stillbirths and related neonatal deaths to a greater extent.[109,110] The challenge now is to translate this evidence into policy and make these interventions accessible to individuals in greatest need[111] in an integrated manner[112] and at a faster pace than secular trends. Implementation and integration will be the focus of the fourth paper in this Series.[113]

#### Contributors

ZAB wrote the first draft of the report with subsequent inputs from all other authors. ZAB and MYY oversaw the systematic review of interventions, with inputs from JEL and RLG. IKF, AR, and EW ran the LiST model and cost estimations, and EB led the research priorities review process. All authors contributed to writing and review of the report.

#### *The Lancet*'s Stillbirths Series steering committee

J Fredrik Frøen, Joy E Lawn, Zulfiqar A Bhutta, Robert Pattinson, Vicki Flenady, Robert L Goldenberg, and Monir Islam.

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#### Conflicts of interest

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