



Revista de Saúde Pública

ISSN: 0034-8910

revsp@usp.br

Universidade de São Paulo
Brasil

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Revista de Saúde Pública, vol. 45, núm. 3, junio, 2011, pp. 607-616

Universidade de São Paulo
São Paulo, Brasil

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How many low birthweight babies in low- and middle-income countries are preterm?

Quantos dos recém-nascidos de baixo peso de países emergentes são pré-termo?

ABSTRACT

OBJECTIVE: To assess the prevalence of preterm birth among low birthweight babies in low and middle-income countries.

METHODS: Major databases (PubMed, LILACS, Google Scholar) were searched for studies on the prevalence of term and preterm LBW babies with field work carried out after 1990 in low- and middle-income countries. Regression methods were used to model this proportion according to LBW prevalence levels.

RESULTS: According to 47 studies from 27 low- and middle-income countries, approximately half of all LBW babies are preterm rather than one in three as assumed in studies previous to the 1990s.

CONCLUSIONS: The estimate of a substantially higher number of LBW preterm babies has important policy implications in view of special health care needs of these infants. As for earlier projections, our findings are limited by the relative lack of population-based studies.

DESCRIPTORS: Infant, Low Birth Weight. Infant, Premature. Developing Countries. Review.

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Received: 5/23/2010

Approved: 12/16/2010

Article available from: www.scielo.br/rsp

RESUMO

OBJETIVO: Estimar a prevalência de recém-nascidos pré-termo entre os recém-nascidos de baixo peso ao nascer de países de renda média ou baixa.

MÉTODOS: Em consulta a bases de dados (PubMed, LILACS, Google Scholar) foram procurados estudos sobre a prevalência de recém-nascidos a termo e pré-termo entre aqueles de baixo peso ao nascer conduzidos após 1990 em países emergentes. Modelos de regressão foram usados para avaliar a proporção de acordo com as prevalências de baixo peso.

RESULTADOS: Com base em 47 estudos de 27 países emergentes, aproximadamente metade de todos os recém-nascidos com baixo peso seriam prematuros, em vez de um a cada três, como estimado em estudos anteriores à década de 1990.

CONCLUSÕES: A estimativa de números substancialmente mais altos de prematuros com baixo peso tem importantes reflexos no planejamento em saúde, uma vez que esses recém-nascidos demandam cuidados especiais. Todavia, os achados são limitados pela falta de estudos populacionais.

DESCRIPTORIOS: Recém-Nascido de Baixo Peso. Prematuro. Países em Desenvolvimento. Revisão.

INTRODUCTION

Preterm babies account for 27% of nearly 4 million neonatal deaths worldwide every year.³¹ Those preterm babies weighing less than 2500 g are more likely to die. Infant mortality rate among preterm low birthweight (LBW) babies is five times higher than that of preterm babies weighing 2500 g or more,⁴⁸ and that of term LBW babies.⁶⁸ The latter group comprises mostly babies with intra-uterine growth restriction (IUGR).³⁰ Because of this much higher mortality, it is important to estimate how many LBW babies are preterm as they require special health care.

In low- and middle-income countries (LMICs), where most infant deaths occur, nearly half of all births take place at home without skilled care,⁵⁷ and newborn babies are neither weighted nor have their gestational age assessed. The United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) have produced country-level LBW estimates using data from health statistics and surveys.⁵⁶ In relation to gestational age distribution, regional estimates of the overall proportion of preterm births were recently published.⁸

The prevalence and number of LBW babies born who have either IUGR or are preterm in developing countries have been recently estimated by scientists of different institutions as part of the Maternal and Child Nutrition Study Group.¹⁰ They have estimated that more than two-thirds of LBW babies born in the developing world have IUGR, and the remaining one third is preterm. These estimates used a predictive equation derived from hospital studies carried out between 1964 and 1990.^{9,13,59,62}

There are reasons for questioning whether the equation derived from pre-1990 studies is still valid in the light of global changes in LBW and preterm prevalence. UNICEF reported a reduction in LBW prevalence – from 18% in 1990–1994 to 16% in 1996–2006 – in all LMICs, and from 23% to 17%, respectively, in the least developed countries.^{55,57} In addition, selected studies indicate a decreasing prevalence of IUGR in some LMICs^{2,7,33} at the same time that others report substantial increases in preterm births.^{7,22,27,49} Data from South America suggest that the proportion of preterm LBW babies has increased among LBW births from 59% (1992) to 70% (2000) in Uruguay (PAHO/WHO Latin American Center for Perinatology, unpublished observations) and from 46% (1996) to 62% (2004) in Brazil.⁴⁷ The latter trend is confirmed in Brazilian birth cohort studies in the city of Pelotas, Southern Brazil, where this proportion increased from 60% in 1993 to 68% in 2004.⁷

In view of recent changes – in opposite directions – in the prevalence of preterm and term LBW babies, we decided to generate a new set of predictive equations using data obtained from post-1990 studies. Therefore, the aim of this study was to assess the prevalence of preterm birth among low birthweight babies in low and middle-income countries.

METHODS

We reviewed major databases (PubMed, LILACS, Google Scholar) for studies on the prevalence of term and preterm LBW babies with field work carried

out after 1990 in countries classified by the World Bank as LMICs.^a Keywords used in the review were preterm births, low birth weight, and low and middle-income countries. The authors were contacted in many instances to provide further information. We also searched websites of the ministries of health in countries mostly in Latin America where this information is available. Although the best was to work with national estimates, they were rarely available and we had to rely on subnational samples. Further information was obtained from randomized trials, either from baseline or endline assessments (the latter was included only when there was no effect of the intervention).

Studies were included only if birthweight was obtained through weighing, but not by surrogates such as reported size of the baby at birth or chest circumference measures, and when estimates of gestational age were based on at least one of the following methods: last menstrual period, ultrasound before 20 weeks, or physical examination (Dubowitz,¹⁵ Ballard,⁵ Capurro¹¹ and Finnstrom¹⁹ methods). Only live births were included. Low birthweight was defined as less than 2500 g, and preterm birth was defined as less than 37 completed weeks of gestation. All studies were conducted after 1990 with the exception of a long-term community study in Gambia over 1976–2003. LMICs were divided by region according to UNICEF classification.⁵⁷

Linear regression and Pearson's correlation coefficients were used to compare our set of post-1990 studies with previous studies.^{62,59} The best predictive equations for estimating preterm LBW from overall LBW prevalence were selected using linear regression, polynomial linear regression and nonlinear models; the latter two were used to account for non-linearity in the relationship between the outcome and low birthweight prevalence. The polynomial regression tested up to the cubic terms. We also assessed non-linear models based on exponential, Gompertz and logistic functions. The models were compared in terms of goodness of fit (Akaike Information Criterion, AIC) and biological plausibility. The non-linear model chosen was:

$$Y = \beta_1 / (1 + \exp(-\beta_2 \times (X - \beta_3)))$$

The standard error for the predictions was obtained through the following expression:

$$\text{s.e.}(\text{prediction}) = [\text{var}(\hat{Y}) + \text{var}(\text{residual})]^{1/2},$$

where \hat{Y} is the fitted value. Confidence intervals were obtained by the expression

$$\hat{Y} \pm 1.96 \times \text{s.e.}(\text{prediction}).$$

All regression models were weighted by sample size and adjusted for clustering at country level as several countries had more than one data source.

To assess whether the results of community-based and facility-based studies presented in the Results section below were statistically different, we used a generalized linear model with region as a fixed factor and type of study as a random factor, with the outcome prevalence as the dependent variable.

RESULTS

Data from 47 studies from 27 LMICs were studied. The Table shows for each study site: country and year of study, method of gestational age assessment, type of study, sample size, and prevalence of LBW, preterm LBW and term LBW. Whenever available, the prevalences of preterm births and preterm babies weighing 2500 g or more were also presented. There were 15 studies from eight Sub-Saharan African countries, 12 studies from four South Asian countries, 10 studies from eight Latin American and Caribbean countries, four studies from three countries in the East Asia and Pacific, four studies from three countries in the Middle East and North Africa, and two studies from Turkey (Central and Eastern Europe and the Commonwealth of Independent States – CEE/CIS region).

Regarding the type of study, 33 were facility-based (prenatal clinics or maternity hospitals), 13 were community-based, and only one was nationwide. Among 12 South Asian study sites, seven were facility-based and five community-based. In Sub-Saharan Africa, only two of 15 studies were community-based, the remaining were all facility-based; and four studies in this region were primarily related to malaria. In Latin America and Caribbean, one was a national study (Argentina), three covered all maternity hospitals in defined geographical areas where home births are very rare, and six were based on a single hospital.

In 19 study sites, gestational age was evaluated by the use of the last menstrual period (LMP) alone, 20 combined LMP with physical examination and/or ultrasound, and eight used only physical examination methods.

Based on this initial comparison of studies, South Asian sites presented the highest prevalence of both term LBW (unweighted mean of 21.8%) and preterm LBW (10.6%) babies. Compared to South Asia, Sub-Saharan African sites had fewer term LBW and preterm LBW babies with mean prevalence of 7.1% and 6.5%, respectively. Preterm LBW mean prevalence in Latin America/Caribbean, Middle East/North Africa, CEE/CIS and East Asia/Pacific studies were 6.1%, 3.0%, 4.9% and 3.9%, respectively. As mentioned before, most studies were facility- or community-based, and therefore not representative of the country as a whole, as this type of study is rarely available.

^a World Bank. How we classify countries. [cited 2008 Nov 15]. Available from: <http://data.worldbank.org/about/country-classifications>

Table. Prevalence of low birthweight and preterm births in selected studies in low- and middle-income countries, 1990–2006.

Country (place or city), year, reference number	Method of GA assessment	Number of cases, type of study	LBW %	PT %	Preterm LBW %	Term LBW %	Preterm ≥ 2500 g %
Latin America and Caribbean							
Argentina, 2006 ^a	LMP	696451, nationwide	7.1	8.1	4.4	2.7	3.7
Argentina (Rosario), 2001–2003 ⁵⁹	LMP, PE, US	630, hospital-based	8.2	14.6	5.7	2.5	8.9
Brazil (Ribeirão Preto), 1994 ⁴⁹	LMP	2839, population-based	11.9	13.7	7.3	4.6	6.4
Brazil (Pelotas), 2004 ⁷	LMP, PE	4231, population-based	10.0	14.7	6.8	3.2	7.9
Colombia (Medellín), 2003–2006 ⁵⁸	LMP	2672, hospital-based	16.4	21.4	11.9	4.5	9.5
Cuba, 2005 ⁶⁰	LMP, PE, US	12510, hospital-based	5.5	4.8	2.9	2.6	1.9
Mexico (Merida), 2002–2004 ⁴⁴	LMP	15178, hospital-based	12.5	12.4	7.7	4.8	4.7
Nicaragua, 2005 ⁶⁰	LMP, PE, US	5590, hospital-based	7.9	6.8	3.7	4.2	3.1
Peru (Lima), 2001–2003 ⁵⁹	LMP, PE, US	1224, hospital-based	5.8	10.0	3.8	2.0	6.2
Uruguay (Montevideo), 2000–2003 ³⁶	LMP	22990, regional population-based	10.4	10.5	7.1	3.3	3.4
South Asia							
Bangladesh (Dhaka), 2003–2004 (unpublished, Arifeen, personal communication)	LMP	3085, community-based	33.7	15.3	8.1	25.6	7.2
Bangladesh (Dhaka), 1993–1995 ⁴	PE (Capurro)	1654, community-based	46.4	16.8	9.9	36.5	6.9
Bangladesh (Dhaka), 1994–1995 ⁶⁸	PE (Capurro)	3123 ^b , hospital-based	30.0	na	11.7	18.3	na
Bangladesh (Dhaka), 1996 ⁴³	LMP	410, community-based RCT	42.9	16.6	16.3	26.6	0.3
India (Gadchiroli), 1995–1996 ⁶	LMP	5919, community-based	41.9	9.8	8.3	33.6	1.5
India, 2002–03 ^d	LMP, PE, US	145623, hospital-based	31.3	14.5	12.2	19.1	2.3
India (Orissa), 1998–2000 ⁵⁴	LMP, PE (new Ballard)	11223, hospital-based	39.8	11.9	10.8	29.0	1.1
India (Nagpur), 2001–2003 ⁵⁹	LMP, PE, US	945, hospital-based	34.1	13.8	9.8	24.3	4.0
India, Vellore, 2001–2003 ⁵⁹	LMP, PE, US	957, hospital-based	15.7	7.4	4.8	10.9	2.6
Nepal (Sarlahi), 1998–2001 ¹²	LMP	685, community-based RCT	43.4	20.4	12.6	30.8	7.8
Pakistan (Akuh), 1990–2006 Bhutta, 2008 (unpublished)	LMP, US	44090, hospital-based	11.8	11.6	7.2	4.6	4.4
Pakistan (Lahore), 1994–1996 ⁴¹	LMP	6142, hospital-based	18.8	na	16.1	2.7	na
East Asia and Pacific							
China, 1998 ³⁴	LMP	22350, regional population-based	5.9	3.5	2.3	3.6	1.2
Tibet (Lhasa), 2005 ⁶⁷	LMP, PE (Dubowitz)	2540, hospital-based	13.6	5.7	5.1	8.5	0.6
Thailand (Mae Sod), 1993–1996 ³⁵	LMP, PE	1201, community-based (malaria)	16.0	11.0	7.0	9.0	4.0
Vietnam (Ho Chi Minh City), 2001–2003 ⁵⁹	LMP, PE, US	1624, hospital-based	5.5	3.6	1.4	4.1	2.2

To be continued

Table continuation

Country (place or city), year, reference number	Method of GA assessment	Number of cases, type of study	LBW %	PT %	Preterm LBW %	Term LBW %	Preterm ≥ 2500 g %
CEE/CIS							
Turkey (Ankara), 1999-2001 ⁵³	LMP, PE, US	3576, hospital-based	7.5	12.5	4.2	3.3	8.3
Turkey (Istanbul), 2000-2001 ¹	PE	5000, hospital-based	9.1	7.9	5.7	3.4	2.2
Middle East and North Africa							
Egypt (Alexandria), 2001-2002 ³	PE	1020, facility-based	7.1	9.4	3.1	4.0	4.0
Egypt (Assiut), 2001-2003 ⁵⁹	LMP, PE, US	957, hospital-based	7.5	13.0	3.7	3.8	9.3
Syria ⁶⁴	LMP	10585, hospital-based	6.6	na	3.4	3.2	na
Tunisia (Monastir), 1995-1997 ³²	LMP	21393, regional, population-based	5.6	na	1.9	3.7	na
Sub-Saharan Africa							
Benin (Cotonou), 1991 ²⁰	LMP	4113, community-based	17.8	14.0	6.9	10.9	7.1
Gambia (West Kiang), 1976-2003 ⁴⁶	PE (Dubowitz)	2977, community-based	13.4	12.3	5.1	8.3	7.2
Gambia (Bansang), 1997 ⁴²	PE (Dubowitz)	313, hospital-based (malaria)	24.0	20.8	17.0	7.0	3.8
Ghana (Ashanti Akim), 2000-2001 ^{38, 39}	LMP, PE (Finnstrom)	831, hospital-based (malaria)	16.0	18.8	9.5	6.5	7.3
Kenya (Mombasa), 1999 ⁴⁰	LMP, PE	661, hospital-based	12.4	na	5.5	6.9	na
Kenya (Meru District) ¹⁴ 1995-1996	LMP, PE	9525, hospital-based	7.0	na	1.4	5.6	na
Nigeria, 2003-2004 ¹⁶	LMP	983, hospital-based (malaria)	10.5	15.0	3.9	6.6	8.4
South Africa (Johannesburg), 2001-2003 ⁵⁹	LMP, PE, US	930, hospital-based	15.0	13.7	7.8	7.2	4.9
Tanzania (Ifakara), 1994-1995 ³⁷	PE (Dubowitz)	910, community-based (malaria)	18.0	8.0	3.8	14.2	4.2
Tanzania (Mwanza), 1997-2000 ⁶⁴	LMP, US	1536, facility-based	8.0	12.0	4.2	4.0	7.8
Tanzania (Dar es Salaam), 2001-2004 ¹⁷	LMP	4214 ^c , facility-based RCT	9.4	16.7	4.5	5.9	12.2
Tanzania (Kilimanjaro), 1999-2006 ²⁴	LMP	14444, hospital-based	8.4	10.0	3.7	4.7	6.3
Zimbabwe (Harare), 1996-1997 ²¹	LMP	542 ^c , facility-based RCT	11.4	18.3	7.0	4.4	11.3
Zimbabwe (Harare), 1997-1998 ¹⁸	PE (Ballard)	3103, hospital-based	20.3	17.1	11.1	9.2	6.0
Zimbabwe (Centenary District), 2001-2002 ⁵²	LMP	1768, hospital-based	12.9	17.4	7.2	5.7	7.2

GA - gestational age; LMP - last menstrual period; PE - physical examination; US - ultrasound before 20 weeks; na - not available

^a Ministerio de Salud Argentina. <http://www.msal.gov.ar/him/site/default.asp>. 2007; ^b estimated; ^c control group; ^d Indian Council of Medical Research. National Neonatal-Perinatal Database: report 2002-2003. New Delhi: Nodal Center at Department of Pediatrics; 2005.

Community-based and hospital-based sites in Latin America/Caribbean showed similar prevalence rates of LBW, preterm LBW and term LBW. In South Asian sites, however, the mean prevalence of LBW and term LBW was much higher in community-based (41.6% and 30.6%) than in hospital-based studies (25.9% and 15.6%, respectively). For Sub-Saharan Africa, there were no significant differences in LBW and preterm LBW prevalences between the two community-based and 13 hospital-based studies, but term LBW babies were more prevalent in community-based than in hospital-based studies (mean prevalence of 11.2% and 6.5%, respectively; $p=0.013$).

On the other hand, the prevalence of LBW was slightly higher in the four studies primarily related to malaria in Sub-Saharan Africa (17.1%) compared to other non-malaria studies (12.4%), although the difference was not statistically significant ($p=0.095$).

First we regressed the prevalence of preterm LBW on overall LBW prevalence in the 47 sites using a comparable approach to that of earlier publications that serve as a basis for current global estimates – linear regression unweighted for cluster or sample size. Figure 1 shows the regression lines from the analyses conducted in 1982,⁶² 1994⁵⁹ and our current estimates, suggesting that the contribution of preterm LBW to LBW population has increased over time. Likewise, the correlation coefficients between preterm LBW and overall LBW prevalence increased from 0.08 ($p>0.05$) in the 1982 analyses to 0.59 ($p<0.001$) in 1994, and finally to 0.72 ($p<0.001$) in the current data.

Several candidate models were assessed to describe the relationship between preterm LBW and LBW prevalence, i.e., polynomial linear and nonlinear models. Simple linear models were not good-fitting ones ($AIC=155.8$). Quadratic linear regression provided a good fit ($AIC=119.2$), but yielded an implausible

model where the predicted prevalence of preterm LBW decreased after LBW prevalence reached 30% (as the model fits a parabola). Among the nonlinear models assessed, the one based on the logistic function provided the best fit ($AIC=124.6$), almost as good as the quadratic model, but without the decreasing prevalence in preterm LBW for high LBW rates. This was the chosen model.

A nonlinear logistic function regression model, weighted by sample size and taking into account the clustering of studies by country, was used to describe how preterm LBW varied according to overall LBW prevalence for the 47 study sites. Figure 2 shows that the prevalence of preterm LBW markedly increases with LBW between 5% and 20%, slows down between 20% and 30%, and reaches a plateau of around 12% when overall LBW prevalence exceeds 30%. It should be noted that all sites with LBW higher than 30% were in South Asia. The predictive equation was a 3-parameter logistic function as follows:

$$\text{Preterm LBW} = b1/(1 + \exp(-b2*(LBW - b3)))$$

where the coefficients are:

$$b1 = 11.96$$

$$b2 = 0.23$$

$$b3 = 9.72$$

DISCUSSION

Our main finding was that preterm infants account for a larger proportion of all LBW babies than is currently assumed.^{59,62} Previous estimates based on pre-1990 studies suggest that around one third of all LBW babies born in LMICs are preterm and two thirds are term,^{10,13} whereas our analyses suggest that preterm babies account for at least half of all LBW babies. Previous models also assumed a linear relationship between total LBW and preterm LBW, whereas we showed a

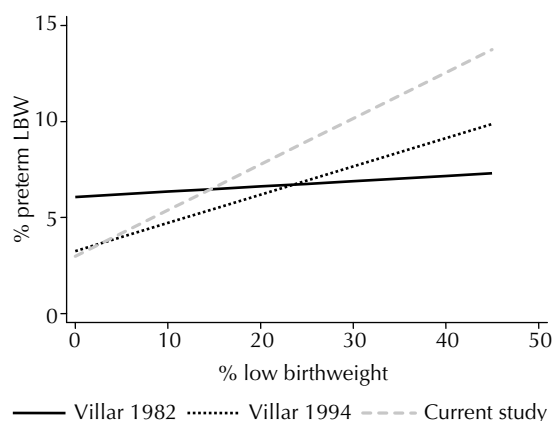


Figure 1. Regression lines of preterm LBW by LBW in LMICs for studies by Villar 1982 (n=25), Villar 1994 (n=60), and current data (n=47).

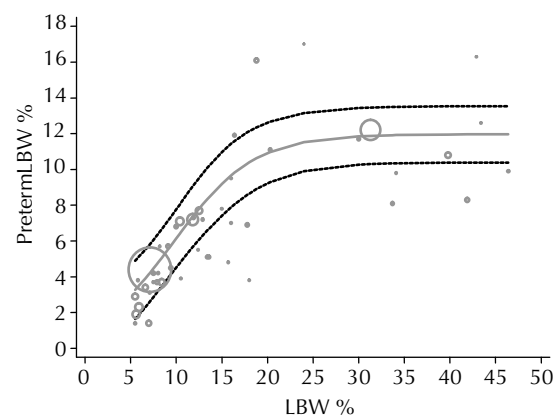


Figure 2. Prevalence of preterm LBW in 47 studies on LBW prevalence in low- and middle-income countries.

curvilinear association. Whether the differences related to earlier studies represent real time trends – either an increase in preterm babies or a decline in term LBW babies – is unclear.

Our finding of high rates of preterm LBW births in areas where term LBW are also highly prevalent, as in South Asia and Sub-Saharan Africa, is not unexpected. In LMICs, IUGR and preterm delivery share several common determinants such as low body mass index, malaria, smoking, pregnancy-induced hypertension, and pre-eclampsia.^{25,29,51,65} Thus, countries with high prevalence of risk factors (such as low maternal body mass index and malaria) with a resulting high prevalence of term LBW are also more likely to present high rates of preterm LBW births. In addition, a number of studies^{7,23,28,45,50} show that preterm births are more frequent among poor populations. For these reasons, the current findings are more biologically and epidemiologically plausible than those from earlier studies based on data collected pre-1990, which showed little variation of preterm rates across a wide range of LBW prevalences.

When we applied our curvilinear regression model to the national LBW estimates provided by UNICEF,⁵⁷ we estimated that 10.3 million of the 20.3 million LBW born each year in LMICs are preterm, compared to the 6.6 million in the previous estimate. Thus, based on our estimates, 3.7 million babies would shift from the term to the preterm LBW category.¹⁰ Nevertheless, given the small number of community-based studies available for world regions where home birth delivery is the rule, any predictions of preterm LBW based on LBW must be interpreted with great caution. Also, the confidence intervals presented in Figure 2 points to the need of careful interpretation of estimates.

Our study has limitations. The data was obtained mostly from hospital-based studies, as few community-based studies with information on birthweight and gestational age were available. However, this was also a limitation of earlier studies^{9,13,59,62} that produced the model for the currently used estimates.¹⁰

In South Asia, the world region with the lowest overall hospital coverage of deliveries (36%),⁵⁷ the five community-based studies included in the present review showed considerably higher prevalences of LBW (41.6%) than those reported in the seven facility-based studies (25.9%). In Sub-Saharan Africa, the two community-based studies showed higher prevalences of term LBW (11.3%) than those in the remaining 13 hospital-based studies (6.5%). One must bear mind these important variabilities when applying the results of our equation to obtain national or regional estimates of preterm LBW.

The datasets ranged in size from a few hundred to over two million births. We were unable to find studies for every country, but included more than one study from the same country when available. Among the 12 South Asian study sites, for example, five were from India, four from Bangladesh, two from Pakistan and one from Nepal. In the 15 Sub-Saharan African studies, there were four from Tanzania and three from Zimbabwe. However, differences in sample sizes and clustering by country were accounted for in the analyses. When the weighted mean regional LBW arising from our analyses was compared with UNICEF regional estimates, the differences were within 10% except for Middle East/North Africa where UNICEF estimate of 14.9% is considerably higher than the 6.7% mean value seen in the studies included in this review. This difference is largely due to the fact that there were no studies from Sudan and Yemen where the estimated LBW prevalence is over 30%.⁵⁷

A second limitation of this study refers to inconsistent methods for assessing gestational age. Most studies relied on the date of the last menstrual period, alone or combined with physical methods and ultrasound, while in eight sites physical examination was the only method of assessment. It is known that the use of LMP alone overestimates both preterm and post-term rates,²⁶ but these same limitations also apply to the previous estimates.^{10,13}

Four of the 15 Sub-Saharan African studies were primarily related to malaria, a known cause of both LBW and preterm births.⁵¹ This is consistent with the present estimates where the mean prevalence of both preterm LBW and term LBW was 8.6% compared to 5.8% and 6.6%, respectively, in the other 11 African studies. However, in a region where 80% of births are in malaria-endemic areas,^{57,66} it does not make sense to exclude these studies from regional estimates.

Low-income countries are unlikely to be able to assess the overall prevalence of LBW preterm infants in the near future, as most births will continue to be at home or in short-staffed health facilities. Our updated equation has considerable advantages over the existing ones that assume a linear relationship. Our model based on post-1990 studies estimates that preterm babies account for at least half of all low birthweight babies in LMICs. This finding that preterm infants account for a higher proportion of those with LBW than currently believed has implications for planning health interventions for this infant population, including skilled providers, incubators, and medicines.

ACKNOWLEDGEMENT

We thank all colleagues who kindly provided additional information about their studies.

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The authors declare no conflicts of interests.