Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index

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Summary

Background Every year, 1·1 million babies die from prematurity, and many survivors are disabled. Worldwide, 15 million babies are born preterm (<37 weeks' gestation), with two decades of increasing rates in almost all countries with reliable data. The understanding of drivers and potential benefit of preventive interventions for preterm births is poor. We examined trends and estimate the potential reduction in preterm births for countries with very high human development index (VHHDI) if present evidence-based interventions were widely implemented. This analysis is to inform a rate reduction target for Born Too Soon.

Methods Countries were assessed for inclusion based on availability and quality of preterm prevalence data (2000–10), and trend analyses with projections undertaken. We analysed drivers of rate increases in the USA, 1989–2004. For 39 countries with VHHDI with more than 10 000 births, we did country-by-country analyses based on target population, incremental coverage increase, and intervention efficacy. We estimated cost savings on the basis of reported costs for preterm care in the USA adjusted using World Bank purchasing power parity.

Findings From 2010, even if all countries with VHHDI achieved annual preterm birth rate reductions of the best performers for 1990–2010 (Estonia and Croatia), 2000–10 (Sweden and Netherlands), or 2005–10 (Lithuania, Estonia), rates would experience a relative reduction of less than 5% by 2015 on average across the 39 countries. Our analysis of preterm birth rise 1989–2004 in USA suggests half the change is unexplained, but important drivers include non-medically indicated labour induction and caesarean delivery and assisted reproductive technologies. For all 39 countries with VHHDI, five interventions modelling at high coverage predicted a 5% relative reduction of preterm birth rate from 9·59% to 9·07% of livebirths: smoking cessation (0·01 rate reduction), decreasing multiple embryo transfers during assisted reproductive technologies (0·06), cervical cerclage (0·15), progesterone supplementation (0·01), and reduction of non-medically indicated labour induction or caesarean delivery (0·29). These findings translate to roughly 58 000 preterm births averted and total annual economic cost savings of about US$3 billion.

Interpretation We recommend a conservative target of a relative reduction in preterm birth rates of 5% by 2015. Our findings highlight the urgent need for research into underlying mechanisms of preterm births, and development of innovative interventions. Furthermore, the highest preterm birth rates occur in low-income settings where the causes of prematurity might differ and have simpler solutions such as birth spacing and treatment of infections in pregnancy than in high-income countries. Urgent focus on these settings is also crucial to reduce preterm births worldwide.

Funding March of Dimes, USA, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institutes of Health, USA.

Lancet 2013; 381: 223–34

Published **Online** November 16, 2012
http://dx.doi.org/10.1016/S0140-6736(12)61856-X

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Introduction

Every year, about 1·1 million neonates die from complications of preterm birth as estimated in 2010.[1] Preterm birth is now worldwide the second most common cause-of-death in children younger than 5 years after pneumonia, and is decreasing at a much slower rate than pneumonia, even increasing in several countries. Additionally, preterm birth is the leading risk factor for 393 000 deaths due to neonatal infections and contributes to long-term growth impairment and substantial long-term morbidity such as cognitive, visual, and learning impairments.[2,3]

The first-ever national estimates of preterm birth (defined as <37 completed weeks of gestation) were recently published in *The Lancet*,[4] undertaken with the WHO, and included a country clearance process in which all UN member states countries were invited to review their estimates and provide feedback. These estimates showed a total of 15 million babies born preterm in 2010, 5% of which were under 28 weeks' gestation.[4] Time trends for 65 countries from the Millennium Development Goals (MDG) Developed region, Latin America, and the Caribbean region, where more reliable data were available, showed that almost all these countries have had increased rates of preterm birth over the past two decades.

Born Too Soon: The Global Action Report on Preterm Birth[5] was based on these estimates and outlined evidence for interventions along the continuum of care from preconception, through pregnancy, birth, and for newborn care.[5] Reduction in preterm mortality in high-income countries has been largely due to improved care and policy changes, and this care has yet to be scaled up in most low-income and middle-income countries.[5] *Born Too Soon* set a goal of 50% reduction of preterm specific mortality by 2025, which was based on historical reductions in the USA and UK, rates of reduction of preterm-specific deaths in well performing low-income and middle-income countries, and an analysis of lives saved with very feasible interventions such as kangaroo mother care and antenatal steroids. The report was a joint effort involving 50 organisations, it has a Foreword by the UN Secretary-General, and contains new commitments by 31 organisations linked to the accountability framework of the Every Woman Every Child movement.[5]

The survival gap for preterm babies is mainly an action gap for intervention implementation low-income and middle-income countries. However, the the worldwide epidemic of preterm birth affects low-income, middle-income, and high-income countries alike, and the gap for preterm prevention is mainly a knowledge gap. Our understanding of the underlying drivers for preterm birth or the potential effect of preventive interventions remains poor, although recent advances in classification of the preterm birth syndrome provide helpful advances. *Born Too Soon* therefore recommended that "a technical expert group will be created to consider a goal for reduction of preterm birth rate by 2025 for announcement on World Prematurity Day 2012."[5,6]

Thus, our aim was to do a multicountry analysis of the trends in preterm birth rates for 2000–10 in countries with more robust data, and to estimate the potential reduction in preterm birth with full implementation of currently proven interventions. A secondary objective was to consider the setting of a preterm birth reduction target for these countries.

Methods

Assessment of national data and time trends for preterm birth rates

Recent national estimates[4] of preterm births were based on 738 reported data inputs from 99 countries, from 1990 to 2010. This analysis identified a paucity of consistent reliable data for countries in regions without robust registration systems. Hence, a statistical model was used to estimate preterm birth rates in 2010 for 184 countries with more than 10 000 livebirths, but it was unable to estimate time trends in low-income and most middle-income countries. Most input data (547 of 738) were from the 65 countries in the Developed, Latin America, and the Caribbean MDG regions. Hence the 1990–2010 time trend analysis was focused on these countries with use of country-level Loess regression to smooth reported data for the 12 countries with adequate data during the 21-year period and statistical modelling with own and regional data for the other 53 countries.[4] Loess regression is a locally weighted regression method, it was used to fit a smooth curve to the country-specific preterm data using a weighted least squares method to

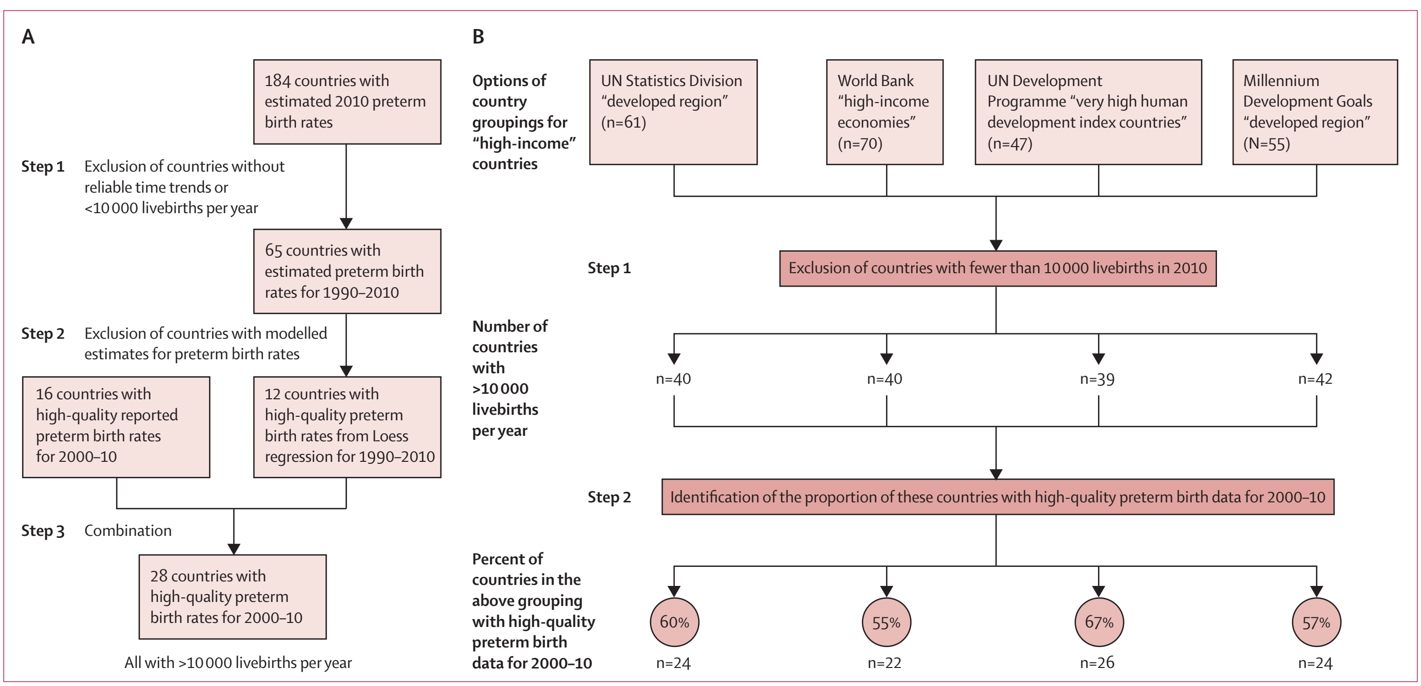

***Figure 1:* Country selection process for preterm birth rate trends analyses**
n=number of countries. (A) Inclusion criteria for countries with reliable preterm birth trend data. (B) Examination of "high-income" country groupings with best fit for countries with high-quality preterm birth data. Data of preterm prevalence from Blencowe H and colleagues.[4] For country groupings see appendix (pp 1–2).

minimise year on year fluctuations. This method makes use of the data available from the specific country to provide estimates for every year, giving more weight to the datapoints nearest to the year estimating for.[7]

Inclusion criteria and regional grouping

We assessed the data from these 65 countries with a focus on the 2000–10 period. High-quality data were available for 28 countries for that period (figure 1A). We excluded countries with fewer than 10 000 livebirths in 2010 from all definitions of high-income countries in accordance with the methodology used in the previous time trends analyses by Blencowe and colleagues[4] (appendix pp 1–2).

To identify the most appropriate regional grouping with a high proportion of the countries having good quality data, we examined various definitions of high-income or developed countries to identify which grouping contained the highest share of these countries with high-quality data availability. We considered the following four options: World Bank "high-income economies", UN Development Programme "Very High Human Development Index" (VHHDI), UN Statistics Division "developed region", and the MDG "developed region". The 26 countries with high-quality data constituted 67% of the 39 UN Development Programme VHHDI countries with more than 10 000 livebirths per year, the highest of the four options examined (figure 1B). Of these 47 countries with VHHDI, 39 had more than 10 000 livebirths per year and were included in our analysis (appendix p 2). 26 of these countries had high-quality reported or Loess data (6% of global preterm births from 2010) and for the remaining 13 countries, we used their own data with modelled adjustment from Blencowe and colleagues[4] (2% of global births in 2010; figure 2, appendix pp 3–4).

To estimate the potential effect of preventive interventions for these 39 countries with VHHDI, we used the 2010 preterm birth rates as the baseline, pre-intervention preterm birth rate (appendix p 5). We analysed the average annual rate of change (AARC) of preterm birth rate for different time periods, including only countries with VHHDI with high-quality data for preterm birth rates spanning at least 5 of the 6 years for every time period (eg, 2000–05, 2005–10; appendix p 6). This exclusion was to minimise the effect of year-to-year fluctuations on the AARC and helped to more accurately represent the overall trend. 23 of the 39 countries with VHHDI had enough data for estimating the AARC for both 2000–05 and 2005–10 time periods.

See Online for appendix

We did a projection of potential reduction in preterm births to estimate the reduction in countries with VHHDI if all countries achieved the same as those with the greatest reduction in preterm birth rates for three different periods: 1990–2010, 2000–10, and 2005–10. The average of the annual rate of change for the two countries with the highest rate of reduction during each period was then used to project preterm birth rates for years 2010 to

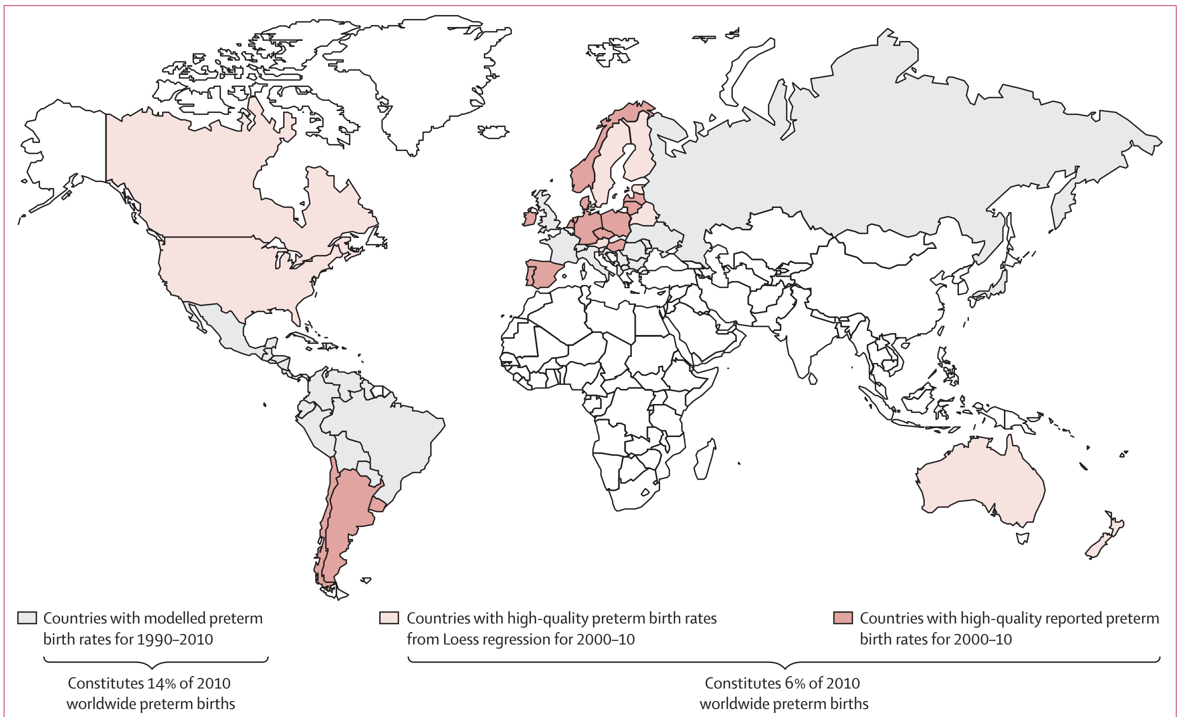

Figure 2: **Preterm birth trend data availability by country, 1990–2010**

Data of preterm prevalence data availability from Blencowe H and colleagues.[4] Some countries with high-quality data only had data for subnational populations (eg, UK and Belgium).

2015 for all countries with VHHDI, weighted by 2010 preterm births for every country (appendix p 7).

Analysis of drivers for rise in preterm birth in USA

We analysed the rise in preterm births in the USA. We selected the USA because of its high preterm birth rate (double most European countries), its rising rates then recent reductions suggesting a changing pattern, and its data availability for rates and drivers, but this analysis was not applied to other countries. We identified potential drivers that might have contributed to the rising rate of preterm births in the USA between 1989 and 2004 on the basis of scientific literature and discussions with the *Born Too Soon* preterm prevention analysis group.[8] To estimate the contributions from every driver, we took the following approach: (1) identify the distribution of mothers affected (eg, maternal age), (2) identify the risk of preterm birth for every category (eg, by maternal age), and (3) calculate the total contribution to the difference in preterm birth rate between 1989 and 2004 for every driver. Importantly, we avoided overlap of contributions from different drivers in the analysis by using preterm birth odds ratios (ORs) from logistical regression modelling that simultaneously controlled for all except the variable of interest using individualised data (eg, maternal age is associated with increased use of assisted reproductive technologies).[8,9] We calculated the contribution to the difference in preterm birth rate between 1989 and 2004 for every age group by multiplying the percentage of mothers in every age group with the corresponding OR and subtracting the result for 1989 from 2004. Details on specific data sources and methodology are presented in the appendix (pp 8–14).[8,10–14]

Estimation of the effect of interventions to reduce preterm birth

We used the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) Review Group report[15] to identify a list of preventive interventions for consideration. The GAPPS team systematically assessed about 2000 intervention studies published up until Dec 31, 2008, and applied an adaptation of the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) criteria.[15] Three preventive interventions had a high level of evidence (smoking cessation, progesterone, and zinc supplementation), but only two (smoking cessation and progesterone) were strongly recommended for implementation for preterm birth prevention and were included in our analysis (table).

For the 18 interventions in the GAPPS review[15] with "very low," "low", and "moderate" evidence of efficacy, or "high" level of evidence for no effect, we searched for new evidence published since 2008 that might change these assessments (appendix p 15). We focused on high-quality reviews such as Cochrane, and identified new reports for seven interventions (cervical cerclage, micronutrient supplementation, protein energy supplementation, iron and folate supplementation, magnesium sulphate supplementation, screening and treatment of asymptomatic bacteriuria, and multivitamins for HIV-positive women). Of these, only cervical cerclage had a notable change in evidence for efficacy on prevention of preterm births.[16,17] New evidence showed that "in women with previous spontaneous preterm birth, singleton gestation, and cervical length less than 25 mm, cervical cerclage significantly prevents preterm birth and composite perinatal mortality and morbidity."[15,16] Thus, we included cervical cerclage in our analysis. The GAPPS review[15] focused on interventions relevant to the low-income and middle-income countries so we also included two interventions of relevance to high-income countries, notably decrease of non-medically indicated caesarean delivery and labour induction and limiting multiple-embryo transfer in assisted reproductive technologies.

For the analysis on decreasing multiple births from assisted reproductive technologies, we used the European average for countries without available reported

	Evidence of efficacy for preterm birth by GRADE criteria	Recommendation for implementation for preterm birth	Rationale for inclusion or exclusion in analysis
Smoking cessation	High (effect)	Strong	Included: GRADE recommendation according to GAPPS
Progesterone	High (effect)	Strong	Included : GRADE recommendation according to GAPPS
Cerclage	High (no effect)	Strong (against)	Included: newer evidence[16] shows efficacy in women with previous preterm birth and short cervix. Potential for implementation expected to be high among HIC, unlike that for LIC and MIC, which was focus of GAPPS
Decrease in non-medically indicated caesarean delivery and induction	NA	NA	Included: relevant in HIC (not included in GAPPS because of the focus on LIC and MIC)
Limit multiple embryo transfer in assisted reproductive technology	NA	NA	Included: relevant in HIC (not included in GAPPS because of the focus on LIC and MIC)
Zinc supplementation	Non-significant	Weak	Excluded: weak GRADE recommendation according to GAPPS

GAPPS=Global Alliance for Prevention of Prematurity and Stillbirth report.[15] New evidence supporting efficacy of cerclage from Berghella and colleagues Obstetrics and Gynecology 2011.[16] GRADE=grading of recommendations assessment, development, and evaluation. HIC=high-income countries. MIC=middle-income countries. LIC=low-income countries. NA=not applicable. Appendix (pp 16–17) for effect estimate applied for each intervention and appendix (p 15) for other interventions that were considered but excluded from analysis.

Table: **Interventions meeting selection criteria for analysis of prevention of preterm birth**

data for total livebirths with assisted reproductive technologies, present rate of multiple births from these technologies, and preterm birth rate associated with each plurality in these technologies.[18] We assumed the target plurality distribution for births with assisted reproductive technologies to be

singleton : twins : triplet = 89·5% : 10·0% : 0·5%

on the basis of expert opinion about plurality distribution if most livebirths these technologies resulted from single embryo transfer.

We did country-by-country analyses of the potential reduction in preterm birth rates for the five included interventions. The general approach was: (1) identify and size of the target population for the intervention, (2) estimate the incremental coverage for the intervention to reach full coverage of the target population, (3) estimate the expected efficacy for the intervention, and finally (4) obtain the estimated impact in reduction of preterm birth rate and preterm births averted (population attributable risk) and combine this for the 39 countries with VHHDI weighted by the country's number of preterm births for 2010.

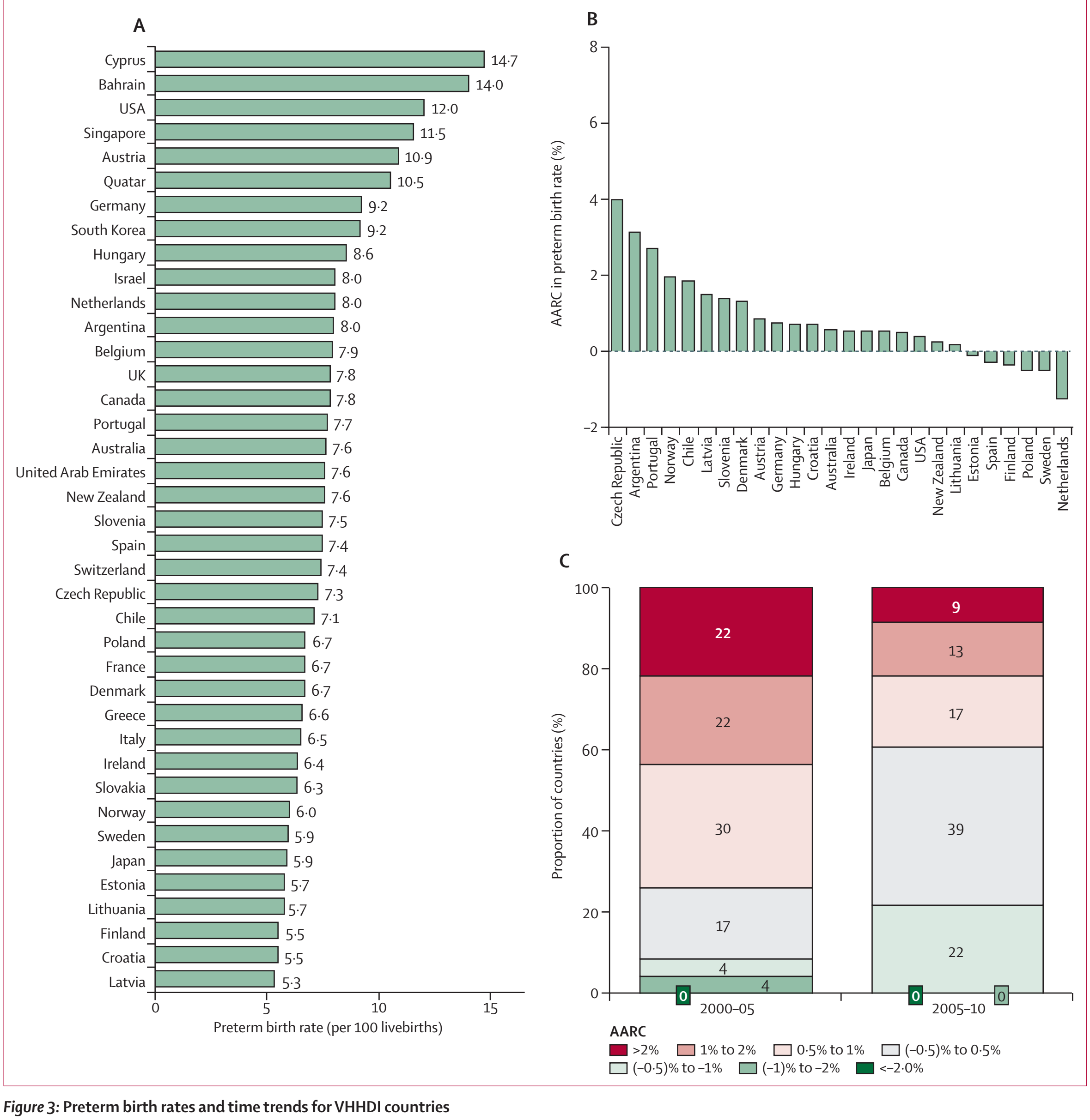

***Figure 3:* Preterm birth rates and time trends for VHHDI countries**

VHHDI=very high human development index. AARC=average annual rate of change. (A) Preterm birth rates per 100 livebirths in 2010 (baseline) for 39 countries with VHHDI. (B) AARC in preterm rates 2000–10 for 26 countries with VHHDI with high-quality data and more than 10 000 births. (C) AARC groupings 2000–05, 2005–10, for 23 countries with VHHDI with preterm birth data spanning at least 5 years within each 6-year period.

Efficacy for every intervention was based on scientific literature applying the following hierarchy: Cochrane Review, meta-analysis, randomised controlled trials, and other studies. The data used and specific methodology for every analysis can be found in the appendix (pp 16–31).[8,10,17–30] For assisted reproductive technologies, efficacy of the intervention was estimated as the difference between the existing rate of preterm births among livebirths associated with assisted reproductive technologies of each plurality (ie, twins and triplets) and that of an ideal plurality distribution (appendix p 17). This so-called ideal plurality distribution among livebirths associated with assisted reproductive technologies was set as a rounded average of performance in countries with VHHDI already with very low multiple births from assisted reproductive technologies (ie, Sweden) and the current European average.[18] For caesarean delivery and labour induction, we assumed a goal of 80% combined elimination for the analysis. This is an optimistic but not unrealistic goal, as experiences in the USA have shown that more than 80% reduction (25% to <5%) in elective delivery between 36 (0/7)–38 (6/7) weeks without a documented medical indication is possible within 2 years.[31] Coverage data were sourced from national health databases and statistical offices.

Estimation of potential cost savings

We calculated the economic cost savings associated with reduction in preterm birth rate using the projected number of preterm births averted for every country and the incremental cost associated with every preterm birth. It has been estimated that the total economic cost, including the costs of medical care services, early intervention services, special education services, and lost household and labour market productivity was US$51600 per preterm birth in the USA in 2005.[32] Other more sensitive cost analysis using gestation-specific additional costs would be preferred but were not possible because of not enough data by country and on the same gestation specific banding.[33] Using purchasing power parity conversion factor from the World Bank, we obtained the estimated incremental cost of preterm birth in the local currency of every VHHDI country (appendix pp 32–35). Then, we converted the cost for every country into US$ using currency exchange rates from the World Bank and Organization for Economic Co-operation and Development (OECD; appendix pp 32–33).

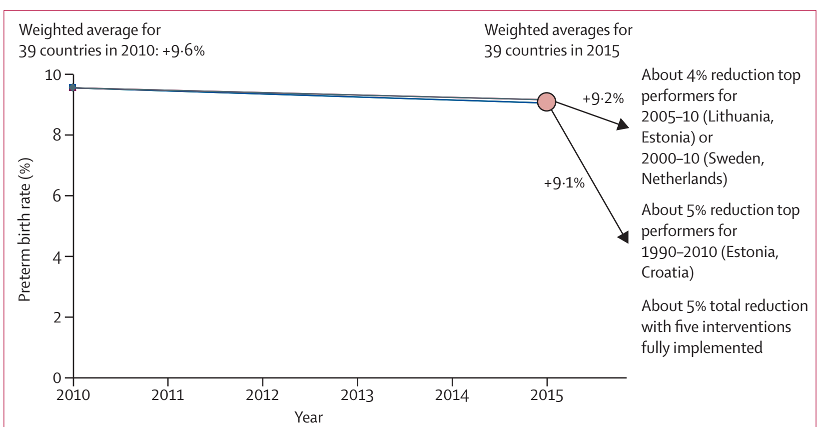

Figure 4: **Preterm birth rates for 2010 in VHHDI countries projected to 2015 considering various scenarios such as AARC for top performing countries in different time periods, or high coverage of the five preventive interventions**

VHHDI=very high human development index. AARC=average annual rate of change. See appendix (pp 16–31) for details.

Role of the funding source

The sponsoring agencies financial management had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HHC, JL, HB, and JEL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The estimated 2010 preterm birth rates varied between countries with VHHDI, from 5·3 per 100 livebirths in Latvia to 14·7 per 100 livebirths in Cyprus (figure 3). 172 datapoints were available for 26 of the 39 countries with VHHDI from 2000 to 2010 (figure 1, appendix p 6)[4] indicating that preterm birth rates have increased for most of the 26 countries between 2000 and 2010 (figure 3). However, on average, the countries with VHHDI have seen a levelling of preterm birth rates more recently from 2005 to 2010. This new finding is shown by an increasing proportion of countries (>60% or 14 of 23 countries) with a stable (0·5% to –0·5%) or decreasing (<–0·5%) preterm birth rate when comparing that for 2000–05 and 2005–10 (figure 3).

National trends in preterm birth rates are a poor predictor of future trends in many of the 39 countries (appendix p 36). We estimated the 2015 preterm birth rate for every country assuming each followed its historic AARC for 2000–10 and 2005–10, or alternatively, as being stable since 2010 (appendix pp 37–38). No consistent pattern was identifiable. In some countries the stable assumption will yield the highest projection, whereas in others the lowest. These two findings (levelling of trends 2005–10 and inconsistent projections based on historic data) suggest that modelling future preterm birth rates with a flat baseline as the counterfactual is an appropriate and conservative approach.

To estimate potential reduction of preterm birth rates if all countries achieved the same progress as that of the best performing countries, we projected the average preterm birth rate for all countries with VHHDI for 2010–15 assuming they all reduced their preterm birth rate as fast as the average of the two best performers for various time periods (1990–2010 for Estonia and Croatia; 2000–10 for Sweden, the Netherlands; and 2005–10 for Lithuania and Estonia; appendix p 7). From the 2010 baseline to 2015, whichever historical time period was used, the projection resulted in roughly 5% relative reduction in preterm birth rate by 2015, similar to the relative reduction of about 5% in our intervention analysis (figure 4).

The preterm birth rate in the USA increased from 10·6% to 12·5% between 1989 and 2004.[11] We estimated the contribution to the increase in preterm birth rate during this time from seven different drivers (figure 5; appendix pp 8–14).[8,10–14] For example, mothers in 2004 were older than in 1989, with a simultaneous increase in mothers older than 40 years and decrease of those younger than 19 years. The ORs for preterm birth (adjusted for all other variables) were highest for the oldest and youngest mothers, at 1·7 times (oldest) and 1·6 (youngest) times that of control (age 20–24 years).[8]

Only about 50% (0·91%/1·90%) of the change in preterm birth rate between 1989 and 2004 can be explained by the seven drivers, with non-indicated cesarean delivery and labour induction together accounting for about 20% (0·4/1·90%) of the change (figure 5). This analysis shows the contribution of these drivers to the change, rather than contribution to the absolute preterm birth rate, which would require a more comprehensive understanding of the pathogenesis of preterm birth than is presently available.

We estimated the potential effect of existing interventions in lowering preterm birth rates in the countries with VHHDI. We focused on five interventions meeting inclusion criteria: smoking cessation, progesterone, cervical cerclage, decreasing non-medically indicated labour or caesarean delivery induction, and decreasing multiple births from assisted reproductive technologies (table).[8,10,17–29] Combining the size of the target population, incremental increase in coverage, and efficacy of interventions, we obtained estimates for potential reduction in preterm birth rate for each intervention (appendix pp 16–17).

In 39 countries with VHHDI, by applying these five selected interventions preterm birth rates can have a relative reduction of an estimated 5%, corresponding to change in absolute preterm birth rate from 9·6% to 9·1% (figure 6, appendix pp 39–40). Reduction of non-medically indicated caesarean delivery and induction of labour has the largest effect, accounting for roughly half of the impact. However, significant variability exists across countries in the absolute impact (about 1% to roughly 8% relative reduction), but also the relative contribution of individual interventions that is variable across countries (appendix pp 41–60). For example, whereas reduction of non-indicated caesarean delivery and labour induction has the highest impact in the USA, it would make a negligible difference in Sweden (figure 6B, C). By contrast, cervical cerclage for women with previous preterm birth and short cervix is estimated to have most impact in Sweden (figure 6C).

If 5% relative reduction is achieved by the included countries, about 58 000 preterm births can be averted annually (appendix pp 61–62), amounting to roughly US$3·0 billion in total economic cost savings (appendix p 32–35). This projected cost savings is significant but still leaves a major cost and burden, highlighting the need for novel preventive interventions against preterm birth with greater impact.

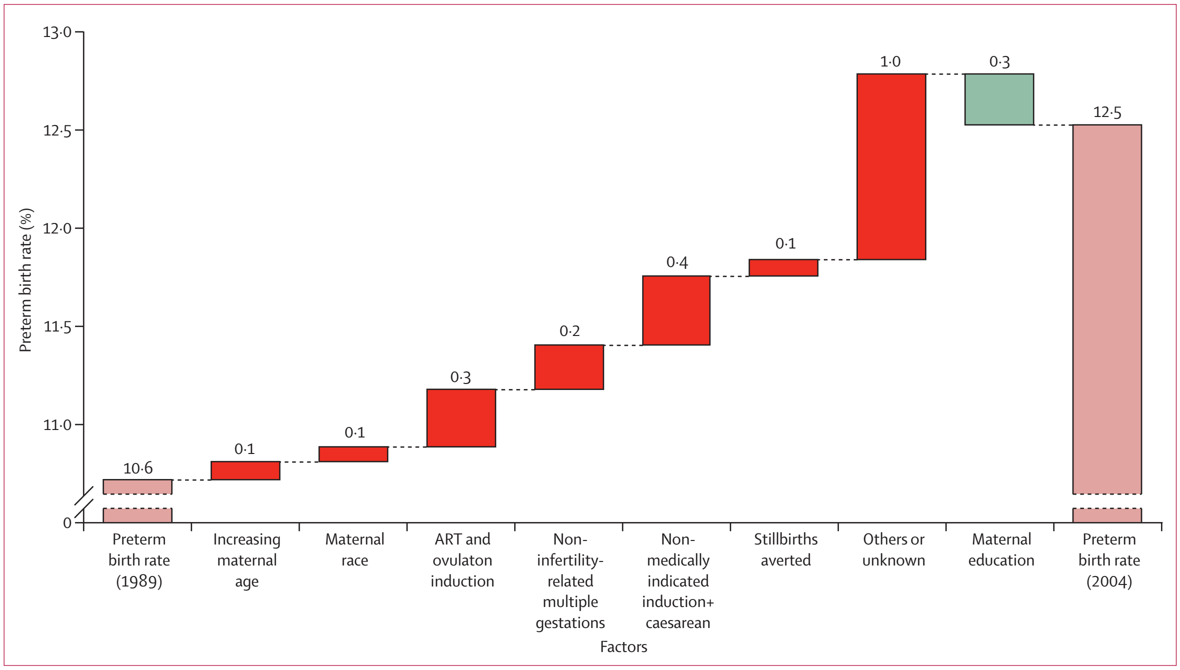

Figure 5: **Analysis of factors contributing to the increasing preterm birth rate in the USA (1989–2004)**
Calculation of population attributable risk aimed to take into account the existence of various risk factors in one woman, eg, increased maternal age and use of ART. ART=assisted reproductive technology. See appendix pp 8–14 for details of analyses.

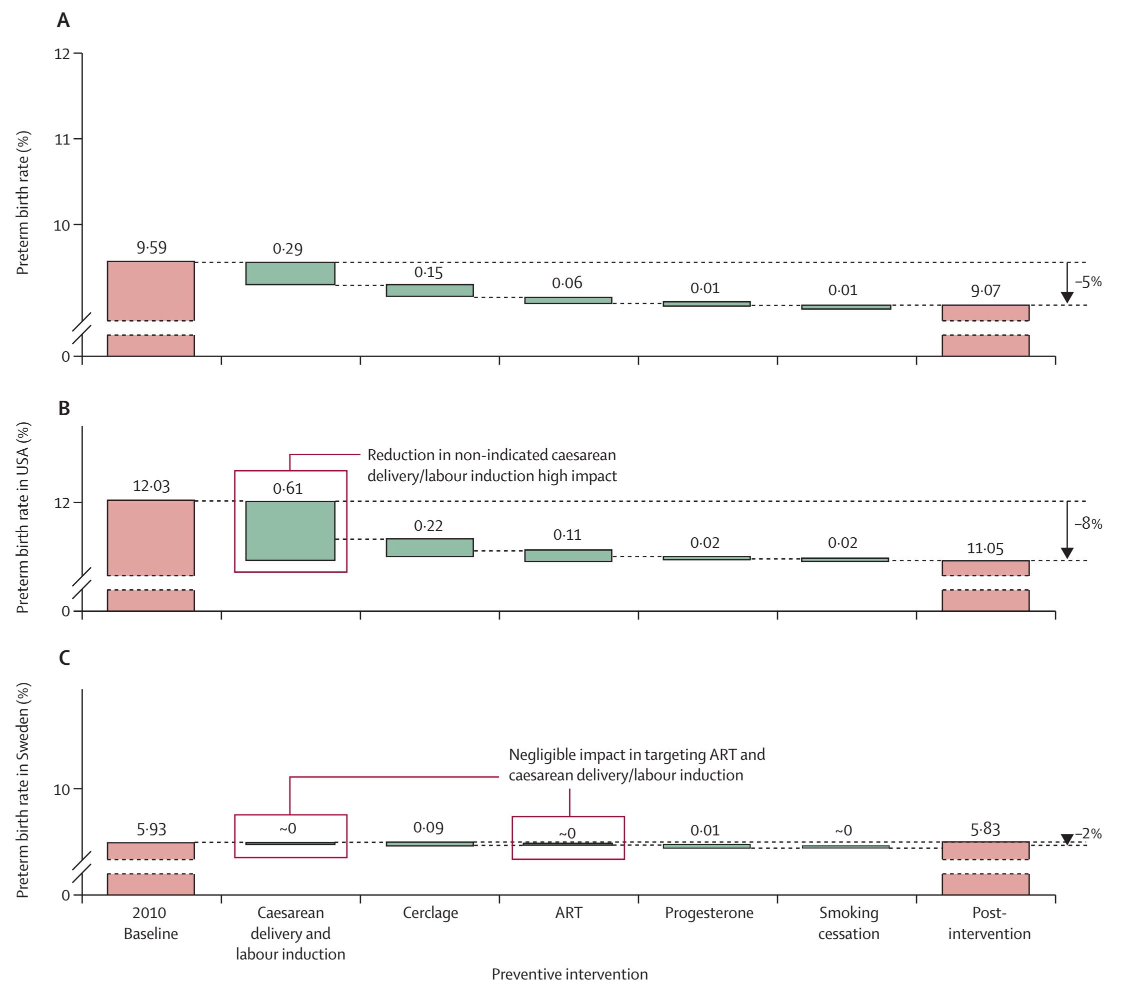

Figure 6: **Projected change from 2010 baseline preterm birth rate showing modelled contribution of the five selected interventions**
VHHDI=very high human development index. (A) For all 39 countries with VHHDI, (B) for USA, and (C) Sweden. See appendix (pp 16–31) for details of analyses, including input data and methods.

Discussion

Although preterm birth is the leading cause of death for children younger than 5 years in high-income countries, second leading cause worldwide, and a major contributor to the Global Burden of Disease, this is the first multi-country analysis of trends in preterm birth rates and the potential for prevention through existing interventions (panel). Shockingly, very little reduction is currently possible. Even with assumed optimum coverage of these interventions in countries with VHHDI, the potential reduction in preterm birth rate is tiny, with about 58 000 preterm births averted across 39 countries, but the associated US$3 billion total economic cost savings is impressive given the complexity of care provided in USA for very preterm babies.

These analyses were limited to the countries with VHHDI because of the scarcity of time trend data in low-income countries, even though rates of preterm births are generally higher in low-income countries. Additionally, several of the interventions we modelled are not relevant for low-income settings—ie, in rural west Africa, the caesarean delivery rate is almost zero, so excess caesarean deliveries are not the issue. Furthermore, some interventions such as cervical cerclage would not be feasible in such settings.

On the basis of these analyses, we propose a target of 5% relative reduction by 2015 on average across the countries with VHHDI. There were two motivations for proposing a near-future target of 2015 as compared with a later date. First, this date is feasible, because in the top-performing countries with VHHDI, AARC in preterm birth translates to about 5% relative reduction in 5 years (figure 4). Second, our hope is that this target will motivate immediate action in the countries with VHHDI, while more effective preventive interventions are being developed. This target is a weighted average for 39 countries, and some countries might achieve greater or smaller reductions. For example, our intervention analysis shows that an 8% relative reduction in preterm birth rate is possible in the USA, but only 2% probable in Sweden (figure 6B, C). Coincidentally, our USA result is remarkably consistent with the rate reduction target of 8% in the USA by 2014 put forth by the Association of State and Territorial Health Officials (ASTHO) and the March of Dimes, with pledges to date from 48 of the 50 states in the USA.

We have provided the analytical underpinning of the proposed 5% relative rate reduction target. Although previous targets have been set (eg, UNICEF Child Survival reduction of low birthweight goal set in 1990, US Healthy People 2020 preterm birth reduction goal, ASTHO), the quantitative basis for those goals are not in the public domain. While the setting of policy goals requires political traction, the transparent assessments of evidence and feasibility are crucial to consider as well, and we believe should be peer reviewed and published.

Half of the increased preterm birth rate in USA between 1989 and 2004 is unexplained by this analysis, which is an important constraint in any analyses of preterm birth rates, and a widely-recognised, fundamental knowledge gap when observing increased spontaneous preterm birth and has implications for prevention. The findings from the USA might not be generalisable for other periods or to other countries, and we have not attempted to do so. Our analysis was constrained by the availability of likelihood ratios for preterm births that simultaneously adjusted for all other variables.[8,34]

When estimating the impact of existing interventions on preterm birth prevention we were able to include only five interventions. Other interventions may have an effect but could not be included because of insufficient data. Teenage pregnancy, for example, is relevant for economies of high, low, and middle income, but age-related preterm birth intervention data are missing. Other maternal chronic disorders such as hypertensive disease of pregnancy, diabetes, and obesity associated with preterm birth are important contributors, but we were unable to estimate the effect of interventions on their contributing factors because of insufficient data regarding preterm-specific effect.[35–38] Interventions such as birth spacing and treatment of maternal infections (eg, syphilis, HIV/AIDS) are important interventions, especially in sub-Saharan Africa where preterm rates are highest, but again no or very few studies have assessed the effect on preterm births.[5,15] Newer studies suggest cervical pessary for women with short cervix might be a promising option awaiting more trials.[39–42] These should all be areas of focus for future studies.

Importantly, although reduction of preterm birth focuses on stopping non-indicated preterm births, in some situations, such as eclampsia, preterm birth is definitely indicated and is the only possible outcome for a live mother or baby or both. Thus, the goal of 0% preterm birth cannot be achieved unless preventive therapies are identified that eliminate all maternal, fetal, and obstetrical complications. Some of the increase in preterm birth is due to improved and totally appropriate obstetric management of poor fetal growth and the trade-off between stillbirth risk and yet minimising preterm birth risk is well recognised.[43] These results provide estimates for the potential effect of interventions, but do not offer guidance on individual clinical decision making. Additionally, despite their potential effect in reduction of preterm births, interventions such as progesterone supplementation and cerclage might have potential risks associated with delayed labour that require further elucidation and must be tracked, such as later neuropsychological impairment.[44]

Our analysis of the preterm birth time trends and modelling of the baseline was constrained by the limited availability of trend data for preterm birth rates at national level. We had to rely on reported or Loess regression-fitted data.[4] Although 60% (14 of 23 with sufficient time trend data) countries with VHHDI have a stable or decreasing preterm birth rate between 2005 and 2010, the remaining 40% are still rising. If this trend were to reverse, and the preterm birth rates in countries with VHHDI rise again, then the estimated net change in preterm births from the 2010 baseline due to the preventive interventions would be even smaller. This is a real possibility given the absence of correlation between historical and future changes in preterm birth rates.

***Panel:* Research in context**

Systematic review

An estimated 15 million babies are born too soon every year, with preterm birth the largest cause of neonatal death worldwide and second leading cause of deaths in children younger than 5 years. In the past two decades, preterm births have increased in all countries with reliable data. However, understanding of the drivers of preterm birth and the most effective interventions to reduce preterm birth rates is poor. We used impact data from systematic reviews, assessing quality of evidence using GRADE, and coverage of interventions obtained from databases in the 39 countries including national health databases and statistical offices. Our analysis for 39 countries with VHHDI examines more recent trends, drivers of preterm birth rate increases in the USA, and estimates the effect of interventions on preterm birth prevalence, including impact data from systematic reviews, and coverage of interventions obtained through database searches including national health databases and statistical offices.

Interpretation

To our knowledge, this is the first analysis to estimate the potential reduction in preterm births across high-income countries through preventive interventions. Our detailed analysis for the most recent decade suggests a levelling off of the previous almost universal increasing rate in high-income countries. However, analysis of previous increases in one country (USA) show that about half of the increase cannot be accounted for. Our new analysis of the effect of full coverage of fairly complex, available interventions, suggests that the scope for reducing preterm birth in these countries is estimated to be small (<5% relative reduction). This analysis highlights the need for the development of new and more effective interventions for preterm births.

Target population and coverage data also posed challenges. These interventions might overlap in their target population, resulting in an overestimation of their effect. We tried to avoid this overestimation by carefully defining the target population for every intervention. For example, efficacy of cervical cerclage was estimated for women with previous preterm birth with short cervix, and that for progesterone was estimated for women with previous preterm birth but without short cervix.[45]

With respect to smoking cessation, only 25 of the 39 included countries had data available of the percent of pregnant women smoking (appendix p 25) and we applied the mean from European countries. We assumed that the OR of preterm birth in mothers who smoked was biological in origin and could be modelled as a global-specific rather than country-specific risk.[26] The reported efficacy of smoking cessation programmes varies greatly depending on the study.[22,28] We identified a single meta-analysis[19] of eight randomised trials that directly reported the efficacy of smoking cessation programmes for pregnant women, which was used for all countries in the analysis and is an obvious simplification in view of probable differences in efficacy of such behavioural interventions across countries.[19,46]

For cervical cerclage, we defined the target population as women with previous preterm birth and with short cervix, since data of the efficacy of cervical cerclage were only available for this population.[17] However, we were only able to identify published data about the present usage of cervical cerclage in all mothers, rather than our defined target population for the USA.[20] We therefore applied the assumption that the use of cervical cerclage was within our target population of women with short cervix and previous preterm birth, which is likely an overestimate, making our analysis conservative. No data of coverage of cervical cerclage were available for countries outside the USA; therefore this estimate was applied to all the included countries with VHHDI, which might differ substantially in obstetric practices.

We used the estimated potential efficacy of progesterone from the recent systematic review.[47] We assumed the target population for progesterone use to be only women with a singleton gestation with previous preterm birth without short cervix.[45,48] This assumption was to avoid overlap of target population with that for cervical cerclage and thus indicates the incremental effect in the population of progesterone on top of cervical cerclage. We were unable to identify national coverage data for progesterone use in countries with VHHDI. In view of this, we assumed that two-thirds of the indicated population has access to progesterone as the maximum possible existing coverage after consultations with experts. This might be an overestimate and would surely vary by country. We expect the potential effect of progesterone to be greater if true present coverage is lower than what we estimated, making our estimate conservative.

With respect to elective caesarean deliveries and inductions without medical indication, the frequency of non-medically indicated labour induction and caesarean delivery is notoriously difficult to estimate.[49] We assumed that only late preterm births could potentially be non-medically indicated and that all moderate or early preterm births delivered through labour induction or caesarean deliveries were medically indicated. Analysis in Canada suggests that the issue is more through induction than caesarean delivery.[50] We applied one published result for the USA from 2002–08, and scaled it to the rest of the world using reported country-specific elective caesarean delivery rates (appendix p 28).[21,24] In view of the recent push to reduce incidence of late preterm births from labour induction or caesarean deliveries, this might be an overestimate. However, in the absence of other data, we chose to use this one result rather than make any new assumptions. Finally, for the purpose of this analysis, we assumed that 80% of the non-medically indicated labour induction and caesarean deliveries could be reduced in our target population. We recognise that this will vary from country to country.

For the analysis on decreasing multiple births from assisted reproductive technologies, the target plurality distribution for births with assisted reproductive technologies that we assumed is more stringent than many existing guidelines for assisted reproductive technologies[29] but for most European countries, the existing plurality distribution among assisted reproductive technologies births is already at or better than our target rate, limiting the potential effect of this intervention.[10,18] In some countries, the target rate might be difficult to achieve in view of current health-care reimbursement schemes for such technologies that may exclude ART; thus, patients must pay out of pocket and may be insistent on other than single embryo transfer. We also assumed that the rate of livebirths associated with assisted reproductive technologies would remain the same, which might differ from actual outcome.[51]

To estimate the total economic cost savings associated with reduction in preterm birth rate, we used the incremental cost associated with the care of an additional preterm birth from the USA Institute of Medicine (IOM) report[32] and extrapolated to the rest of the countries with VHHDI, applying the purchasing power conversion in this extrapolation. The IOM report might substantially understate the cost of preterm birth. A high-quality study[33] for England and Wales estimated the average cost of a preterm birth to be about $35 471. This cost is almost 40% more than the roughly $25 688 we estimated for the UK using the US estimates from IOM and scaling based on purchasing power parity, suggesting that our $3 billion estimate of total cost might be substantially understated. We were unable to identify similar cost estimates for all countries with VHHDI, but recognise that there is a growing body of work on this topic, and a more detailed country-by-country analysis would be valuable taking into account the gestational spectrum, which has been shown to substantially affect costs.[33]

Although the present analysis focuses on the countries with VHHDI, applicability of these selected interventions extends beyond these countries. For example, the prevalence of caesarean deliveries in some middle-income countries is extremely high (eg, 46% for Brazil, 38% for Mexico, and 26% for China); thus, the reduction of non-medically indicated caesarean deliveries could potentially have a large impact on reduction of preterm birth rate.[21] Smoking in young women continues to rise in many emerging economies and cessation programmes might have a larger effect in these societies. There are other preventive interventions, ranging from birth spacing to treating maternal infection, notably malaria, HIV, and syphillis, or improving nutrition, which are highly relevant for low-income and middle-income countries. These were not included in our present analysis because they did not have sufficiently robust preterm-specific impact data for inclusion and were less applicable to the countries with VHHDI.

By the year 2025, countries that take action now could potentially halve their deaths due to preterm births—a very large potential reduction on the mortality side, driven by current low coverage of care in low-income and middle-income countries.[5] However, on the prevention side, by 2015 at best we can reduce the preterm rates by only 5% in the richest countries if all countries can match the rate of relative reduction in preterm births among the top-performing countries and if these rather challenging existing interventions can be scaled up. Surely this humbling and shocking finding must lead to strategic prioritisation of research into prevention of preterm births in countries with VHHDI. The path ahead includes improved appropriate classification for the causes of preterm birth, allowing for better diagnosis and risk stratification, followed by development of novel prevention interventions based on better understanding of the underlying aetiologic, intergenerational, and genetics studies.[52–54] We hope that these new interventions, once developed, will also be rapidly translated from high-income countries to the rest of the world where the burden of preterm birth is even higher.

Contributors

HHC did the analysis and drafted the report. JL provided guidance on the analysis, oversaw the process, and edited the report. HB and JEL provided estimated and time trends data of preterm birth rates, drafted the report, and provided input throughout. EM, EML, ACS, SW, and SKL provided input throughout. SC-S, CYS, JLS, and CPH supported the effort, oversaw the process, and provided input throughout. All authors reviewed the report.

Conflicts of interest

We declare that we have no conflicts of interest. March of Dimes, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, and Global Alliance to Prevent Prematurity and Stillbirth all receive grants from government, foundations and charitable organisations for research into preterm birth prevention.

Acknowledgments

The time of HHC, JL, and SC-S was funded by the March of Dimes and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. JEL's time was funded by a grant from the Bill & Melinda Gates Foundation to Save the Children's Saving Newborn Lives programme. HB's time was funded by a grant from the Bill & Melinda Gates Foundation to the Child Health Epidemiology Reference Group. We thank Simon Cousens of the London School of Hygiene and Tropical Medicine and Craig Rubens of the Global Alliance to Prevent Prematurity and Stillbirth for technical review. We are grateful to Lori McDougall of the Partnership for Maternal Newborn and Child Health, Lily Kak of USAID, Tola Ladejobi of Boston Consulting Group, Judith Palais, and Rachel Diamond of the March of Dimes for support.

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