Lancet Breastfeeding Series Paper 1

Breastfeeding in the 21st Century: epidemiology, mechanisms and lifelong impact.

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Abstract

The importance of breastfeeding (BF) in low and middle- income countries (LMICs) is well recognized, but there is less consensus on its importance in high-income countries (HICs). In LMICs, only 37% of children under 6 months are exclusively breastfed. With few exceptions, BF duration is very short in HICs. Our meta-analyses indicate protection against child infections and malocclusion, and increased intelligence, as well as likely reductions in overweight and diabetes. We did not find associations with allergic conditions including asthma, blood pressure or cholesterol, and there was an increase in dental caries. For nursing women, there was protection against breast cancer and increased birth spacing, as well as likely protection against ovarian cancer and type 2 diabetes. Scaling up BF to near universal level could prevent 823,000 underfive deaths a year, as well as 20,000 deaths due to breast cancer. Recent epidemiological and biological findings expand upon the known benefits of BF for women and children, rich and poor alike.

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Introduction

"In all mammalian species the reproductive cycle comprises both pregnancy and breast-feeding: in the absence of latter, none of these species, man included, could have survived", wrote Bo Vahlquist in 1981.[1] Three years earlier, Derek and Patrice Jelliffe in their classical book "Breast milk in the modern world"[2] stated that *"breast-feeding is a matter of concern in both industrialised and developing countries because it has such a wide range of often underappreciated consequences."*[3] The Jelliffe's anticipated that breastfeeding (BF) would be relevant to *"present-day interest in the consequences of infant nutrition on subsequent adult health"*. [3] These statements were challenged by the American Academy of Pediatrics in 1984: *"if there are benefits associated with breast-feeding in populations with good sanitation, nutrition and medical care, the benefits are apparently modest"*.[4]

In last three decades, BF recommendations have evolved markedly (webappendix 1). Results from epidemiological studies and growing knowledge of the roles of epigenetics, stem cells and the developmental origins of health and disease strongly support the ideas put forward by Vahlquist and the Jelliffe's. Never before in the history of science, has so much has been known about the complex importance of BF for both mothers and children.

In the first of two Lancet articles, we describe current patterns and past trends in BF throughout the world, review its short and long-term health consequences for the child and mother, estimate potential lives saved by scaling up BF, and summarize recent insights on how BF may permanently shape the life course.

The second article[5] covers the determinants of BF and the effectiveness of promotion interventions. It discusses the role of BF in HIV transmission and how knowledge on this issue evolved in recent years, and examines the lucrative market of breastmilk substitutes, the environmental role of BF, and its economic implications.

In the context of the post-2015 development agenda, the two articles document how essential BF is for building a better world for future generations in all countries, rich and poor alike.

Methods

The following standard indicators were studied:[6]

- Early initiation of BF: proportion of children born in the last 24 months who were put to the breast within one hour of birth;
- Exclusive BF under 6 months: proportion of infants 0–5 months of age who are fed exclusively with breastmilk; this indicator is based on the diets of infants under 6 months during the 24 hours before the survey (in order to avoid recall bias), not on the proportion who are exclusively breastfed for the full 6-month period;
- Continued BF at 1 year (12-15 months): proportion of children 12–15 months of age who are fed breastmilk;
- Continued BF at 2 years (20-23 months): proportion of children 20-23 months of age who are fed breastmilk.

Because few high-income countries (HICs) report on the above indicators, additional indicators were calculated to allow global comparisons:

- Ever BF: infants reported to have been breastfed, even if for a short period;
- BF at 6 months: in HICs, the proportion of infants who were breastfed for 6 months or longer; in LMICs with standardized surveys, the proportion of infants aged 4-7 months (median age of 6 months) who are breastfed;
- BF at 12 months: in HICs, the proportion breastfed for 12 months or longer; in LMICs, the proportion of children aged 10-13 months (median age of 12 months) who are breastfed.

The last three indicators were used exclusively for comparisons between HICs and LMICs. Otherwise, we report on the standard international indicators (see webappendix 2)

For low and middle-income countries (LMICs), we reanalysed national surveys carried out since 1993, including Demographic and Health Surveys (DHS) (http://www.measuredhs.com/aboutsurveys/dhs/start.cfm), Multiple Indicator Cluster Surveys (MICS) (http://www.childinfo.org/) and others (see webappendix 3). Virtually all had response rates above 90% and adopted standardized questionnaires and indicators.

For all HICs with 50,000 or more annual births, we carried out systematic reviews of the published and grey literature and contacted key informants (see webappendix 4). Many countries did not have information on BF from national samples. Response rates were often in the 50-70% range, indicators were seldom standardized and recall periods tended to be long. Administrative or other data were used when surveys were not available. If needed, we estimated the proportion of infants breastfed at 12 months based on information available for BF at 6 months, and vice-versa. Time trends were obtained using multilevel linear regression models (hierarchical mixed models) that take into account that countries contribute with two or more surveys for the analysis. Departures from linearity were explored using fractional polynomial regression models.[7] In all analyses, country data were weighted by their populations of children under two years. Webappendix 5 describes statistical methods.

Systematic searches of the literature and, whenever possible, meta-analyses were carried out for outcomes postulated to be associated with breastfeeding (see webappendix 6).

The Lives Saved Tool (LiST)[8] was used to predict how many deaths of children under five years would be prevented if 2013 BF patterns were scaled up in the 75 countries that are part of the Countdown to 2015,[9] which account for over 95% of all such deaths globally. We assumed that 95% of children under one month and 90% of those under six months would be exclusively breastfed, and 90% of those aged 6-23 months would be breastfed. The relative risks for the protection against all infectious causes of death obtained from our new meta-analyses were applied to all infectious causes of death among children under two years of age, and also to the 15% of deaths due to complications of prematurity that occur after the first week (see webappendix 7).

We also estimated the potential number of breast cancer deaths preventable by extending BF duration (see webappendix 8).

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Epidemiology: levels and trends

We obtained complete information for 127 out of all 139 LMICs (webappendix 3), accounting for 99% of the children from such countries. For HICs, we were able to obtain data on 37 out of 75 countries, but for several countries only a subset of the indicators were available (webappendix 4), so that these data must be interpreted with caution.

Figure 1 shows the proportion of children aged around 12 months who are breastfed in 153 countries. The highest prevalences are in Sub-Saharan Africa, South Asia and parts of Latin America. In most HICs, BF prevalence at 12 months of age is below 20% (webappendix 4). Important differences were observed, for example, between the UK (<1%) and the USA (27%), and between Norway (35%) and Sweden (16%).

Figure 2 shows BF indicators according to country income groups. Information on early initiation, exclusive BF or continued BF at 2 years was not available for most HICs. We found a strong inverse correlation (Pearson's r=-0.84; P<0.001; see webappendix 9) with log gross domestic product per capita; regression analyses showed that for each doubling in the latter, BF prevalence at 12 months decreased by 10 percent points.

The vast majority of mothers in all country groups started breastfeeding; only three countries (France, Spain and USA) had rates below 80%. However, early initiation is low in all settings, and so is exclusive breastfeeding. BF at 12 months is frequent in low and lower-middle-income settings, but uncommon elsewhere.

Except for early initiation, prevalence of all indicators decreases with increasing national wealth. Low-income countries show high BF prevalence at all ages, but initiation and exclusive BF rates are unsatisfactory even in these countries.

Surprisingly, most national level breastfeeding indicators are not strongly correlated (webappendix 9). There is only a moderate correlation (Pearson's r = 0.54) between exclusive and of continued BF at 1 year in LMICs . Whereas continued BF prevalence is high throughout West and Central Africa (top left of Figure 3), the exclusive breastfeeding rates vary widely. Countries from Eastern and Southern Africa tend to have somewhat lower rates of continued BF but higher rates of exclusive BF than their Western Africa neighbours. In Latin America and the Caribbean, as well as in the CEE&CIS region, both indicators tend to be lower than in Africa. South Asia shows relatively high rates of both indicators whereas the Middle East / North African countries present lower rates. Finally, countries from East Asia and the Pacific region show moderate to high prevalences of both indicators.

Among children aged under 6 months in LMICs, 36.3 million (63%) were not exclusively BF at the time of the last national survey. The corresponding percentages for low, lower middle and upper middle income countries were 53%, 61% and 63%, respectively. Among 6-23 month old children, 64.8 million (37%) were not receiving any breastmilk, with corresponding rates of 18%, 34% and

55% in the three country groupings. In total, 101.1 million children in LMICs are not breastfed according to international recommendations.

Most LMICs have data from several surveys over time, making it possible to explore time trends both at national level and for children in the poorest and richest 20% of families. Our analyses were restricted to surveys for which breakdown of BF indicators by wealth quintiles was possible (214 surveys for exclusive and 217 for continued BF; see webappendix 5) representing 83% of the total 2010 population of children under two years in LMICs. We report linear trends as there was no evidence of departures from linearity. Exclusive BF rates increased slightly from 24.9% in 1993 to 35.7% in 2013 (Figure 4). Among the richest 20%, the increase was much steeper, from 15.8% to 35.5%, respectively, whereas the poorest 20% followed the general trend. Continued BF at 1 year (12-15 months) dropped slightly at global level (from 76.0% to 73.3%), particularly due to a decline among the poor, as prevalence among the rich was stable.

In summary, early initiation and exclusive BF rates are below 50% in most countries. Continued BF is one of the few nutrition indicators for which poor countries perform better than rich countries. Unusually, data availability and quality is better in poor than in rich countries, which may reflect how little importance BF receives in the latter. Exclusive and continued BF prevalence are only moderately correlated, suggesting that countries require different promotion strategies. In addition to national income levels, there are also important regional differences in BF patterns. For LMICs as a whole, exclusive BF rates are increasing slightly, while prevalence of continued BF at 1 year is declining.

Epidemiology: within-country inequalities

We analysed 98 surveys from LMICs to investigate within-country inequalities according to wealth quintile (webappendix 10). We found that wealth related inequalities in exclusive BF are small but disparities in continued BF rates are consistent: the poor tend to breastfeed for longer than the rich in all country groupings, but particularly in middle-income countries. Similar results based on 33 countries have been recently reported. [10]

The literature review of studies from high-income countries showed that high-income, educated women show higher BF rates. [11-19] BF initiation in the USA was more common among mothers with lower education up to the 1960's but since then the social gradient had been reversed.[4]

BF is one of few positive health related behaviours in LMICs that is less frequent among the rich, both between and within countries. The low rates of continued BF among the rich raise the possibility that poor mothers will move towards breastmilk substitutes, a concern that is reinforced by declining rates among the poor.

Short term effects on the child: mortality and morbidity

Table 1 shows the results of 28 meta-analyses on the associations between BF and outcomes in the child and mother, of which 22 were commissioned for this series.

Because studies varied regarding feeding classifications, for several outcomes we compared longer versus shorter BF durations (e.g., never versus ever BF; BF for less or more than a given number of months; and for a few outcomes longer versus shorter durations of exclusive BF). We tested for heterogeneity due to the type of BF categorization, and in its absence we pooled the different definitions. We describe the results of randomized trials on how BF promotion affects health, nutrition or development outcomes, but not of trials where the endpoint was restricted to BF indicators; these are reviewed in the second article in the series.[5]

Table 1 includes the results of the meta-analyses, and presents their potential limitations, including confounding, effect modification, reverse causation and publication bias.

Only three studies provide information on mortality according to exclusive, predominant, partial, or no BF in the first six months of life. A strong protective effect is evident, with exclusively breastfed infants showing only 7% of the risk of death as those who were not breastfed. Another three studies showed that infants younger than six months who were not breastfed presented 3.5 (boys) and 4.1 (girls) fold increases in mortality compared to those who received any breastmilk, and that protection declined with age.[20] These results are supported by studies on children aged 6-23 months, among whom any BF was associated with a 50% reduction in deaths (Table 1).

The above studies were from LMICs, but BF may also protect against deaths in HICs. A meta-analysis of 6 high-quality studies showed that ever BF was associated with a 36% (95% CI 19;49%) reduction in sudden infant deaths.[21]. Another meta-analysis of 4 RCTs showed a 58% (95% CI 4;82%) decline in necrotizing enterocolitis,[21] a condition with high case-fatality in all settings.[22]

In terms of child morbidity, there is overwhelming evidence from tens of studies, mostly from LMICs, that BF protects against diarrhoea and respiratory infections (Table 1), including three randomized controlled trials.[23] Approximately half of all diarrhoea episodes and one third of respiratory infections would be avoided by BF. Protection against hospital admissions due to these diseases is even greater: 72% and 57%, respectively.

The risks associated with breastmilk substitutes in terms of biological and chemical contamination are discussed in webappendix 11.

Our reviews suggest important protection against otitis media in children under 2 years, mostly from high-income settings, but inconclusive findings for older children (Table 1). There was no clear evidence of protection against allergic conditions: no association with eczema or food allergies and some evidence of protection against allergic rhinitis under age 5 years. When the 29 studies on asthma were analysed, there was statistical evidence of a 9% (95% CI 2;15%) reduction, but effects were smaller and non-significant when analyses were restricted to 16 studies with tighter control of confounding – reduction of 5% (95% CI -6;15%) – or to the 13 cohort studies – 6% reduction (95% CI -11;20%).

Our analyses of oral health outcomes (Table 1) found that BF was associated with a 68% reduction (95% CI 60;75%) in malocclusions, based on 49 studies carried out mostly in LMICs. Most studies were restricted to young children with deciduous teeth, but malocclusion in this age group is a risk factor for malocclusion in permanent teeth.[24,25] On the other hand, BF longer than 12 months and nocturnal feeding were associated with 2-3 fold increases in dental caries in deciduous teeth, possibly due to lack of oral hygiene after feeding.

Information on BF and child growth was derived from 17 studies, including 15 RCTs, mostly from middle-income countries. Attained weight and length at around 6 months did not differ, but there

was a small reduction (-0.06 Z scores; 95% CI 0.00;-0.12) in body mass index or weight for length among children in the BF intervention group, based on intent-to-treat analyses (Table 1).

Long term effects: Obesity, NCDs and intelligence

We updated existing meta-analyses [26] on the associations between BF and outcomes related to non-communicable diseases (Table 1). Most studies are from high-income settings.

Based on all 113 studies identified, longer BF was associated with a 26% reduction (95% CI 22; 30%) in the odds of overweight and/or obesity prevalence.[27] The effect was similar in studies from high and from low or middle-income countries. The only BF promotion trial that reported on this outcome did not detect an association; in this trial, there were important early differences between intervention and comparison groups in terms of exclusive BF, but by age 12 months only 19% and 11% of children, respectively, were breastfed.[28 29] A 2005 meta-analysis[30] of breastfeeding and mean body mass index included 36 articles of which 11 included adjustment for socioeconomic status, maternal smoking and maternal body mass index; their pooled effect did not suggest an association with BF. In our review,[27] 23 high quality studies with sample sizes greater than 1,500 and adjustment socioeconomic status, maternal BMI and perinatal morbidity showed a pooled reduction of 13% (95% CI 6;19%). As mentioned above, the pooled analysis of randomized trials of breastfeeding promotion in children suggested a small reduction (-0.06 Z scores; 95% CI 0.00;-0.12) in body mass index or weight for length.

For type-2 diabetes incidence, the pooled results from 11 studies indicate a 35% reduction (95% CI 14%;51%). Only three studies were deemed to be of high quality, indicating a potentially important, but non-significant reduction of 24% (95% CI ranging from a 60% reduction to a 47% increase). The direction and magnitude of the association with diabetes are consistent with findings on overweight. An earlier review indicated a possible protection against type-1 diabetes, based on a small number of studies.[21]

The meta-analyses for systolic (43 studies) and diastolic (38 studies) blood pressure, and total cholesterol (46 studies) provide no evidence of protective effects of BF.

BF was consistently associated with higher performance in intelligence tests among children and adolescents, with a pooled increase of 3.4 IQ points (95% CI 2.3;4.6) based on 16 observational studies that controlled for several confounding factors including home stimulation (Table 1). Nine studies also adjusted for maternal intelligence, showing a pooled effect of 2.6 points (95% CI 1.3;4.0). A large randomized trial reported an increase of over 7 IQ points at 6.5 years of age,[31] and a similar effect was reported in a non-randomized trial where preterm infants were fed formula or breastmilk.[32] Positive associations with attained schooling were reported from Great Britain,[33 34] New Zealand[35] and Brazil,[36] but a joint analysis of four LMIC cohorts showed mixed results.[37] A recent publication from Brazil including 30-years follow up suggested an impact of breastfeeding on intelligence, attained schooling and adult earnings; the latter was largely mediated through increased IQ.[38]

A 2007 review suggested that BF may reduce the risk of acute lymphocytic and acute myelogenous leukemias. [21]

Effects on the mother

Table 1 shows the results of new reviews on lactational amenorrhea, breast and ovarian cancer, type 2 diabetes and osteoporosis. We also cite existing reviews on diabetes, weight retention and maternal depression. Most studies are from HICs, except for lactational amenorrhea.

The role of BF in birth spacing is well recognized. In 2003, it was estimated that in countries where continued BF is prevalent, such as Uganda and Burkina Faso, 50% more births would be expected in the absence of BF.[39] Our review (Table 1) confirms that increased breastfeeding, and in particular exclusive or predominant BF, were associated with longer periods of amenorrhea. BF promotion RCTs also confirm this effect.[40]

There is evidence of a robust inverse association between BF and breast cancer (Table 1). The largest individual level analysis on this topic included about 50,000 cancer cases from 47 studies,[41] representing about half those included in our meta-analysis. Each 12-month increase in lifetime BF was associated with a reduction of 4.3% (95% CI 2.9;6.8%) in the incidence of invasive breast cancer. This analysis included thorough adjustment parity and other confounders; nulliparous women were excluded. The results did not vary significantly according to menopausal status. Our meta-analysis suggests a higher magnitude of protection, but when restricted to the 14 studies with fine adjustment for parity and exclusion of nulliparae women, the reduction comparing longer versus shorter BF durations was equal to 7% (95% CI 3%;11%).

The meta-analysis of 41 studies on BF and ovarian cancer shows a 30% reduction associated with longer BF (95% CI 25;36%). Confounding by parity may affect the results but socioeconomic confounding is unlikely. The pooled reduction, based on studies with fine adjustment for parity and exclusion of nulliparae women, was 18% (95% CI 14;42%).

We also reviewed the evidence on osteoporosis, finding no evidence of an association between BF and bone mineral density in the four studies available (Table 1).

Recent reviews were available for maternal type-2 diabetes, postpartum weight change and depression. A meta-analysis of six cohort studies on diabetes showed an odds ratio of 0.68 (95% CI 0.57;0.82).[42] In light of this finding, one would also predict an association with overweight, but a review of 54 articles on the possible role of BF on postpartum weight change was inconclusive.[43] Few studies are available the long term association between nursing and adiposity. After the latter review was published, an analysis of 740,000 British women with long-term follow-up showed that mean BMI was 1% lower for every 6 months that the woman had breastfed.[44] A qualitative review of 48 studies showed clear associations between BF and reduced maternal depression,[45] but it is more likely that depression affects BF than the opposite.

Estimating lives saved for children and mothers

The Lives Saved Tool[8] estimates that 823,000 annual deaths would be saved in 75 high-mortality LMICs in 2015 if breastfeeding was scaled up to near universal levels. This corresponds to 13.8% of the deaths of children under two years of age. Among preventable deaths, 87% would have occurred among infants under six months, due to a combination of high death rates and low prevalence of exclusive BF.

We also estimated potential impact on breast cancer mortality (webappendix 7). Globally, existing rates of BF avert an estimated 19,464 annual breast cancer deaths relative to a scenario in which no women breastfed, using the estimates of protection from the pooled study (Table 1).[41] The low-income regions with long BF durations (Africa and South Asia) account for 58% of currently prevented deaths, despite only accounting for 36% of the global population included in this

analysis. We also estimate that an additional 22,216 lives a year would be saved by increasing BF duration from current levels to 12 months per child in high-income countries, and 2 years per child in LMICs. We cannot model the same effect in all countries given the differences in data availability, and the fact that very few children in high-income countries are breastfed longer than 12 months. Latin America, CEE/CIS and the high-income countries would benefit most because of their higher incidence of breast cancer and also shorter BF durations.

Conclusions

As described by Vahlquist,[1] the reproductive cycle includes pregnancy and BF. The latter has been largely neglected by medical practice, leading to the assumption that breastmilk may be replaced with artificial products without important detrimental consequences. This is particularly critical in HICs, where fewer than one in every five children are breastfed by the age of 12 months. For each doubling in national GDP per capita, BF prevalence at 12 months decreases by 10 percent points.

Modern epidemiology and biology confirm that relinquishing BF has major long-term effects on the health, nutrition and development of the child as well on women's health. Possibly, no other health behaviour can influence such varied outcomes in the two individuals who are involved: the mother and the child. Recent findings on immunology, epigenetics, microbiome and stem cells will likely be followed by other, even more exciting discoveries on the exquisite personalized medicine provided by human milk.

Our global analyses show that over 80% of newborns receive breast milk in virtually all countries. However, only about half are put to the breast within the first hour, even though such recommendation was issued more than 25 years ago.[46] As 60% of the world's children are now delivered by skilled assistants,[9] further promotion of early initiation is possible. In most countries, exclusive BF rates are well below 50%, and the correlation with the duration of any BF is only moderate. This signals the need to tailor BF support strategies to specific patterns observed in each country. In the poorest countries, late initiation and low rates of exclusive BF are the main challenges. In middle and high-income countries, short overall duration of BF represents an additional challenge.

Our time trend analyses show that, for LMICs as a whole, exclusive BF increased by about 0.5 percent point a year since 1993, reaching 35% in 2013. In 2012, the 56th World Health Assembly set as a target for 2025 to "*increase the rate of exclusive breastfeeding in the first 6 months up to at least 50%"*.[47] This requires a doubling of the recent annual increase, to more than 1 percent point a year in the next decade, which is already the rate for the richest 20%. In light of the benefits of exclusive BF and of current achievements by leading countries, one wonders if a more ambitious target should not be aimed at. The Assembly did not set a goal for continued BF.

In terms of inequalities, we show that BF is one of the few positive health behaviours that is more prevalent in poor than in rich countries. We also show that poor women breastfeed for longer than rich women in LMICs, whereas in HICs the pattern is in the opposite direction. These results suggest that BF patterns are currently contributing to reducing the health gaps between rich and poor children in LMICs, which would be even greater in the absence of BF.

In LMICs, there are no inequalities between rich and poor mothers in exclusive BF rates. Time trend analyses suggest that this is because rich mothers are adopting exclusive BF at a much faster rate than the poor; only 20 years ago, the latter had substantially higher rates of exclusive BF. In

contrast, continued BF is still more common among the poor, but rates are dropping among these while remaining stable among the rich. Protecting BF among the world's poor is therefore a major priority.

Our systematic reviews emphasize how important BF is for all women and children, regardless of where they live and irrespective of whether they are rich or poor. Appropriate BF practices prevent child morbidity due to diarrhoea, respiratory infections and otitis media. Where infectious diseases are common causes of death, BF provides major protection, but even in high-income populations it lowers mortality due to causes such as necrotizing enterocolitis and sudden infant death syndrome. Current evidence shows that BF enhances human capital by increasing intelligence. BF also helps nursing women by preventing breast cancer. In addition, our review suggests likely effects on overweight and diabetes in breastfed subjects, and ovarian cancer and diabetes in mothers.

The only harmful consequence of BF we detected was an increase in dental caries among children breastfed for over 12 months; in light of the many benefits of BF, this observation should not lead to discontinuation of BF but rather to improved oral hygiene.

Findings from our systematic reviews are limited by the observational nature of most of the available data on BF and by the limitations of meta-analyses.[48,49] Experimental data are scant because BF promotion activities must be highly effective to change feeding patterns to an extent that leads to measureable impact on short and long-term outcomes.

Moreover, confounding may occur because BF is associated with higher socioeconomic position in HICs. Our reviews included sub-analyses of studies with tight control for confounding. Whenever possible, we also carried out separate analyses of studies from LMICs, because the poor tend to breastfeed for longer in these countries (webappendix 10), in contrast to what is observed in HICs. Interpretation of associations is also affected by the fact that non-breastfed infants receive different diets in different countries, for example animal milk in most poor societies and formula in middle and high-income populations. The association between BF and overweight, for example, is likely affected by the diet of infants who are not breastfed.

There is no consensus regarding whether breastfeeding protects against overweight and diabetes,[21,26,30] particularly because of potential residual confounding. Although the evidence is not as strong as for infections or intelligence, we argue that there is growing evidence of protection. Our meta-analyses showed that the association persisted when restricted to higher quality studies, and was also present in studies from low and middle income settings. The association appears to be specific: for example we found no effect on blood pressure or blood lipid levels, for which confounding patterns are similar. Last, the randomized trials of breastfeeding promotion in infancy indicate a reduction in adiposity.

Scaling up BF practices to almost universal levels is estimated to prevent 823,000 annual deaths, or 13.8% of all deaths of children under the age of 24 months in the 75 Countdown to 2015[9] countries. It should be noted that the target of 95% exclusive BF under six months is ambitious, as currently the highest national prevalences are 85% for Rwanda and 76% for Sri Lanka. We also used a target of 90% for any BF from 6-23 months, but five countries already have levels that are above this target (Nepal, Rwanda, Ethiopia, Burundi and Guinea). We acknowledge that these targets are ambitious, but the estimates show the potential for lives saved if mothers and children

adhered to international recommendations. In spite of differences in methods, our estimates are consistent with those from the 2013 Lancet Nutrition Series (804,000 deaths),[50] but are higher than those from the 2010 Global Burden of Disease study (540,000 deaths);[51] in the latter, the assumptions and methods are not sufficiently detailed to understand the reasons for the discrepancy. BF is potentially one of the top interventions for reducing under-five mortality, and the modest changes in BF rates since 2000 have contributed to the fact that most LMICs failed to reach the fourth Millennium Development Goal.[52] We show that increasing exclusive BF should be the first priority for reducing infant deaths.

As an example of the potential to save women's lives, we estimated that current rates of BF prevent almost 20,000 annual breast cancer deaths, and another 20,000 are preventable by scaling up BF practices (webappendix 8).

To achieve its full impact, BF should continue up to the age of two years. Protection against infectious diseases mortality and morbidity extends well into the second year of life; for example, BF prevents half of deaths due to infections among children aged 6-23 months. Protection against otitis media, a common childhood illness throughout the world, also extends to two years and possibly beyond. Studies of overweight and obesity show that longer durations of BF are associated with lower risk, as do studies of IQ showing a clear dose-response association with duration. Breast cancer is reduced by lifetime duration of BF among women, with a 6% reduction for each 12 months.[41] Ethnographic research shows that total BF duration ranges between two and four years in most traditional societies,[53] and our review of the literature supports current international recommendations about the total duration of BF, in rich and poor countries alike.

Data availability on BF patterns shows a highly unusual pattern. HICs seem to neglect BF to such an extent that most of them are unable to report on reliable, standardized indicators. This is in sharp contrast to the high data quality on LMICs, as a consequence of the regular conduct of standardised surveys such as DHS and MICS. This is a rare inversion of the usual global distribution of availability and coverage of health statistics.

At a time when the launch of the Sustainable Development Goals is approaching, we were able to demonstrate how essential the protection, promotion and support of BF is for achieving many of the goals by 2030. BF is clearly relevant to the 3rd goal on health, which includes not only maternal and child health but also non-communicable conditions and diseases such as breast cancer, diabetes and overweight/obesity. It is relevant to the 2nd goal on nutrition, as well. The impact of BF on intelligence and on human capital is relevant to the 4th (education), 1st (poverty) and 8th (inclusive economic growth) goals. Finally, by helping close the gap between rich and poor, BF can contribute to goal number 10 – reducing inequalities.

Panel: Search Strategy

Information on the associations between BF and outcomes in the child or mother was obtained from 28 systematic reviews and meta-analyses, of which 22 were commissioned for this article.

We reviewed the following conditions for young children: child mortality; diarrhoea incidence and hospitalization; lower respiratory infections incidence, prevalence and hospitalization; acute otitis media; eczema; food allergies; allergic rhinitis; asthma or wheezing; infant growth (length, weight and BMI or weight/length); dental caries; and malocclusion. Among older children, adolescents and adults, systematic reviews were carried out for systolic and diastolic blood pressure; overweight and obesity; total cholesterol; type-2 diabetes and intelligence. For mothers, systematic reviews covered the following outcomes: lactational amenorrhea; breast and ovarian cancer; type-2 diabetes; postpartum weight change and osteoporosis.

Webappendix 5 describes the search terms.

Panel: Key Messages

- Children who are breastfed have lower infectious morbidity and mortality, fewer dental malocclusions and increased intelligence, which persists until later in life. There is also growing evidence that breastfeeding protects against overweight and diabetes.
- Breastfeeding also brings benefits to women, including prevention of breast cancer and birth spacing, as well as likely reductions in diabetes and ovarian cancer.
- High-income countries show shorter breastfeeding duration than low and middle-income countries, but even in the latter only 37% of infants under six months are exclusively breastfed.
- Scaling up breastfeeding is estimated to prevent 823,000 child deaths and 20,000 breast cancer deaths per year.
- Modern biology is revealing novel mechanisms that characterize breast milk as the ultimate personalized medicine for infants.
- Breastfeeding promotion is important in rich and poor countries alike, and may contribute to reaching the forthcoming Sustainable Development Goals.

Panel: Breastmilk: the most exquisite personalised medicine.

The nutritional advantages of breastfeeding and its protection against infection are well recognised. Recently it has become apparent that critical imprinting events may be modulated, with potential lifelong effects for the infant[54]. These may be mediated directly or through effects upon the infant microbiome. The ability of the microbiome to regulate host responses in infancy depends on individual species, which modulate T cell polarisation and immune regulation, metabolic responses and adipogenesis, possibly even brain development and cognitive functioning .[55,56]. Abnormal colonisation patterns have deleterious long term impact upon immune and metabolic homeostasis. It is thus remarkable that a mother's breastmilk transmits elements of her own microbiome and immune responses, and also provides specific prebiotics to support growth of beneficial bacteria.

Delivery mode initially determines whether the gut flora of the mother (vaginal delivery) or the skin flora of the attendants (caesarean section) dominates the initial colonisers.[57], which induce a significant immune response in the infant. Feeding mode is the second fundamental determinant of the infant microbiome. Breastfed infants maintain persistent microbial differences, independent of delivery mode [58,59], due to the effects of human milk oligosaccharides (HMO). Human milk contains a much wider variety of sugars than other mammalian milks: up to 8% of its calorific value is provided in the form of undigestible HMO which function as prebiotics to support growth of specific bacteria. They cannot be utilised by most enteric organisms, but notably support growth of *Bifidobacterium longum biovar infantis*, which has co-evolved to express the enzymes needed for HMO utilisation.[54]. Importantly, there is significant inter-individual variation in maternal HMO production, which in turn underpins the pattern of flora acquisition by the infant[60]. There is thus specificity of interaction between breast milk and the infant microbiome, causing different bacterially-induced effects upon the infant's metabolism and immunity.

This specificity of interaction is further underpinned by the mother's entero-mammary axis. To maintain her own gut homeostasis, the mother's intestinal dendritic cells take up individual bacteria from the lumen and transport these to gut lymphoid follicles [55], where T cells are committed to a regulatory phenotype and B cells shifted towards IgA. Programmed dendritic cells and lymphocytes re-enter the circulation from there before homing back to the gut through interaction between their induced $\beta 7$ integrins and locally-expressed mucosal vascular addressin cell adhesion molecule (MAdCAM-1). MAdCAM-1 is expressed within mammary endothelium during pregnancy, allowing selective uptake by the breast of gut-programmed cells.[61] The consequences of enteromammary trafficking include release into colostrum and breast milk of dendritic cells containing live maternal gut bacteria, T cells expressing gut-derived $\beta 7$ integrins and plasma cells producing IgA specific for maternal gut bacteria. Breast milk thus contains a dominance of immune cells of gut-related phenotype ($\gamma\delta$ cells, $\beta 7$+ cells) that have matured within the mother's intestine.[62] Breastmilk cytokines also vary depending upon the mother's immunological experiences. There is thus a coordinated input to the infant's nascent mucosal immune system, specific for the mother's microbiome, in which individual bacterial types are favoured and tolerogenic immune responses transmitted. Caesarean section, perinatal antibiotics and failure to breastfeed are the three major factors that impact on this co-evolved imprinting process. An important study of flora acquisition and immune responses in primates identified clear differences in both gut bacterial composition and mucosal immune responses in breastfed compared to formula fed macaques , persisting to adult life.[63]

In addition to changes mediated through the flora, individual breastmilk components may directly affect epigenetic programming of the infant [64]. The usual adverse impact of peroxisome proliferator-activated receptor-γ (PPAR-γ) polymorphisms upon adiposity and metabolism is prevented by breastfeeding, possibly due to the content of PPAR modulating constituents such as long-chain polyunsaturated fatty acids (PUFA) and prostaglandin J [65]. Protection against breast cancer for the breastfeeding mother may also be mediated through PPAR modulation[65]. Lactoferrin, a major breastmilk component, binds bacterial CpG motifs and blunts mucosal NF-κB responses to the flora. Microvesicles called exosomes are secreted into breast milk, and may inhibit atopic sensitisation dependent on maternal immune experience[66]. Breastmilk fat globules contain numerous secreted micro-RNA's, whose expression is modulated by maternal diet, which are predicted to target multiple genes within the infant (Munch). There is also evidence that multipotential stem cells are secreted into breastmilk and may persist within the infant[67].

Human breastmilk is thus not only a perfectly adapted nutritional supply for the infant, but probably the most exquisitely specific personalised medicine that he/she is ever likely to receive, given at a time when gene expression is being fine-tuned for life. This is an opportunity for health imprinting that should not be missed.

557 **Table 1.** Results of meta-analyses on the associations between BF and outcomes in the child and mother.

Outcome	Types of comparison (breastfeeding categories)	Number of studies	Age range of outcome	Pooled effect (95% CI)	Confounding and effect modification	Other biases	Conclusions	Reference
EFFECTS ON CHILDREN, ADOLESCENTS OR ADULTS ACCORDING TO BF PATTERN								
Mortality due to infectious diseases	Exclusive versus predominant	3	< 6 mo	OR: 0.68 (0.52; 0.88)	All studies from LMICs, where confounding by SEP would likely underestimate the effect of BF. Confounder-adjusted studies showed similar effects.	Studies that avoided reverse causation (BF being stopped because of illness) showed similar effects. No evidence of publication bias but very few studies available.	Consistent evidence of major protection. Few studies used the 4 BF categories in young infants, but evidence from other studies comparing any versus no BF is very consistent.	Sankar 2015[68]
	Exclusive versus partial	3		OR: 0.35 (0.20; 0.61)				
	Exclusive versus none	2		OR: 0.07 (0.03; 0.16)				
	Any versus none	9	6-23 mo	OR: 0.48 (0.38; 0.60)				
Diarrhea incidence	More versus less BF (e.g. exclusive versus non-exclusive; predominant versus partial; partial versus none; any BF versus no BF, etc.)	15	<5 yr	RR: 0.69 (0.58;0.82)	Most studies from LMICs, where confounding would likely underestimate an effect. Confounder-adjusted studies showed similar effects. Three BF promotion RCTs (not included here) showed protection against diarrhea morbidity (pooled OR: 0.69 (0.49; 0.96).	Few studies that allowed for reverse causation also showed protection. Publication bias is unlikely to explain the findings as results from large and small studies were similar.	Strong evidence of major protection against diarrhea morbidity and hospitalizations, particularly among young infants, based on a large number of studies.	Horta 2013[23]
		23	< 6 mo	RR: 0.37 (0.27; 0.50)				
		11	6 mo - <5 yr	RR: 0.46 (0.28; 0.78)				
Diarrhea hospitalization		9	< 5 yr	RR: 0.28 (0.16;0.50)				
Lower respiratory infections incidence or prevalence	More versus less BF (e.g. exclusive versus non-exclusive; predominant versus partial; partial versus none; any BF versus no BF, etc.)	16	< 2 yr	RR: 0.68 (0.60; 0.77)	Most studies from LMICs, where confounding would likely underestimate the effect of BF. Confounder-adjusted studies showed similar effects. The only available RCT showed a RR of 0.85 (0.57; 1.27), a non-significant reduction in hospitalizations.	Studies that avoided reverse causation showed similar effects. No evidence of publication bias.	Strong evidence of a reduction in severe respiratory infections among breastfed children, based on a large number of studies.	Horta 2013[23]
Respiratory infections hospitalization		17	<2 yr	RR: 0.43 (0.33; 0.55)				
Acute otitis media	More versus less BF (ever versus	11	≤2 yr	OR : 0.67 (0.62, 0.72)	Most studies carried out in HICs. Several studies failed to	High heterogeneity (I^2= 84%) among the	Consistent evidence of	Lodge 2015[69]

	never; exclusive BF at 6 months versus not exclusive BF at 6 months; any BF for ≥ 3-4 versus ≤ 3-4 months)	5	>2 yr	OR: 1.21 (0.60; 2.45)	adjust for important confounders.	5 studies of children >2 yr. Some evidence of publication bias, however study size only accounted for a limited proportion of the overall heterogeneity.	reduction in acute otitis media during the first 2 yr of life associated with longer durations of BF, based on 11 studies. No evidence of protection after 2 yr.	
Eczema	More versus less BF (ever versus never; exclusive BF at 6 months versus not exclusive BF at 6 months; any BF for ≥ 3-4 versus ≤ 3-4 months)	17	≤2 yr	OR: 0.95 (0.85; 1.07)	About one-third of the studies are from LMICs, and results are similar to those from HICs. Few studies among young children account for reverse causation. Several studies failed to adjust for essential confounders. The protective effect of asthma was smaller and not significant in 16 studies with thorough control for confounders (OR: 0.95; 95% CI 0.85; 1.06) and in the 13 cohort studies (OR: 0.94; 95% CI 0.80; 1.11). There were too few studies to estimate association with asthma in adults.	Some evidence of publication bias, with smaller pooled effect sizes in larger studies. The 10 studies on food allergy in children ≤ 5yr were highly heterogeneous (I^2= 88%).	No evidence of an association between BF and eczema or food allergies.	Lodge 2015[69]
		20	>2 yr	OR: 1.09 (0.99; 1.20)				
Food allergies		10	≤ 5yr	OR: 1.07 (0.90; 1.26)				
		4	>5yr	OR: 1.08 (0.73; 1.26)				
Allergic rhinitis		5	≤ 5yr	OR: 0.79 (0.63,0.98)			Possible protection against allergic rhinitis among children <5 yr, based on only 5 studies; no evidence for those older than 5 yr.	
		9	>5yr	OR: 1.05 (0.99,1.12)				
Asthma or wheezing		29	5-18 yr	OR: 0.91 (0.85; 0.98)			Inconclusive evidence on the association between BF and the risk of asthma or wheezing.	
Length	Randomized trials or quasi-experiments comparing children receiving BF	17	≈6 mo	Z scores : +0.03 (-0;02; 0.08)	Most studies are from middle income countries. Confounding is unlikely because 15 of the 17 studies were randomized trials. Analyses were based on intent	Evidence of publication bias for BMI, with small studies showing larger reductions.	No evidence of an effect on BF promotion on weight or length at 6 months of age; some	Giugliani 2015[70]
Weight		16		Z scores : +0.03 (-0;06; 0.12)				
BMI or weight/length		11		Z scores : -0.06 (-0;12; 0.00)				

	promotion interventions with control children				to treat, so that low compliance with BF promotion may underestimate the magnitude of the effect.		evidence supporting a reduction in BMI or weight for length.	
Dental caries	BF > 12 mo versus ≤ 12 mo	4	<6 yr	OR: 2.69 (1.28-5.64)	Most studies not control for the introduction of sugary foods and drinks. Most studies from HICs, where high SEP would be expected to negatively confound the association.	Publication biases veer toward studies with that show association between these breastfeeding beyond 12 months and on demand and dental caries.	Consistent evidence that BF > 12 mo and BF on demand have detrimental effects on deciduous teeth.	Lodge 2015[69]
	BF on demand or nocturnal feeding versus not [in breastfed children]	6	<6 yr	OR: 2.90 (2.33-3.60)				
Malocclusion	Never versus ever BF; longer versus shorter duration of exclusive BF; or longer versus shorter duration of any BF	41	Childhood, adolescence and adulthood.	OR: 0.32 (0.25-0.40)	80% of the studies from LMICs. Because malocclusions are not associated with SEP nor with any other known determinant of BF patterns, it is unlikely that these results are affected by confounding.	Some evidence of publication bias but the association was also present in the larger and better designed studies.	Consistent evidence of a major, two-thirds reduction in malocclusions in deciduous teeth among BF subjects	Peres 2015[71]
Systolic blood pressure	Never versus ever BF; or longer versus shorter BF duration	43	Childhood, adolescence and adulthood.	mm Hg: -0.80 (-1.17; -0.43)	Three quarters of the studies from LMICs. Evidence of residual confounding as effect was found in studies from HIC but not from LMICs.	Evidence of publication bias for systolic blood pressure studies.	No evidence of a reduction in blood pressure associated with BF	Horta 2015[27]
Diastolic blood pressure	Never versus ever BF; or longer versus shorter BF duration	38	Childhood, adolescence and adulthood.	mm Hg: -0.24 (-0.50; 0.02)				
Overweight and/or obesity	Never versus ever BF; longer versus shorter duration of exclusive BF; or longer versus shorter duration of any BF	113	Childhood, adolescence and adulthood.	OR: 0.74 (0.70; 0.78)	In HICs, residual confounding by SEP is a possibility; however, the effect size was similar in studies from LMICs (one third of all studies). Twenty-three high quality studies showed a smaller pooled reduction of 13% (95%	Some evidence of publication bias with larger effects in small studies, but even large and well-controlled studies showed a 20% reduction in	Suggestive evidence of protection, including high-quality studies and those from low or middle income settings.	Horta 2015[27]

					CI 6% to 19%).	prevalence.		
Total cholesterol	Never versus ever BF; or longer versus shorter BF duration	46	Childhood, adolescence and adulthood.	/mmol/L: -0.01 (-0.05; 0.02)	No evidence of heterogeneity with nearly all studies showing small effects. Three quarters of the studies from HICs.	No evidence of an association.	No evidence of an association.	Horta 2015[27]
Type-2 diabetes	Never versus ever BF; longer versus shorter duration of exclusive BF; or longer versus shorter duration of any BF	11	Childhood, adolescence and adulthood.	OR: 0.65 (0.49; 0.86)	Only 2 out of 11 studies from LMIC showing 14% reduction; residual confounding may affect HIC studies.	Small number of available studies; no evidence of publication bias.	Limited evidence of protection, based on 11 studies.	Horta 2015[27]
Intelligence	Never versus ever BF; or longer versus shorter BF duration	16	Childhood, adolescence and adulthood.	IQ points: 3.44 (2.30; 4.58)	In HIC (14 of the 16 studies), residual confounding by SEP is a possibility; however, the effect was also present in 2 studies from LMICs. One high quality RCTs showed a significant increase in IQ of over 7 points.	Some evidence of publication bias with larger effects in small studies, but even large studies showed an effect. Nine studies with adjustment for maternal IQ showed difference of 2.62 points (1.25; 3.98)	Consistent effect of about 3 IQ points in observational studies; also present a large RCT on this topic.	Horta 2015[27]
EFFECTS ON WOMEN WHO BREASTFED								
Lactational amenorrhea	Highest versus lowest duration of BF	13	Women (<1 yr post-partum)	RR : 1.17 (1.04-1.32)	Most studies from LMICs. Residual confounding unlikely. Strongest effects when exclusive or predominant BF are compared with partial (RR: 1.21) or no BF (RR: 1.23).	No evidence of publication bias.	Consistent effect on prolonging lactational amenorrhea, especially for exclusive or predominant BF.	Chowdhury 2015[72]
Breast cancer	Highest versus lowest duration of BF	76	Adult women	OR : 0.81 (0.77; 0.86)	Three quarters of the studies are from HICs. Parity reduces the risk of breast cancer and is also associated with greater lifetime BF duration. Most studies failed to adjust	Some evidence of publication bias but the association was also present in the larger and better designed studies.	Consistent protective effect of BF against breast cancer in a large number of well-designed	Chowdhury 2015[72]

					appropriately for parity and therefore tend to exaggerate effect size. A thoroughly adjusted pooled analysis of 47 studies shows an OR of 0.96 for each 12 months of BF.[41]		studies, of a 4.3% reduction per 12 months of BF in the better controlled studies.	
Ovarian cancer	Highest versus lowest duration of BF	41	Adult women	OR: 0.70 (0.64; 0.75)	Only 6 studies from LMICs. Confounding by parity may affect the results but socioeconomic confounding is unlikely. Studies with fine adjustment for parity and exclusion of nulliparous showed less protection with OR: 0.82(0.75-0.89)	Some evidence of publication bias, with smaller pooled effect sizes in the 22 studies with samples greater than 1,500 women - OR: 0.76 (0.69; 0.84).	Suggestive evidence of a protective effect of BF.	Chowdhury 2015[72]
Osteoporosis (distal radius)	Highest versus lowest duration of BF	4	Adult women	SDS: -0.132 (-0.260;-0.003)	All studies from HICs. High heterogeneity in the distal radius analyses with the largest study showing no association and smaller studies showing protection; for femoral neck, none of the studies found an association.	Not assessed due to small number of studies.	Insufficient evidence	Chowdhury 2015[72]
Osteoporosis (femoral neck)		4		SDS: -0.142 (-0.426; 0.142)				
Type-2 diabetes	Highest versus lowest duration of BF	6	Adult women	RR: 0.68 (0.57; 0.82)	Several confounding factors were adjusted for. Significant protection also found for 3- and 12-month increases in BF duration. Five of the 6 studies are from HICs. All six showed protection.	Small number of available studies; no evidence of publication bias.	Limited evidence of protection against type-2 diabetes among women who breastfed for longer periods, based on 6 studies	Aune 2013[42]
Postpartum weight change	Qualitative review	45	Women (<2 yr post-partum)	Not estimated because of different outcome measures at variable post-partum ages.	Studies were highly variable. Most studies found no association. Of the five studies with high methodological quality, four reported beneficial effects. Nearly all studies from HICs.	Not assessed in the published review.	The role of breastfeeding on post-partum weight change is uncertain.	Neville 2014[43]

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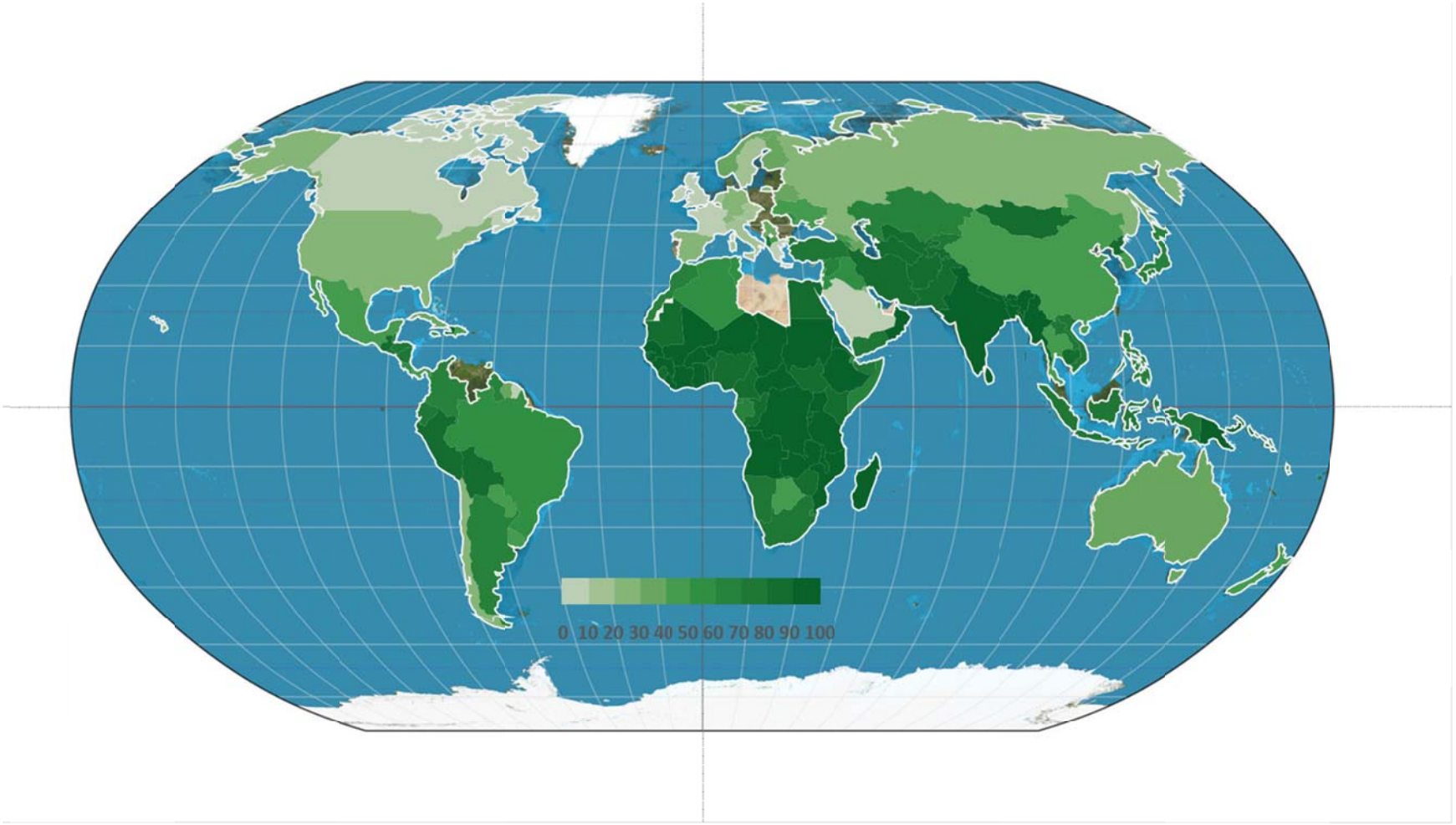
Notes:

In several reviews, the summary effect sizes represent the pooled results of studies comparing longer versus shorter BF durations (either never versus ever BF; exclusive BF for more than x months versus less than x months; or any BF for more than x months versus less than x months). Separate results for each type of categorization are available in the web annexes.

Acronyms - HIC: high-income countries; LMIC: low and middle-income countries; SEP: socioeconomic position; OR: odds ratio; RR: risk ratio; RCT: randomized controlled trial; SDS: standard deviation scores.

Figures

Figure 1. Percent of children who receive any breastmilk at 12 months of age, by country (data from 153 countries, 1995-2013). Countries without data are shown as terrain view.



574 **Figure 2. BF indicators by country income group in 2010 (analyses of national surveys using**
575 **standard indicators, weighted by national populations of children under two years. Data**
576 **on up to 153 countries.**

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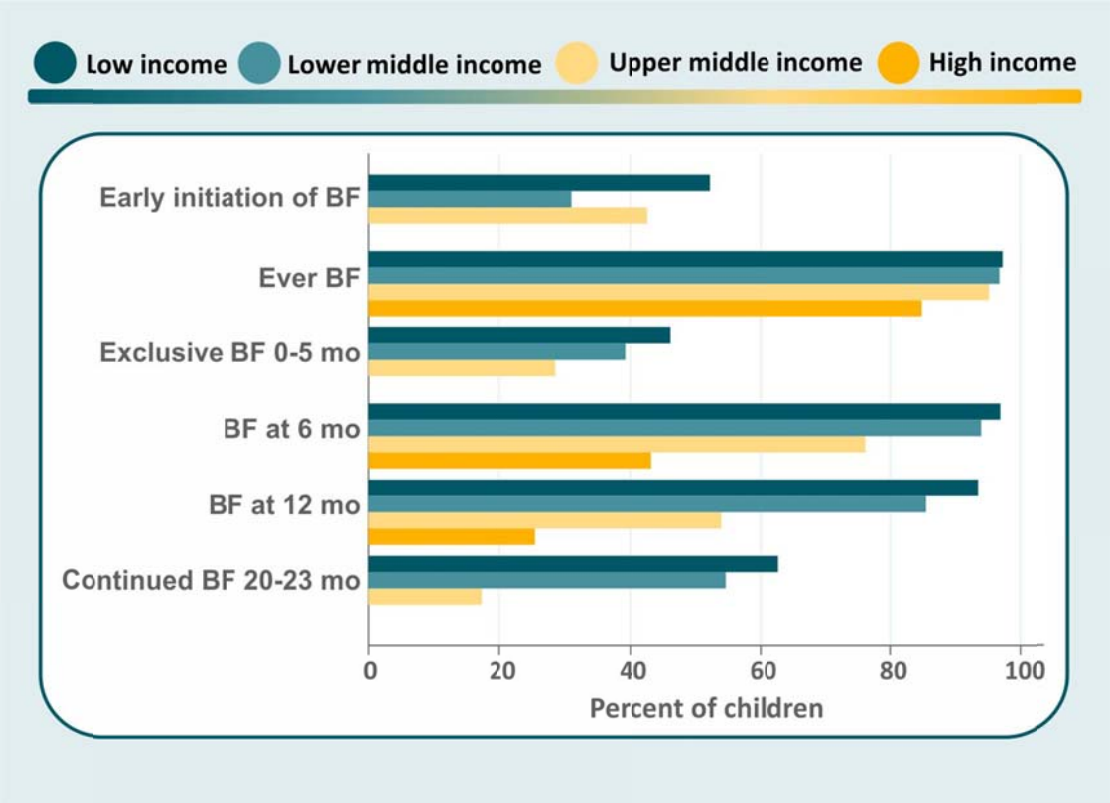

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Figure 3. National-level proportions of children aged 12-15 months who are breastfed, according to exclusive BF in children aged 0-5 months. Countries are color-shaded according to the regions of the world (UNICEF classification). Based on the most recent survey from 117 countries (2000-2013).

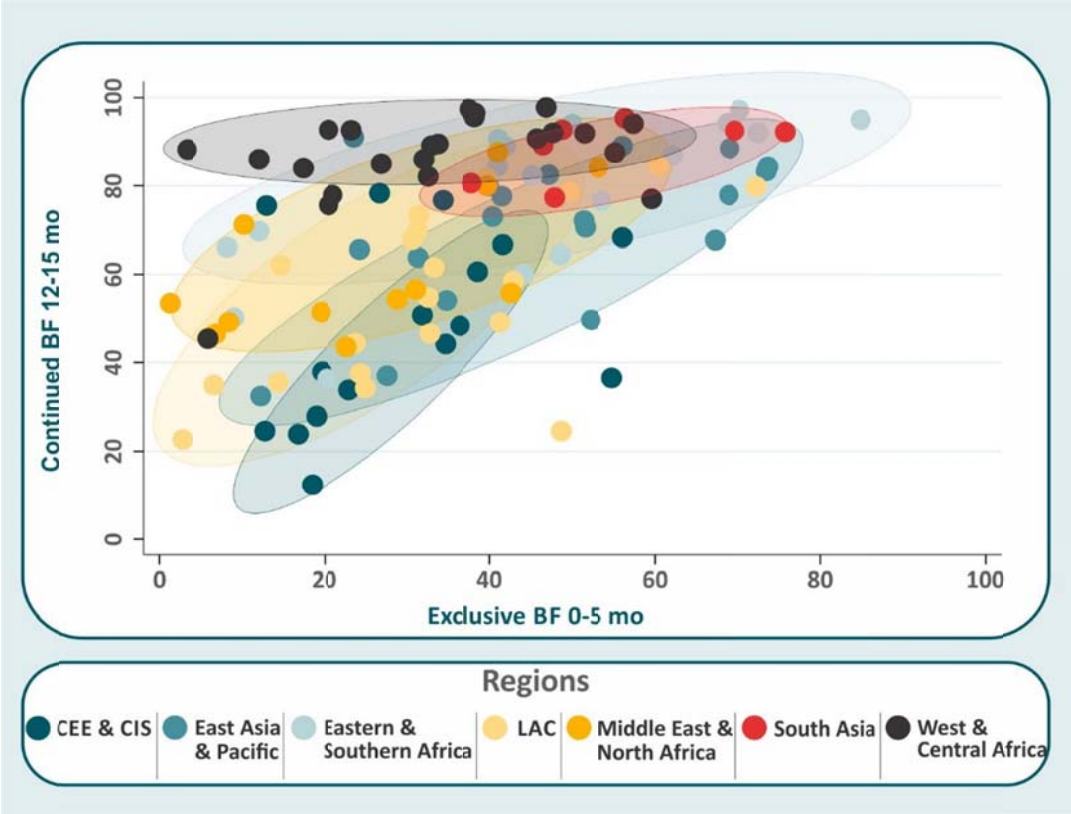
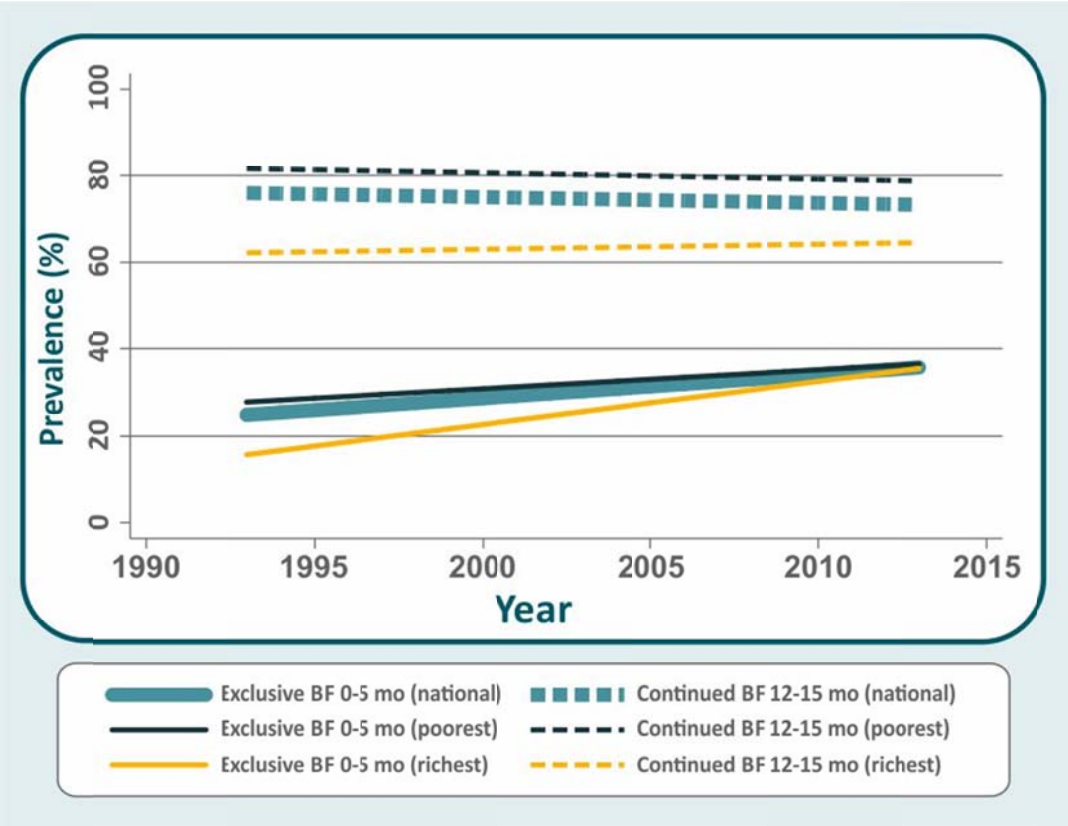


Figure 4. National and wealth quintile-specific time trends in exclusive BF 0-5 months (solid lines) and continued BF 12-15 months (dotted lines) , 1993-2013, weighted by national populations of children under two years at the time of the survey. Analyses restricted to 66 countries with information on household wealth.



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