

Advancing Early Childhood Development: from Science to Scale 3



Investing in the foundation of sustainable development: pathways to scale up for early childhood development

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Building on long-term benefits of early intervention (Paper 2 of this Series) and increasing commitment to early childhood development (Paper 1 of this Series), scaled up support for the youngest children is essential to improving health, human capital, and wellbeing across the life course. In this third paper, new analyses show that the burden of poor development is higher than estimated, taking into account additional risk factors. National programmes are needed. Greater political prioritisation is core to scale-up, as are policies that afford families time and financial resources to provide nurturing care for young children. Effective and feasible programmes to support early child development are now available. All sectors, particularly education, and social and child protection, must play a role to meet the holistic needs of young children. However, health provides a critical starting point for scaling up, given its reach to pregnant women, families, and young children. Starting at conception, interventions to promote nurturing care can feasibly build on existing health and nutrition services at limited additional cost. Failure to scale up has severe personal and social consequences. Children at elevated risk for compromised development due to stunting and poverty are likely to forgo about a quarter of average adult income per year, and the cost of inaction to gross domestic product can be double what some countries currently spend on health. Services and interventions to support early childhood development are essential to realising the vision of the Sustainable Development Goals.

Introduction

The first Sustainable Development Goal (SDG) is to “ensure that all human beings can fulfil their potential in dignity and equality”.¹ Protecting, promoting, and supporting early childhood development is essential to enable everyone to reach their full human potential.

In 2007, a *Lancet* Series estimated that 200 million children younger than 5 years in low-income and middle-income countries (LMICs) were at elevated risk of not reaching their human potential.² A second *Lancet* Series in 2011 identified risks and protective factors, and growing evidence of the effectiveness of interventions to prevent loss of human potential.^{3,4}

In this Series on early childhood development, Paper 1 takes stock of what has been achieved in the era of the Millennium Development Goals (MDGs).⁵ Paper 2 reviews effective interventions and new findings in neuroscience and genetics.⁶ Scientific evidence confirms conception to age 3 years as the time during which adverse exposures exert the greatest harm, and effective interventions the greatest benefit. The development of young children has been neglected to date in favour of emphasis on survival and preparation for school. For this reason, the focus in this paper is on optimisation of development at scale during early childhood.⁶

We argue that the burden of poor development is larger than currently estimated because we lack global data to include additional risk factors. This burden makes it imperative to scale up effective interventions to protect,

promote, and support early childhood development. We identify crucial elements of the pathways to successful scale-up, including political prioritisation, creation of supportive policy environments, the use of existing

Lancet 2017; 389: 103–18

Published Online
October 4, 2016

[http://dx.doi.org/10.1016/S0140-6736\(16\)31698-1](http://dx.doi.org/10.1016/S0140-6736(16)31698-1)

This is the third in a Series of three papers about early childhood development

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Key messages

- The burden of poor child development is currently underestimated because risks to health and wellbeing go beyond stunting and extreme poverty.
- Effective interventions for early childhood development are now available and can feasibly be integrated into existing systems in health, education, and social and child protection.
- The scale-up of early child development programmes rests on political prioritisation of efforts to address deep social problems such as poverty, inequality, and social exclusion through interventions starting early in the life course.
- Policies that alleviate poverty and buttress family resources create a supportive environment to promote, protect, and support early childhood development at scale.
- Health and nutrition services are ideal starting points to scale up interventions for early childhood development. Efforts to promote nurturing care of young children built onto existing services for maternal and child health and nutrition are affordable.
- Societies around the world pay a high price, now and into the future, for not acting to protect children and promote early child development. The 43% of children younger than 5 years of age in low-income and middle-income countries, who are at elevated risk of poor development because of stunting or extreme poverty, are likely to forego about a quarter of average adult income per year. The benefits forfeited at a country level can be up to two times the gross domestic product spent on health.
- Services and interventions to support early childhood development are essential to ensuring that everyone reaches their potential over the life course and into the next generation, the vision that is core to the Sustainable Development Goals.

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See Online for appendix

delivery systems to build further efforts, and affordability. Action in all sectors is important to promote early childhood development, particularly in education and in social and child protection.

In this paper, we highlight the role of the health and nutrition sector as an entry point to scaling up of programmes for early childhood development. It has extensive reach to women and children during the crucial period from conception throughout early childhood, and is thus well placed to deliver early childhood development services to women, families, and the youngest children, together with education, and social and child protection. Further, there is good evidence of effectiveness, feasibility, and affordability of inclusion of interventions for early childhood development in reproductive, maternal, newborn, and child health (RMNCH) services. UNESCO,⁷⁻⁹ UNICEF,¹⁰ the World Bank,¹¹ and other agencies¹² are committed to promotion of early childhood development, and WHO's commitment is expressed in leadership of the Global Strategy for Women's, Children's and Adolescents' Health 2016–2030. Finally, the Strategy, supported under the UN Secretary General's Every Woman Every Child initiative, offers new opportunities for linking child health, nutrition, and development.¹³

We address affordability by estimating the additional costs of including two scalable, evidence-based interventions for child development in the existing maternal and child health package, and the probable costs of inaction to both individuals and societies. We conclude with a call for actions that are essential for enabling all children to begin life with improved prospects for health, prosperity, and equality, essential to achieve the SDGs in “strengthened global solidarity”.

Millions of young children are at risk of falling behind

“There can be no equality of opportunity without... appropriate stimulation, nurturing, and nutrition for infants and young children. Conditions of poverty, toxic stress and conflict will have produced such damage that they may never be able to make the best of any future opportunities. If your brain won't let you learn and adapt in a fast changing world, you won't prosper and, neither will society.”

World Bank Group President Jim Yong Kim, Oct 1, 2015

250 million children (43%) younger than 5 years in LMICs are estimated to be at elevated risk of not achieving their human potential because of stunting or exposure to extreme poverty.⁵ Increasing numbers of children, including in high-income countries (HICs), are surviving but begin life at a disadvantage because they do not receive the nurturing care necessary for their physical and psychological development. Little is yet being done during the essential first years of life when the effects of risk, and also plasticity, are greatest—a crucial gap in

interventions to accelerate improvements in children's early development at scale.

To test potential underestimation of this burden, we explored the implications of additional risks to children's development beyond poverty and stunting by conducting an illustrative analysis from 15 countries with available Multiple Indicator Cluster Surveys in 2010 or 2011 to examine risks posed by adding low maternal schooling (completed primary school only) and child maltreatment (severe punishment of children aged 2–5 years, such as hitting a child as hard as possible, or with a belt or stick). The estimated proportion of children at risk of stunting or extreme poverty in these 15 countries increases substantially from 62.7% (95% CI 62.0–63.4) to 75% (75.0–76.0) when low maternal schooling and child maltreatment are added, with large disparities among subnational social and economic groups (appendix pp 1–6).

In addition to these risks, millions of children globally are exposed to armed conflict and community unrest.¹⁴ Furthermore, millions more are living with disabilities, or with displaced or immigrant families,¹⁵ parents living with HIV, or mothers who are depressed.^{16,17}

To redress these challenges to child development, countries worldwide must scale up systemic actions to promote, protect, and support early childhood development, ensuring that the most vulnerable children and families are reached.

A multi-sectoral framework to promote the development of young children across the life course

Child development is part of the life course, including preconceptional health and wellbeing of adolescents and continuing into the next generation of young people who grow up and become parents. Promotion of health and wellbeing across the life course requires interventions through services and programmes of several sectors, most notably health and nutrition, education, and child and social protection, in the context of a supportive environment of policies, cross-sectoral coordination, and financing. These multiple inputs create a framework within which actions to promote early childhood development can be initiated and expanded (figure 1).

At the heart of this framework is the nurturing care of young children, provided by parents, families, and other caregivers. Nurturing care, defined in Paper 1 of this Series, comprises caregiver sensitivity to children's physical and emotional needs, protection from harm, provision of opportunities for exploration and learning, and interactions with young children that are responsive, emotionally engaging, and cognitively stimulating.⁵

The second paper of this Series concludes that a range of interventions delivered from preconception, through pregnancy and birth, the newborn period, infancy, and early childhood can support nurturing care and have

proven benefits for child development, including for health, growth, and learning (panel 1). These interventions are delivered ideally through the coordinated services of several sectors.⁶ Many of these interventions also have benefits for survival and prevention of morbidities and, in some cases, disabilities.

We focus on parenting programmes to promote nurturing care, of which among the most widely implemented in LMIC settings are the WHO–UNICEF Care for Child Development (CCD)¹⁸ and Reach Up and Learn, a parent support programme tested in trials in Jamaica during the past 20 years, which is now expanding to other regions. CCD originated as a module of Integrated Management of Childhood Illness, and can be delivered by home visitors and community workers as well as facility-based providers through various health, education, family, and social protection services (panel 1).¹⁹ Early field testing demonstrated the ability of health workers to implement the counselling sessions while also attending to tasks of sick child consultation, as well as mothers' recall and ability to perform the recommended activities at home. Findings from several trials^{19–21} have shown improvements in home environment and children's development with CCD, suggesting that the programme can be incorporated into existing health services at relatively low cost.²² CCD has been integrated into programmes across various sectors, including child survival and health, nutrition rehabilitation, early learning (infant day care and preschool education), social protection (families participating in a cash transfer programme, prevention of violence and abuse), mental health, and services for families with developmentally disabled children (appendix pp 7–14). The time is ripe for the scale-up of interventions like CCD.

Essential elements to accelerate scale-up of programmes for early childhood development

Overview

We identify several elements critical to scale up programmes,^{23,24} including political prioritisation, implementation of policies that enable families to provide young children with nurturing care, delivery systems through which effective interventions can be scaled feasibly, governance structures to ensure that young children's holistic needs are addressed, and affordability.

Political prioritisation of early childhood development and financing

Many HICs have long-running, large-scale programmes for early childhood development that are led and financed by government. We reviewed ten programmes in English-speaking countries identified as successful examples of partnerships involving multiple stakeholders from different sectors working together to improve children's health and development (appendix pp 15–31).²⁵

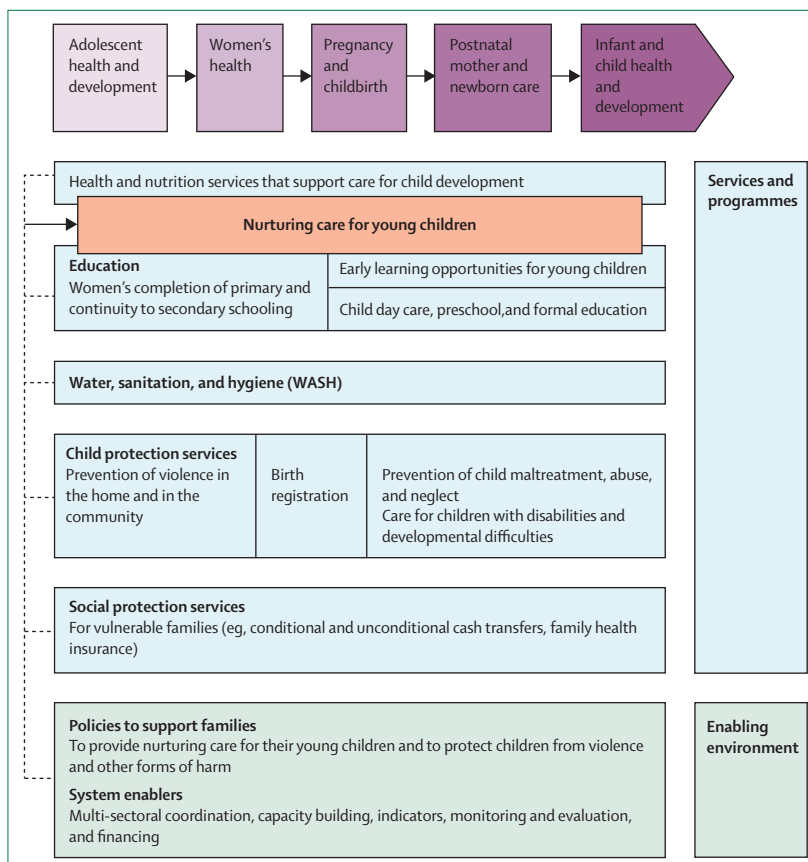


Figure 1: Framework to promote young children's development through a multi-sectoral approach

These programmes include Early Head Start in the USA and Sure Start in the UK.

We also analysed scaled up programmes for early childhood development in three LMICs and one HIC. These countries were selected to exemplify variation in aims, entry points, governance, and coordination (panel 2; appendix pp 32–47). Chile, India, and South Africa demonstrate commitment by governments to scale up interventions through legislation and financing, with achievement of universal coverage in Chile and South Africa. Bangladesh demonstrates government and civil society partnership to assist families with children who have developmental difficulties.

Programmes for early childhood development everywhere are challenged by inadequate and uncertain funding, and inefficient flows of resources across sectors and from central to local levels of government. Management and monitoring, including the documentation of successes and learning from missteps, and numbers of trained staff are insufficient. Programmes struggle to achieve uniform quality and to demonstrate impact on child development outcomes across all implementation contexts through carefully designed evaluations, true also of programmes in HICs.²⁶

For the Reach Up and Learn programme see <http://www.reachupandlearn.com>

Panel 1: Examples of interventions known to effectively improve early childhood development

Interventions

- Iodine supplementation before or during pregnancy
- Antenatal corticosteroids for women at risk of preterm birth
- Magnesium sulphate for women at risk of preterm birth
- Antiplatelet agents for women at risk of pre-eclampsia
- Delayed cord clamping⁵
- Therapeutic hypothermia for hypoxic ischaemic encephalopathy
- Kangaroo Mother Care for small infants (eg, birthweight <2000 g)
- Breastfeeding and complementary feeding promotion, education, and support
- Responsive caregiving with simulation and early learning opportunities
- Iron and multiple micronutrient supplementation for infants and children
- Deworming
- Treatment of moderate and severe acute malnutrition
- Interventions for common (parental) mental disorders including in the perinatal period
- Smoking cessation interventions
- Elimination of environmental toxins (eg, lead, mercury, pesticides)
- Parent support programmes
- Early childhood care and education

Examples of supportive policy environment

- Paid parental leave and paid sick leave to enable parents to provide care
- Breastfeeding breaks at work
- Paid sick leave to enable parents to provide nurturing care
- Minimum wage sufficient to lift families out of poverty
- Tuition-free pre-primary education
- Poverty alleviation strategies

The interventions are further reviewed by Britto and colleagues in Paper 2 of this Series.⁶

Involvement and mobilisation of parents, families, and communities—important drivers of demand for access and quality—has been insufficient, and although there are signs that demand for quality preschools is increasing in LMICs,²⁷ demand for services for young children aged 0–3 years must be encouraged.²⁸

Our analysis of these country programmes illustrates the importance of political prioritisation, legislation, and policy, and the use of existing systems and financing in scale-up.²⁹ The typical successfully scaled up programme for early childhood development is motivated by political concerns about social inequality, poverty, and social exclusion; informed by local and global scientific and economic evidence; has a vision of comprehensive and integrated services for children and families that is informed by whole-of-government and joined-up thinking; founded by statute or formally communicated government strategy; funded by government; and led by a government department or agency working collaboratively with other departments and civil society organisations, in many cases reporting to a senior executive political body such as the Cabinet or Council of Ministers. The importance of political prioritisation has also been shown for programmes to improve nutrition, breastfeeding, and newborn health (appendix pp 15–31).^{23,30–32}

Creation of a policy environment that supports nurturing care of young children

Laws and policies can improve child development by increasing access and quality of health and other services, as well as money and time for parents to provide nurturing care for their young children. We examine a subsection of policies that are core to social determinants of health: family income and time for working parents to devote to their children, as well as access to free pre-primary education. Access varies by rural and urban areas and other parameters. For illustrative purposes, we discuss five transformative policies for which there are robust global data on levels, duration, country coverage, and progress achieved in the past two decades (table 1). A breakdown of access to these policies by country income level is included in the appendix (pp 48–58). Global data for important policy areas are still lacking, for example, those regarding child day care for working parents. Discrepancies between policy adoption and implementation must also be addressed, in addition to the wide disparities in benefits between caregivers engaged in formal and informal work. Nonetheless, policies and laws have an enabling effect even at less-than-complete levels of implementation (appendix pp 48–58, figure 2).

Delivery systems for scaling up of evidence-based interventions for early childhood development

Many efforts to promote early childhood development are dependent on non-governmental services,⁵ which are frequently limited in scope and inequitable in coverage.⁴⁸ Interventions are also dependent on skilled human resources and (unless built on existing service systems such as health, education, and social and child protection) face severe supply-side constraints. The case studies (panel 2) illustrate that national scale-up of programmes for early childhood development can be achieved by building on existing systems.

The importance of this approach is exemplified by the rapid scale-up between 2000 and 2009 of more than 120 cash transfer programmes in LMICs, growing from 28·3 million beneficiaries in 2001 to 129·4 million in 2010 (appendix pp 59–70). Lessons learned are that the main drivers of expansion of cash transfer programmes included political commitment and popularity, operational ease, advances in information technology and banking, rigorous evidence that they are effective, and support from international organisations. Colombia, Ecuador, and Mexico have built programmes for early childhood development onto existing cash transfer programmes.^{49–51}

Given the extensive benefits of health and nutrition interventions on children's development,⁶ and opportunities for the health sector to reach young children and their families during pregnancy and the first years of a child's life,⁵² we propose that existing

Panel 2: Examples of scaled-up programmes for early childhood development

Chile Crece Contigo (ChCC): multisectoral services for early childhood development delivered through government and non-governmental programmes

Chile has a scaled-up system of early childhood development provision guaranteed by law and fully funded by government (appendix pp 33–35). Initiated in 2007, the ChCC provides universal and targeted interventions for early childhood development from gestation to age 4 years in all 345 municipalities. With strong support from political leadership, the Ministry of Social Development coordinates with the Ministries of Health and Education. ChCC's point of entry is prenatal care in public hospitals and currently reaches about 80% of the target population of pregnant women and their unborn children. The Biopsychosocial Development Support Programme includes access to maternal–child primary health care, screening, and referrals for children with developmental delays, and care for children admitted to hospital. ChCC ensures that children younger than 4 years living in a family with risk factors for poor early development also have access to age-appropriate stimulation and education from nursery school to preschool, and that their families are referred to additional social protection services including cash transfers and home visits. ChCC offers high-quality information about early childhood development to families and providers through a radio show and its website.

India's Integrated Child Development Services (ICDS): one of the earliest and the world's largest early childhood development programme

ICDS is the world's largest community-based outreach programme to promote the early development of children from economically disadvantaged backgrounds (appendix pp 36–39). The nationwide programme, launched in 1975 and funded by the government, aims to deal with high rates of child mortality, malnutrition, and poor learning outcomes. It provides a package of services (medical checks, immunisations, referral services, supplementary feeding, preschool education, and health and nutrition education for adolescent girls and mothers) through a network of 1.4 million Anganwadi (courtyard) centres and workers. In 2014, the scheme served 104.5 million beneficiaries, including 46.7 million children between birth and 3 years, 38.2 million children between 3–6 years, and 19.6 million pregnant and lactating women. Many different government departments and programmes are involved, led at the central level by the Ministry of Women and Child Development. Although the government committed to universalising ICDS for all eligible beneficiaries in 1995, the political will to truly expand and enhance the programme has only been evident in recent years and the programme continues to be under-resourced. ICDS was restructured in 2013–14 to shift focus on children younger than 3 years of age, convert Anganwadi into Early Childhood Development

Centres, strengthen the early childhood stimulation and early learning components, improve infrastructure, and allow flexibility in implementation.

Grade R in South Africa: a universal school preparatory year provided through public education and non-governmental community programmes

A comprehensive early childhood development programme to address inequalities arising from racist policies was envisioned by anti-apartheid activists working to prepare for a post-democratic education system (appendix pp 40–43). Since then, commitment to address poverty and inequality from the beginning of a child's life has been reiterated by government and backed by civil society. A preschool or reception year was planned as part of the programme, and a pilot programme implemented in 1997; Grade R was introduced nationally in 2005. 10 years later, some 80% of children aged 4.5–6 years attend a free preschool class (Grade R), most attached to public primary schools but also at some accredited, government-funded, community-based crèches. The highest uptake has occurred in the poorest areas of the country as parents take advantage of low-cost and safe child day care, a school lunch programme, and the expectation that their children will be better prepared for formal schooling. Grade R is built on the education system, including teacher training, management, financing, monitoring, and quality control. School health services are provided, including disability screening. The programme as a whole is coordinated by an inter-departmental steering committee led by the Minister of Social Development, who reports to the Cabinet. Under the new South African National Early Childhood Development Policy, a pre-Grade R class (starting at age 3.5 years) is planned, as is a re-invigorated programme aimed from pregnancy to age 3.5 years to promote maternal wellbeing and early childhood development through the health sector.

Bangladesh's child development centres (Shishu Bikash Kendra [SBK]): a public–private partnership to support young children with disabilities and their families

A public–private partnership, funded through a combination of government and development resources, was established in 2008 to ensure early screening, assessment, intervention, treatment, and management of the entire range of developmental delays, disorders, impairments, and disabilities (appendix pp 44–47). The Dhaka Shishu Hospital and the government's Health, Population, and Nutrition Sector Development Programme have established child and family-friendly SBK centres within key public hospitals across the country. Core teams of multidisciplinary professionals (child health physicians, child psychologists, and developmental therapists) have been trained to provide services, including psychosocial services, to families and to empower parents and primary care providers to optimise their child's development.

(Continues on next page)

(Panel 2 continued from previous page)

Multidisciplinary SBKs provide a range of free services to poor families in 15 tertiary government hospitals, extended recently to eight semi-government and private hospitals to meet the needs of relatively high-income urban families. Services are anchored in paediatric outpatient departments to reach at-risk children from birth through adolescence, to facilitate linkages with other relevant clinical departments, and to build the competence of undergraduate and postgraduate medical students. A partner

non-governmental organisation for developmentally disabled children has established early mother-child intervention programmes and inclusive schools offering school meals adjacent to several of the SBKs where children are referred for education and rehabilitation. Between 2009 and 2016 there were more than 200 000 child visits to the 15 government hospital SBKs, with up to three-quarters of children showing neurodevelopmental improvement on follow-up.

RMNCH services are important entry points for early childhood development interventions.⁵³

Many existing programmes for early childhood development are built on health services, and 11 of 15 such programmes identified by Engle and colleagues³ showed positive effects. There are several other country reports of the feasibility of building activities for early childhood development into health and nutrition services,⁵⁴ and an inventory of CCD implementation illustrates integration into health services in a range of countries (appendix pp 7–14).

We identified multiple opportunities in health and nutrition services into which interventions to promote nurturing care and improve child developmental outcomes have been feasibly and effectively incorporated (panel 3; appendix pp 71–76). These interventions can be provided by non-specialist trained providers within primary health care and community services.

Opportunities also exist in other sectors, which is important for the continuity of support from early childhood into schooling. For example, in the education sector, child development can be supported through various early learning opportunities, including early child day care,^{67,68} preschools, and parent education.^{59,69} Interventions can also be provided through child and social protection services, including cash transfer programmes.^{70,71}

To effectively integrate interventions into existing services, a systematic approach is required to prepare the system. This approach involves learning about implementation in a scalable unit such as a district, and testing and further refining the approach in different settings before scaling up. National and local institutions must be strengthened to ensure that staff have adequate competencies to deliver the services with high quality and that there is community demand for services. The approach requires systems investments that align with the principles of universal coverage.^{72,73}

Governance of multisectoral coordination and monitoring to deliver quality services equitably

Responsibility for multisectoral coordination typically lies with a senior lead government department or agency working collaboratively with other departments and civil society organisations, usually reporting to the Cabinet or other senior government executive. However, there is no

established precedent for how to organise governance of programmes for early childhood development; there are multiple potential entry points and several models of coordination are in place. Sectors can serve children and families independently under a structure for sharing responsibility (eg, China, Cameroon), with so-called zones of convergence that are nationally planned, provincially guided, and flexibly adapted at a local level.⁷⁴ Coordination can also be organised under a single ministry, in collaboration with other sectors, for example through a multisectoral committee (eg, South Africa, India, Bangladesh [panel 2], Jamaica, Brazil).⁷⁵ A third approach is coordination through a high-level central council or similar body (eg, Colombia,⁷⁴ Chile [panel 2],⁷⁶ Ghana, Rwanda).⁷⁵

Affordability

To assess the affordability of incorporating interventions to promote early childhood development into existing health and nutrition services, we estimated the additional costs of two interventions aimed at supporting nurturing care of children. The first is based on CCD and the second on support for maternal depression, based on the WHO Thinking Healthy package, because it bolsters nurturing care.⁷⁷ We selected these two interventions because they are well defined, have proved effective, and have sufficient available data about their costs for a simulation.

We modelled the effects of expanded coverage for these two interventions towards universal coverage by 2030. We used an integrated approach to estimate the use of existing services and systems, and the health worker requirements to scale up these services (appendix pp 77–86). The analysis covered 73 high-burden countries, and two scale-up scenarios (medium and high) compared with a scenario of maintained current coverage (low). The high scale-up scenario would attain 98% coverage by 2030 among all parents in these countries, whereas the medium scale-up projection would lead to, on average, 58% coverage. Resource needs were modelled by country and year (2016–30), with inputs based on WHO recommended practices and applying country-specific price data.

Table 2 shows that the additional investment for attaining the high coverage scenario over the next 15 years would total US\$34 billion for both interventions. The average

	Benefits	Progress*	Gaps
Paid parental leave for new mothers and fathers	Paid maternity leave is associated with multiple health benefits for children. It can support bonding between mother and child, increase initiation and duration of breastfeeding, and improve the likelihood of infants being vaccinated and receiving preventive care. ^{33,34} New fathers are more involved with their young children when they take leave from work and they take on more child-care responsibilities after the leave ends ³⁵	Since 1995, eight countries have enacted paid maternal leave, 55 approved an increase in leave duration, and 21 increased their wage replacement rates. The proportion of countries across all income groups offering full pay or close to it grew from 66% in 1995 to 73% in 2014. Today in all but eight of 193 UN countries, paid maternal leave is guaranteed and most countries provide at least 12 weeks of leave, paying at least two-thirds of workers' wages. More than three-quarters of countries with paid maternal leave guarantee between 85% and 100% of wages for all or part of the leave period through some combination of employer, employee, and government contributions	Paid parental leave covers the informal sector in some countries but not in all. Although 49% of countries encourage men to participate in caregiving by making leave available to both mothers and fathers, only 40% of countries provide paid leave specifically designated for fathers, and only one in five of these provide it for more than 2 weeks, far shorter than for mothers
Breastfeeding breaks at work	Breastfeeding has substantial benefits for maternal and child health and development. It significantly reduces risks of infant mortality, diarrhoeal disease, respiratory illness, malnutrition, and chronic diseases, and improves neurocognitive development. ³⁶ The guarantee of paid breastfeeding breaks is associated with increased rates of exclusive breastfeeding ³⁷	In the past 20 years, the global share of countries that have laws providing for breastfeeding breaks increased from 63% to 72%, which in the vast majority of cases is paid. South Asia and the Middle East and north Africa have shown the largest increases (>15%) between 1995 and 2014. 72% of countries guarantee breastfeeding breaks for at least the 6 months WHO recommends for exclusive breastfeeding. In 22% of countries both paid breastfeeding breaks and paid maternal leave are guaranteed for this period ³⁸	Access to breaks for breastfeeding is variable in the informal sector and many women are unable to breastfeed in formal jobs if a location for pumping and refrigeration of breastmilk is unavailable or child care is far from work
Paid leave for child health care	The ability to take leave to care for children's health is crucial to nurturing care for young children ³⁹	45% of countries provide paid leave for mothers or fathers that could be used to tend to children's health needs, 10% provide unpaid leave, and 3% provide paid leave but only to mothers	Large gaps remain because 42% of countries still do not guarantee leave, paid or unpaid, to address children's health needs, and parents in the informal economy have no provision
Income support—minimum wage	When parents are not able to earn adequate income, children's basic needs, including health care and education, cannot be met and early childhood development suffers. Policies that support poverty-reducing growth have a crucial part to play in reducing the number of young children raised in poverty. ⁴⁰ Although the evidence is somewhat mixed, an adequate increase in minimum wages has the potential to improve the lives of millions of children whose parents work in the formal economy. ^{41,42} Minimum wages might also raise earnings of workers in the informal economy ⁴³	As a means to lift workers out of poverty, minimum wage policies are in place in 88% of countries. Unemployment insurance is a crucial safety net for families when they face individual work disruption and during national economic downturns	Although in 41% of countries a minimum wage of more than purchasing power parity-adjusted US\$10 per day is mandated, many countries still do not guarantee an income that is above the international poverty level of \$2 per day per person for a parent supporting a child; 12% of countries have not set an official minimum wage level, and in many countries (55%) the growth in minimum wage lags behind the growth of gross domestic product (figure 2). Although 90% of countries provide income protection during unemployment, the informal economy is mostly not covered
Tuition-free pre-primary education	Developmentally appropriate early education is crucial to child cognitive development, ensuring future successful learning experiences in diverse contexts. ⁴⁴ It is important for children across all demographic groups to have access to tuition-free primary school. The estimated benefit-to-cost ratio for investments targeted at increasing preschool attendance in low-income and middle-income countries ranges from 6·4:1 to 17·6:1 ³	Primary school is prioritised globally and there is significant progress toward universalisation, but there are marked disparities in pre-primary educational preparation: only 43% of countries with available policy data provide at least 1 year of tuition-free pre-primary education. Of these, only 4% are low income (figure 2). The average gross enrolment rate is 34 points greater for countries with free pre-primary education (80%) compared with countries where it is neither tuition-free nor compulsory (46%)	Free pre-primary education is not available even in many high-income countries. In 40% of high-income countries and in 57% of middle-income countries, free pre-primary education is not available. Only 9% of countries in sub-Saharan Africa, 19% of countries in east Asia and the Pacific, and 20% of countries in the Middle East and north Africa offer at least one free pre-primary year. Only 25% of countries provide the recommended 2 years of tuition-free pre-primary education, ⁴⁵ most of which are middle-income and high-income countries (92%), mostly located in Europe and central Asia or Latin America and the Caribbean

*Sample size varies based on the availability of globally comparative data. The sample size for paid leave for mothers and fathers of infants is 193 countries; for breastfeeding breaks is 192 countries; for paid leave for child health care is 185 countries; for minimum wage policies is 177 countries; for income support during unemployment is 182 countries; and for tuition-free pre-primary education policies is 163 countries. For further details and to download the original dataset, please visit www.worldpolicycenter.org.

Table 1: Policies to support parental income and nurturing care needed to promote early childhood development

additional investment needed for the supply side of the health system is half a dollar per capita in the year 2030, ranging from US\$0·20 in low-income countries (which have lower prices than in high-income countries) to \$0·70 in upper-middle-income countries per year. In the medium coverage scenario, the additional cumulative total investment needed for the intervention is estimated at \$16 billion, equivalent to \$0·20 per person per year. For both interventions, service delivery costs through primary care are the main cost driver at 83% of cost, followed by

15% for training and communication or media, and 2% for commodities to support maternal depression interventions.

An average half a dollar per person, per year represents an additional 10% over previously published estimates for a comprehensive set of RMNCH services.⁷⁸ Current empirical evidence and these modelled data suggest that interventions to promote nurturing care can be added to existing platforms for health delivery at little additional cost. Given the large number of assumptions used in our model (appendix pp 77–86), our cost

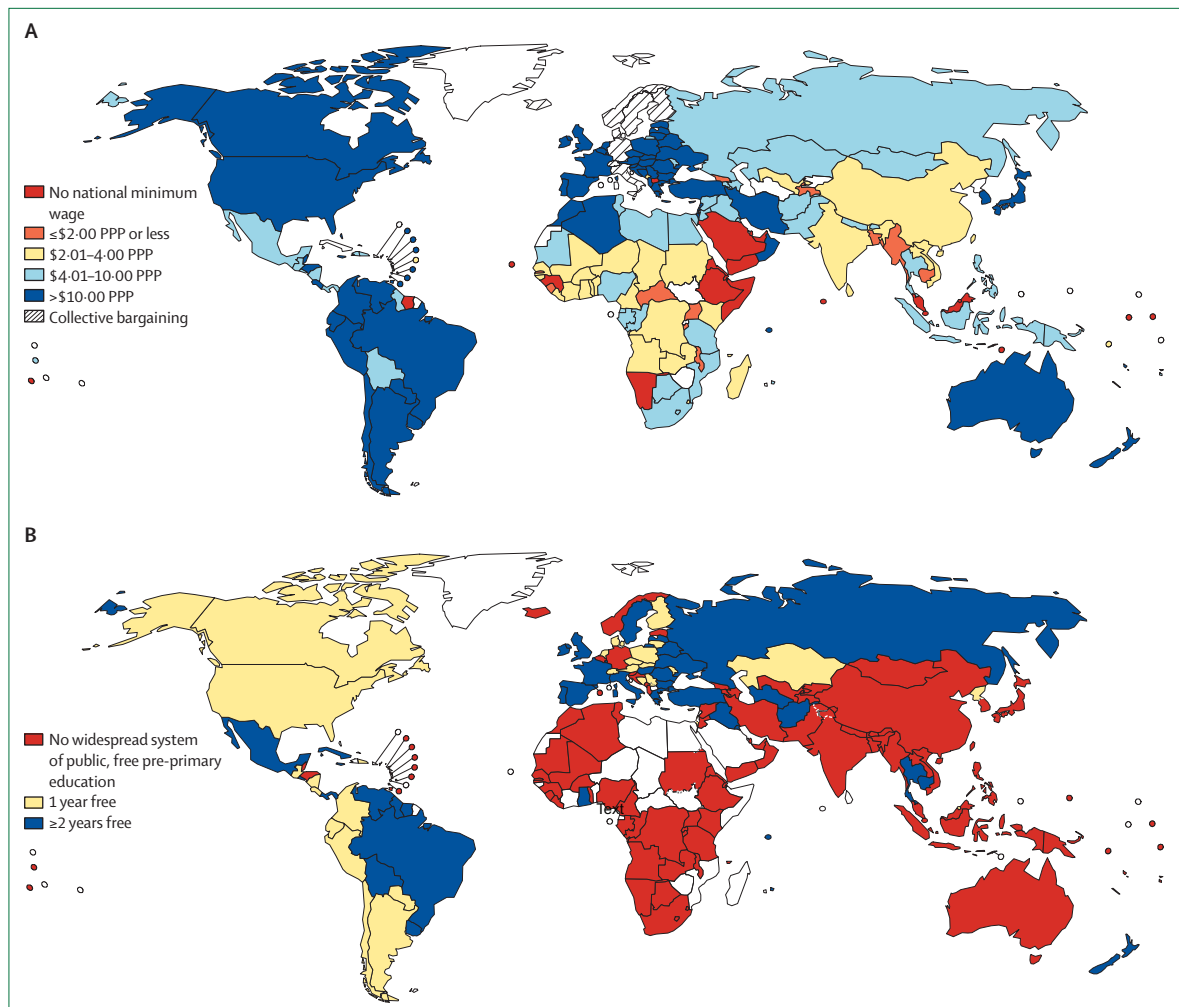


Figure 2: Global provision of minimum wage (A) and free pre-primary education (B) in 2012

Figures prepared using data from the WORLD Policy Analysis Center: Public Use Data on Poverty (appendix pp 48–58).⁴⁶ PPP denotes the amount of money required to purchase the same bundle of goods and services across countries. For international comparability, minimum wages established by law are converted to daily rates and adjusted using the PPP. Pre-primary education is defined as ISCED-0, educational early childhood services and programmes attended by children from the age of three up to the age of entry into primary school.⁴⁷ PPP=purchasing power parity.

estimates should be interpreted as indicative. Although data for the cost-effectiveness of nurturing care interventions are scarce,⁷⁹ available evidence suggests that implementation of these interventions represents value for money. More data are needed about the coverage and benefits of interventions to improve nurturing care using a lifetime perspective of their effects on health, wellbeing, and adult productivity and income, especially from LMICs.

The personal and societal costs of inaction

Interventions to integrate and promote child development within RMNCH services are feasible (panel 3) and affordable (table 2). In this section, we demonstrate that the costs of not acting immediately to expand services to improve early childhood development are high for individuals and their families, as well as for societies.

To estimate the lifelong disadvantage for individuals of global inaction, we updated the average percentage loss of adult income per child at risk of suboptimal development (estimated in 2007),² and incorporated additional data about associations between schooling and adult income.^{80,81} For the 43% of children estimated to be at risk of poor development due to extreme poverty and stunting, their average percentage loss of adult income per year is likely to be 26% with uncertainty levels between 8% and 44% (appendix pp 87–89), exerting a strong downward economic pull and trapping families in poverty.

To estimate societal costs, we simulated illustrative costs of inaction (ie, the net benefits forgone that depend on both benefit–cost ratios and the extent of undercoverage) of not intervening to improve early healthy development. The costs of inaction are not a substitute for benefit–cost ratios for marginal decisions. The simulations were made

Panel 3: Evidence of effective inclusion of early childhood development interventions in health and nutrition services

Hospital inpatient care

- Kangaroo Mother Care for preterm and small-for-gestational-age (SGA) babies has been found to contribute to reduced risk of infections and improved breastfeeding and growth, maternal–infant bonding and maternal confidence, survival,⁵⁵ and cerebral motor function during adolescence.⁵⁶

Follow-up after discharge

- Post-hospital discharge follow-up of preterm infants, including early stimulation, is associated with improved infant motor development and infant intelligence quotient, persisting into preschool age.⁵⁷

Maternal and child primary care services, including antenatal, childbirth, and postnatal care, as well as sick and well child visits

- Maternal care, including promotion of breastfeeding antenatally and optimising maternal nutrition and care reduces SGA.⁵⁸
- A parenting intervention integrated into primary care visits in three Caribbean countries improved parenting knowledge and child cognitive development.⁵⁹
- Care for Child Development (CCD) as part of sick child consultations in health facilities in Turkey resulted in home environments with increased learning opportunities at 1 month follow-up.²⁰
- CCD delivered as part of well child visits in health facilities in China resulted in higher cognitive, social, and linguistic scores 6 months after intervention.²¹
- A home stimulation programme for caregivers to implement with their HIV-infected children was supervised during regular 3-monthly clinic visits in South Africa, which resulted in significantly higher cognitive scores at 12 months.⁶⁰
- Developmental monitoring of children in primary health-care services has been found to be an effective, family-centred strategy to identify children with developmental difficulties or delays, parent education and support, and timely referral to other services for further assessment and early interventions.⁶¹

Home visiting services, community groups, and community outreach

- A meta-analysis of perinatal interventions for maternal mental health done through home visits found maternal benefits in addition to, when measured, improved child cognitive development, growth, and immunisation.⁶²
- Children who participated with their mothers in CCD play groups, led by lady health workers in Pakistan (and reinforced by home visits), showed higher developmental outcomes and had fewer episodes of illness than the controls; and their mothers showed a reduction in maternal depression, compared with children who did not participate.¹⁹
- Home-based early stimulation and support integrated into primary care visits in Jamaica improved parenting knowledge and child cognitive development.⁵⁹
- Group-based, peer-mediated parent training for caregivers of children with developmental disorders in Pakistan led to improvement in children's disability and socioemotional difficulties, reduction in stigmatising experiences, and enhanced family empowerment to seek services and community resources for the child.⁶³

Nutrition interventions to prevent and treat under-nutrition

- Child stimulation, delivered together with food supplementation, enabled malnourished children in Jamaica to achieve developmental scores similar to those of non-malnourished children, and enhanced their educational attainment and economic productivity compared with untreated malnourished children.^{64,65}
- Several trials examining potential synergies between nutrition and early child stimulation interventions have shown mixed results.^{19,54} Findings from a systematic review⁶⁶ suggested that nutritional interventions benefit nutritional and sometimes developmental status, stimulation interventions consistently benefit child development, but not nutrition, and too few studies to date have examined synergies to draw conclusions.⁶⁶

for selected developing countries with sufficient data under strong assumptions and limitations, and we provide sensitivity analysis for alternative values of the key underlying benefit–cost ratios (appendix pp 94–119). Some costs of inaction are apparent in infancy, and others emerge in later childhood, but many effects are not fully manifested until adulthood. Median benefit–cost ratios have been estimated by others to be roughly 18:1 for stunting reduction,⁸² 4:1 for preschool education, and 3:1 for home visits for children with signs of language delay,¹² making them good investments.

We computed the aggregate costs of inaction and their standard errors from available data for not reducing stunting to 15% prevalence (table 3)⁸³ and not improving child development through universal preschool coverage

and home visits for children with scores of 2 SD or more below the mean on a language development test (table 4).⁸⁴ For both scenarios, we adopted a 3% discount rate and a 30 year time horizon in the labour market. We calculated the costs of inaction as a percentage of gross domestic product (GDP) and for comparison also provide annual country expenditure on health (for stunting) and education (for preschool and home visit coverage) as percentages of GDP.

The costs of inaction as a percentage of GDP are given with their standard errors, calculated with several assumptions (appendix pp 94–119), including that estimates of costs and impacts based on small studies, not nationwide interventions, can be scaled up without reducing benefit–cost ratios substantially. Simulations of

	Country category	Number	High prevalence scenario		Medium prevalence scenario	
			Additional costs compared with low scenario (total 2016–30), billion US\$	Additional per-person costs compared to low scenario (year 2030)	Additional costs compared with low scenario (total 2016–30), billion US\$	Additional per-person costs compared to low scenario (year 2030)
Nurturing care and support for maternal depression combined	Upper middle income	11	17.3	0.7	8.5	0.3
	Lower middle income	32	15.5	0.4	6.6	0.15
	Low income	30	1.6	0.2	0.9	0.1
	Total	73	34.46	0.46	16.0	0.21
Nurturing care only	Upper middle income	11	8.0	0.3	4.1	0.2
	Lower middle income	32	7.4	0.2	3.4	0.1
	Low income	30	0.7	0.1	0.4	0.0
	Total	73	16.10	0.22	8.00	0.11

Table shows estimates for scaling up of nurturing care for children and support for maternal depression in 73 countries, in 2011 US dollars (appendix pp 77–86).

Table 2: Affordability calculated as additional estimated costs for scaling up support

	Costs of inaction as proportion of GDP (SE)	Total governmental expenditure on health as proportion of GDP
Bangladesh	5.6% (1.82)	3.7%
Democratic Republic of the Congo	2.5% (0.86)	3.5%
Ethiopia	7.9% (2.57)	5.1%
India	8.3% (2.65)	4.0%
Kenya	5.4% (1.75)	4.5%
Madagascar	12.7% (4.17)	4.2%
Nepal	3.4% (1.12)	6.0%
Nigeria	3.0% (0.96)	3.9%
Pakistan	8.2% (2.65)	2.8%
Tanzania	11.1% (3.59)	7.3%
Uganda	7.3% (2.37)	9.8%

Table shows estimates based on seven sub-Saharan African and four south Asian high-prevalence countries with sufficient data. GDP=gross domestic product. SE=standard error.

Table 3: Costs of inaction for not reducing stunting to 15% prevalence

how costs of inaction change with different benefit–cost ratios are provided in the appendix (pp 94–105). There are also considerable challenges in estimating impacts, particularly those that occur after substantial lags. Further, the estimates are context-specific and contexts are likely to vary importantly (eg, with regard to prices, resources, preferences, or macroeconomic conditions) across countries and over time. Our assumption is that, in the future, contexts will yield about the same returns to reducing stunting as found in the past. Finally, our estimates do not adjust for possible general equilibrium effects on returns to more skilled workers, which might work in either direction depending on the induced shifts in supplies of and demands for such workers.

Total government health expenditure covers the provision of health services (preventive and curative),

	Cost of inaction as a proportion of GDP (SE)		Total governmental expenditure on education as total proportion of GDP
	Home visits	Preschool	
Guatemala	1.4% (0.96)	3.6% (0.94)	2.8%
Nicaragua	2.1% (1.38)	4.1% (1.08)	..
Colombia	0.2% (0.14)	0.9% (0.24)	4.9%
Peru	0.1% (0.11)	0.4% (0.12)	3.3%
Ecuador	0.3% (0.21)	0.2% (0.05)	4.2%
Chile	0.05% (0.02)	0.3% (0.07)	4.6%

Table shows estimates for identified children in six Latin American countries with sufficient data. GDP=gross domestic product. SE=standard error.

Table 4: Costs of inaction of not improving child development through universal preschool and home visits

family planning activities, nutrition activities, and emergency aid designated for health, but does not include provision of water and sanitation or the private cost of time in health-enhancing activities (appendix p 97). The costs of inaction as a percentage share of GDP do not change if both the numerator and denominator are adjusted for general price movements between 2011 and 2013 (appendix pp 94–119).

The costs of inaction as a percentage of GDP are given with their standard errors calculated on the basis of the underlying estimates (appendix pp 94–119), described above. General governmental expenditure in 2013 on education (current, capital, and transfers) includes expenditure funded by transfers from international sources to governments.⁸⁵

Given our assumptions, the costs of inaction for stunting in high prevalence countries are large. For instance, India is experiencing costs of inaction twice what it currently spends on health by not taking action to reduce stunting from 48% to 15%. These costs are

Contribution of improved early childhood development to achieve the goal	
Goal 1: eradicate poverty	Early childhood development interventions increase adult productivity and income, and reduce inequities ⁶⁵
Goal 2: end hunger and improve nutrition	Interventions to promote nurturing care help to improve young children's growth and development ⁹¹
Goal 3: ensure healthy lives	Supporting early childhood development increases quality of home care practices, protects against stress, increases timely care seeking for childhood illness, and reduces risks of chronic disease and mental ill health in adulthood ⁹²
Goal 4: ensure lifelong learning	Early stimulation increases duration of schooling, school performance, and adult income ^{65,81,82}
Goal 5: achieve gender equality	Early childhood development interventions improve opportunities and motivation for learning, particularly for girls, so that boys and girls can benefit equally from schooling and enter the job market ⁹³
Goal 10: reduce inequality in and among countries	Early childhood stimulation and food supplementation interventions enable children with low birthweight or stunting, or living in extreme poverty, to attain developmental outcomes similar to their peers ^{3,44,64}
Goal 16: promote peaceful societies	Children who are well nourished, healthy, and secure have improved coping strategies, even in conditions of adversity ⁹⁴
Goal 17: strengthen the means of implementation	Early childhood development interventions have the potential to strengthen coordination across sectors for common health, social, and economic goals, and to bring together international, governmental, and civil society partners (panel 2)

SDG=Sustainable Development Goal.

Table 5: Investing in early childhood development is essential for attainment of the SDGs

considerable: \$176·8 billion (95% CI 100·9–262·6) per birth cohort at nominal exchange rates; and \$616·5 billion (365·3–898·9) at exchange rates adjusted for purchasing power parity.⁸⁶

The costs of inaction for not improving child development through preschool education are lower than for stunting, because of fairly good access to preschools in these countries (table 4; appendix pp 106–119). However, the costs of inaction for not improving child development through preschool and home visits rise sharply in settings with few preschool services, as is the case in Guatemala (35% of children in preschool) and Nicaragua (40% of children in preschool), in addition to settings with high prevalence of children at risk of poor development, which is anticipated for many countries in south Asia and sub-Saharan Africa.

Although the uncertainty is fairly large, as reflected in the standard errors, the simulated means seem to be considerably different from zero for both stunting and preschool interventions. For home visits, the simulated means are relatively high, in particular for Guatemala and Nicaragua, but with a large amount of uncertainty.

Pathways to scaling

“The Sustainable Development Goals recognise that early childhood development can help drive the transformation we hope to achieve over the next 15 years.”

UN Secretary-General Ban Ki-moon, Sept 22, 2015.

In line with global strategies and action frameworks that support the SDGs,^{87,88} we suggest five actions to accelerate global scale-up of early childhood development across multiple sectors that reach the most disadvantaged children.

Expand political will and funding through advocacy for the SDGs

The SDGs call for equitable opportunities for people everywhere to achieve their full potential, and for all countries to prioritise the most vulnerable and those currently left the farthest behind. Millions of children are currently denied the possibility to lead safe, decent, dignified, and rewarding lives and to access lifelong learning opportunities that enable them to participate fully in society. There are gross inequalities in children's exposure to factors that threaten their development. The life course perspective of the SDGs provides new impetus for collaboration and innovation to protect and support early childhood development and advance global progress towards equity and lifelong opportunities for all.

The MDGs showed that investments and areas of action in focus can be increased rapidly.^{89,90} Under the broader SDG umbrella, investment in early childhood development has become not only an aim in itself, but also a requisite to achieve the SDGs to address poverty, inequality, and social exclusion and to promote peace and security (table 5). SDG target 4.2 under the learning goal provides unprecedented opportunity to scale up early childhood development services for young children, and has been integrated in the Global Strategy for Women's, Children's and Adolescent's Health, as well as the Strategic Plan (2014–20) of the Global Partnership for Education.

This definitive moment is stimulating bold new commitments and actions by national policy makers and the global stakeholder community to intensify and coordinate investments in early childhood development. Global leadership in the UN (eg, WHO, UNICEF, World Bank) has signalled support for the health sector to use its reach to pregnant women, families, and young children to promote early childhood development.^{95–97}

Encourage the adoption and monitor the implementation of policies to create supportive environments for families to provide nurturing care for young children

Our conceptual framework (figure 1) identifies key interventions (panel 1) across several sectors that are needed to achieve benefits⁹⁸ across the lifecycle and into subsequent generations.⁹⁹

Governments, with the technical and funding assistance of development partners, must ramp up efforts to analyse their situation, identify gaps and priority areas for intervention, and develop sustainable and costed action plans to promote early childhood development at scale. Local considerations of costs and cost-effectiveness drive where and how much to invest. Additional empirical data are needed about cost-effectiveness of the full range of early childhood development services, beyond those modelled in table 4. Nevertheless, the evidence for effective interventions (panel 1)¹⁰⁰ and for programmes and policies at scale (panel 2) shows that investment in early childhood development can be made through mutually reinforcing policies and services across different sectors (figure 1).¹⁰¹

Build capacity to promote early childhood development through existing health, nutrition, education, social, and child protection services

Based on our analysis of scaled up programmes, the integration of interventions for early childhood development into existing platforms for service delivery is an effective and efficient way to reach large numbers of families and children.^{72,102} Although there is no uniform pathway to scale up services for early childhood development, we highlight three key considerations.^{72,102}

First is local adaptation. Services need to be adapted to local context, address existing beliefs and practices, and be delivered through channels that are acceptable and feasible. Findings from multiple studies¹⁰³ have shown the importance of engaging community members at an early stage to create understanding, build ownership, and make optimal use of local resources. Formative research is needed, as a principle, to complete a rigorous process of adaptation design and testing.¹⁰⁴

Second is competency-based capacity building. Front-line workers (eg, physicians, nurses, midwives, and community health workers) are usually the first point of contact for young children and their families. However, basic training curricula for primary health workers often do not include the essential knowledge and skills to promote early childhood development.

Pre-service and in-service training are the two most common opportunities to build competencies. A review of principles related to fidelity, quality, and capacity for integration of child development into health services found that a structured curriculum, concrete messages,¹⁰⁵ and supportive supervision are important to ensure quality of services.¹⁰⁶

The final consideration is ensuring quality of care. Incremental scale-up, rapid learning cycles, and continuous improvement are essential to establish and maintain quality and coverage of services and achieve impact at scale.¹⁰⁷ Among many challenges is the already stretched health workforce, giving impetus to the movement to expand paraprofessionals (including community health workers) and families as resources to support nurturing care for children.^{108,109} Technology can facilitate training, service delivery, data collection, and programme improvement.¹¹⁰

Strengthen multisectoral coordination in support of early childhood development and facilitate community engagement

In many countries, services for early childhood development are provided through a disjointed set of non-governmental organisations that can be brought together with government services, as has been done in the Chile Crece Contigo programme (panel 2). Bridges must be built between health and nutrition, education, and social and child protection, among others, to address the multiple needs of young children, especially the most vulnerable.

Often, even when high-level horizontal coordination is achieved, implementation and integration frequently fall short at the local level. Therefore, vertical coordination to local levels is also needed to ensure effective implementation.

More attention must be given to engagement of families and communities to understand the importance of early childhood development and the crucial part they play in their children's learning. This engagement further enables families and communities to demand and monitor quality of services to support their young children.¹⁰⁶

Ensure accountability for early childhood development services, increase research, and foster global and regional leadership and action

Accountability is essential to strengthen coordination of early childhood development services, including through improved data collection, analysis, and action. A global monitoring framework with clear indicators of policies, programmes, and outcomes for early childhood development is needed.¹¹¹

Ensuring the inclusion of a core set of indicators—which go beyond access and process, and hold stakeholders accountable for child development outcomes—in the global metrics for the SDGs is of paramount importance. SDG target 4.2, which calls for universal access to high-quality early childhood development, care, and pre-primary education, most directly addresses early childhood development (table 5).¹¹² The Global Partnership for Education 2020 and the global community united under Every Woman Every Child have a unique opportunity to support

indicator 4.2.1: “Percentage of children under 5 years of age who are developmentally on track in health, learning and psychosocial wellbeing.” Indicators of early childhood development outcomes and of household resources and caregiver behaviours are included in Demographic and Health Surveys and Multiple Indicator Cluster Surveys and work is underway to expand these to cover children 0–3 years of age.

Although the scientific evidence for investing in early childhood development is strong, more is needed to generate political will. Research that links detailed longitudinal data about policies and programmes with outcomes, allowing causal modelling, is essential. An initial policy and research agenda has been developed through a WHO-led research priority exercise for early childhood development using the Child Health and Nutrition Research Initiative methodology.¹¹³ Key themes emerging from the exercise include awareness and promotion, identification of risk factors, indicators, impact of interventions, implementation science for interventions, integration and coordination, and use of health economics and social protection strategies.¹¹⁴

We suggest the appointment of a UN Special Advisor for Early Childhood Development as a way to put the issue high on political agendas, facilitate coordination, and promote accountability. The shift in focus from child survival to child development has been solidly initiated under the umbrella of the SDGs. We must now act to ensure that the investments are made in early childhood development that are essential for the future health, wellbeing, economic productivity, prosperity, peace, and security of individuals and nations.

Conclusion

Strong biological, psychosocial, and economic arguments exist for intervening as early as possible to promote, protect, and support children’s development, specifically during pregnancy and the first 2–3 years.^{5,6} An emphasis on the first years of life is articulated within a life course perspective that also requires quality provisions at older ages, especially during child day care and preschool, following on through schooling and into adolescence so as to capitalise on dynamic complementarities between investments made during successive lifecycle stages.¹¹⁵

Health services are particularly well placed to reach children early with services that support families to deliver nurturing care and facilitate early childhood development.^{52,100} Coordination with education is needed to promote learning, and with social and child protection to reach the most vulnerable populations. Evidence consolidated in this Series points to effective interventions and delivery approaches at a scale never envisaged before. All sectors must play their part in supporting families to provide nurturing care for children. However, the time has come for the health sector to expand its vision of health beyond prevention and treatment of disease to include the promotion of nurturing care for

young children as a crucial factor in the realisation of the human potential of all people. The UN Secretary General’s new Global Strategy for Women’s, Children’s and Adolescents’ Health provides the framework to translate this vision into action and, together with education, social, and child protection, and other sectors, build the foundation for “the transformation we all hope to achieve over the next 15 years”.

Contributors

LMR, GLD, BD, and JL conceptualised and wrote the paper. LMR, ZAB, RP-E, and JEL did literature reviews. JH, FLB, JRB, CL, TD, ZAB, KS, PG, and RP-E did data analysis and interpretation. JH and LMR contributed figures. All authors reviewed the drafts, made critical additions and editions, and approved the final submission.

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Declaration of interests

We declare no competing interests.

Acknowledgments

We thank L Curry and K G Watt. Funding for the preparation of the Series, including three meetings of the authors, was provided by the Bill & Melinda Gates Foundation and the Conrad N Hilton Foundation through the US Fund for UNICEF and WHO, respectively. The sponsors had no role in conceptualising, analysing, interpreting, or writing the paper.

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