

Manuscript Number:

Title: Nurturing Care: Science and Effective Interventions to Promote Early Childhood Development

Article Type: Invited Series

Keywords: Early Child development, interventions, systematic review, health, education, nutrition, child protection, social protection, intervention packages,

Corresponding Author: Dr. Pia Britto,

Corresponding Author's Institution: UNICEF

First Author: Pia Britto

Order of Authors: Pia Britto; Pia Britto; Stephen Lye; Kerri Proulx; Aisha Yousafzai; Stephen Matthews; Rafael Perez-Escamilla; Nirmala Rao; Patrick Ip; Lia Fernald; Harriet MacMillan; Mark Hanson; Theodore Wachs; Haogen Yao; Tyler Vaivada; Hirokazu Yoshikawa; Adrian Cerezo; James Leckman; Zulfiqar Bhutta

Abstract: Abstract

Background

Even though global attention to early childhood development has been increasing, an estimated 43% of children under 5 years of age in low and middle income countries are not achieving their developmental potential (Black, et al., in series). The aim of this paper is to synthesize reviews of the new science and impact of interventions at critical time periods that address risk factors and conditions contributing to poor development outcomes.

Methods

We conducted a synthesis of systematic reviews of health, nutrition, education, child protection, social protection, and parenting interventions (from 2011-2015) from preconception through the transition to primary school. The interventions were intended to promote nurturing care and protection behaviours in addition to caregiver and child well-being. We also searched the reference lists of recent overviews in health and nutrition that included evidence-based interventions across the sectors.

Findings

Only a few interventions reviewed were multi-sectoral and most were implemented primarily as single sector interventions. To make them smarter and sustainable to improve developmental outcomes, the interventions need to: (i) include elements of nurturing care and protection; (ii) be implemented as packages that combine interventions across sectors to target multiple risks; (iii) be applied at developmentally appropriate times during the life-course; and (iv) build

on existing delivery platforms to enhance feasibility of scale-up and sustainability.

Interpretation

While interventions will continue to be improved as new understanding of early human development emerges, the evidence is now strong about what can be done to improve implementation and consequently improve the development, health, and well-being of young children. Drawing on this knowledge, action is needed to support parents, caregivers, and families in providing the nurturing care and protection that young children need to achieve their developmental potential.

Funding:

Bill and Melinda Gates Foundation

Conrad N Hilton Foundation

UNICEF

Nurturing Care: Science and Effective Interventions to Promote Early Childhood Development

Authors:

Pia Rebello Britto, Stephen Lye, Kerrie Proulx, Aisha K Yousafzai, Stephen G Matthews, Rafael Perez-Escamilla, Nirmala Rao, Patrick Ip, Lia C Fernald, Harriet MacMillan, Mark Hanson, Theodore Wachs, Haogen Yao, Tyler Vaivada, Hirokazu Yoshikawa, Adrian Cerezo, James F Leckman, Zulfiqar A Bhutta together with the Paper 2 Working Group and the Early Child Development Series Steering Committee

Paper 1

Black, M. et al. Early Child Development Coming of Age: From science to practice.

Paper 3

Richter, L.M. et al. Investing in the Foundations of Sustainable Development: Nurturing Care to Optimise Early Childhood Development

Author Affiliations

Pia Rebello Britto PhD, Senior Advisor, UNICEF

Prof Stephen Lye PhD, Executive Director, Fraser Mustard Institute for Human Development, University of Toronto

Kerrie Proulx PhD, Fraser Mustard Institute for Human Development, University of Toronto

Prof. Aisha K Yousafzai PhD, Department of Paediatrics and Child Health, Aga Khan University, Karachi, Pakistan

Prof. Stephen G Matthews PhD, Fraser Mustard Institute for Human Development, Departments of Physiology, Ob-Gyn and Medicine, University of Toronto, Toronto, ON, Canada

Prof Rafael Perez-Escamilla PhD, Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA

Prof Nirmala Rao PhD, Faculty of Education, The University of Hong Kong

Patrick Ip FRCPCH, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Prof Lia C. H. Fernald PhD, School of Public Health, University of California Berkeley, Berkeley, CA, USA

Prof Harriet MacMillan PhD, Departments of Psychiatry and Behavioural Neurosciences, and of Pediatrics, Offord Centre for Child Studies, McMaster University, Hamilton, ON, Canada

Prof Mark Hanson, MD, PhD, Institute of Developmental Sciences and NIHR Biomedical Research Centre, University of Southampton and University Hospital Southampton, UK

Prof Theodore Wachs PhD, Department of Psychological Sciences, Purdue University, West Lafayette, IN, USA

Haogen Yao PhD, Teachers College, Columbia University, New York, NY, USA

Tyler Vaivada MSc, Center for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada

Prof Hirokazu Yoshikawa PhD, New York University Steinhardt, New York, NY, USA

Adrian Cerezo, PhD, Department of Biology, University of Missouri, St. Louis, MO, USA

James F Leckman, MD, PhD, Yale Child Study Centre, Yale School of Medicine, New Haven, CT, USA

Prof Zulfiqar A Bhutta PhD, Center for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada

Paper 2 Working Group:

Kristin Connor, Andrea Constantinof, Alison Fleming, Michelle F Gaffey, Kristy Hackett, Alison Mildon, Vasilis G Moisiadis, Daniel W Sellen

Early Child Development Series Steering Committee:

Zulfiqar A. Bhutta, Maureen Black, Pia Rebello Britto, Bernadette Daelmans, Gary L. Darmstadt, Tarun Dua, Paul Gertler, Jody Heymann, Joan Lombardi, Florencia López Bóo, Stephen Lye, Harriet MacMillan, Rafael Perez-Escamilla, Nirmala Rao, Linda M. Richter (chair)

Acknowledgments:

MH is supported by the British Heart Foundation

Correspondence:

Pia Rebello Britto, UNICEF, 3 UN Plaza, New York, NY 10017
Pbritto@unicef.org

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Bill and Melinda Gates Foundation
Conrad N Hilton Foundation
UNICEF

Word Count: 277 words

Nurturing Care: Science and Effective Interventions for Early Childhood Development

Introduction

Even though attention to early childhood development (ECD) has been increasing globally, 43% of children under 5 years of age in low- and middle-income countries (LMICs) are at the risk of not achieving their developmental potential (Black, et al., in series). We suggest that our failure to enable these children to do so is, at least in part, due to our failure to exploit the scientific understanding of what shapes children's development and use that evidence to take action at scale.

A large array of social contexts – from home to parental work, child care, schooling, wider community, and policy influences – impact early childhood development (1). Arguably the single most powerful and proximal context is that of caregiving in the immediate home and care contexts of young children. Care provided is often primarily by mothers, but also by fathers, siblings, grandparents, and extended family and sometimes in communities through child care. The role of parents, which begins before conception, is essential for survival(2) and the legacy of parenting lasts beyond the transfer of genetic material.(3) Nurturing care and protection consists of a core set of inter-related functions: behaviours, attitudes, and knowledge of caregiving (e.g., health, hygiene care); stimulation (e.g., feeding care, behaviours through talking, singing, playing); responsiveness (e.g., contingent communication, early bonding, attachment, trust); and safety (e.g., routines, protection from emotional and physical harm).(4, 5)

The brain has evolved to adapt and modify in response to a wide range of positive and negative early experiences. Biobehavioural studies in recent years have also demonstrated that prenatal - and even preconceptional - environment can induce effects on the structure and function of the developing brain. The key processes through which experiences affect the infant's developing brain are through the care and protection received from parents and other caregivers. Nurturing care and protection promotes these developmental adaptations and reduces young children's exposure to adversity.

The literature on ECD interventions has expanded considerably (Black, et al., this series). Interventions to improve child health, growth, learning, and development are primarily sectoral and implemented through health, nutrition, education, parenting, and child and social protection interventions. Addressing the complexity of risks and adversity goes beyond single sector solutions to a comprehensive approach for enhancing young children's developmental potential, requiring combinations of interventions that can include nurturing care and protection in sectoral interventions. (6, 7) This may require a range of approaches including integration of interventions into packages as well as cross-sectoral coordination for implementation.

The aim of this paper is to synthesize systematic reviews of parenting, health, educational, nutritional, child and social protection interventions to highlight how programmes across different sectors can enhance nurturing care and protection and thereby improve early childhood development. Given that the sensitivity to experience varies across the early life course, the review is organized around developmental periods, starting from preconception through the transition to primary school. The recommendations emphasize how nurturing care and protection can be combined or packaged together with interventions across developmental periods and sectors. The recommendations also discuss how existing service platforms may be utilized to scale up the integration of nurturing care and protection (which are further elaborated upon by Richter et al. (this series) (3).

Nurturing Care Across Early Development: Implications Interventions

Advances in developmental science have provided an understanding of windows of time when development of specific capacities and abilities is nurtured.(8) A critical period is a maturational stage in the lifespan when the nervous system is especially sensitive to environmental stimuli. Critical periods are more clearly defined in the development of animal brains; in humans, there are multiple and overlapping sensitive and vulnerable periods with significant implications for periods of greatest sensitivity to interventions.(9) The review of the science is presented across the early life course because nurturing care and protection take on different forms based on the developmental stage of the young child. The review focused on the holistic nature of developmental outcomes that link health, growth, learning, and psychosocial well-being. Further the review takes into consideration risk and the experience of early adversity because universal approaches to interventions may need to be supplemented with more targeted approaches taking into consideration the intensity and chronicity of adversity.

The period of early human development is one of enormous change and is characterized by a high degree of plasticity in brain organization. (10, 11) The rapidly developing brain is highly sensitive to input from the surrounding world, which allows for the rapid acquisition of language, cognitive skills, and emotional, and social competencies. Nurturing experiences in the early years come first and foremost from the parents, but also from the wider family and the community. These experiences have lifelong benefits, including an increased ability to learn, greater achievement in school and later life, citizenship, involvement in community activities, and overall quality of life.(12, 13) Human infant development anticipates and relies on care by adults that is nurturing, caring, enriching, and protective. These interactions provide the early environments needed for developmental progression to occur and protect infants and children from the negative impact of stress.

Biological and psychosocial basis of caregiving behaviour

The onset of maternal and paternal caregiving in humans is triggered by hormonal signals beginning in pregnancy (e.g., oxytocin and lactogens) and through experiences in response to their infants.(14, 15) Hormones and experiences acquired during interactions with young children act through the medial preoptic area and downstream projections, as well as closely related systems, including the amygdala, mesolimbic and mesocortical dopamine systems, and prefrontal cortex. (14) These brain systems are activated in women and men in response to their infants.(16) Different brain systems enhance nurturing by supporting infant-mother attachment, as well as emotional wellbeing, learning and memory, attention, and executive functions.(17)

There is a growing literature showing that one of the most powerful predictors of caregiving behaviour is how caregivers, especially mothers, were cared for themselves.(18) Children who grow up neglected or abused by their parents, or under conditions of extreme distress within their families, are at risk of developing a host of unhealthy behaviours that affect their own lives. When these children grow up, they tend to be less equipped to take on a parenting role and, in the context of adverse circumstances and the absence of social support and/or intervention, they are more likely to perpetuate a cycle of adverse caregiving across generations. A mother's genes interact with her own early life experiences to alter her stress reactivity, affect her well-being, cognitive function, and nurturing care of infants and children.(19, 20)

Maternal nutrition and health

The importance of optimal nutrition and healthy body composition for young women during preconception and pregnancy on child outcomes is well established.(21-23) Maternal nutrition (both under- and overnutrition) influences fertility, oocyte development/maturation, pre-implantation development as well as fetal growth and development, and the health and cognitive development of offspring in later-life. (22, 24, 25) Evidence suggests that linear growth is correlated across generations (26) and short maternal stature is associated with low birth weight, stunting, childbirth complications, and increased child mortality. There is also strong empirical evidence supporting a link between maternal obesity and offspring obesity as a result of epigenetic mechanisms affecting the fetus and young child.(27) The ability of a mother to support the health and development of her children is critically dependent on her own health and well-being before, during, and after pregnancy. Exposure to infections, environmental toxins, and physical and mental health issues not only negatively impact her own long-term well-being, but that of her children. (28, 29)

Breastfeeding

The benefits of early initiation and continued exclusive breastfeeding on neonatal survival and infant neurodevelopmental and cardiometabolic outcomes are well established. (30, 31) Studies also suggest that exclusive breastfeeding may protect against elevated body mass index (BMI) in children through mechanisms that include alterations in early growth trajectories and leptin signaling.(32) In addition to its nutritional properties and role in maternal-child bonding, new evidence shows that breast milk promotes the establishment of a healthy microbiome(33) and the development of taste preferences in infants.(34)

Depression and life stressors

Non-psychotic mental disorders in women (including depression and anxiety) are among the commonest morbidities of pregnancy and the postnatal period (35) impacting fertility, pregnancy complications, and fetal/child development. (36-38) Most recently, evidence is emerging that paternal stress can also influence pregnancy and neurological outcomes in offspring.(39, 40) A higher prevalence of antenatal and postnatal depression is generally reported in women in LMICs than women in high-income countries (HICs).(41, 42) Major negative life events during pregnancy increase the risk for preterm birth and low birth weight(43) and are associated with children's increased risk for behavioral and mental health problems and reduced cognitive performance.(38) The timing of the stress in pregnancy is critical, with poorer outcomes increased when stress occurs in the first trimester,(44) resulting in reduced growth of brain structures,(45) altered gene expression and epigenetic modifications,(46) and altered adaptive immunity.(47)

Stresses experienced due to adversities, which include poverty, prolonged nutritional deficiencies, maltreatment (including physical, sexual, emotional abuse, and neglect) and exposure to community violence can be associated with changes in the shape and volume of various brain structures in children and adults.(48) Maltreatment is associated with reduced mid-sagittal area and hippocampal volume.(48) Regions of the brain that are involved in learning and memory, as well as structures involved in communication between brain regions are particularly sensitive. Children who receive inadequate care, especially in the first 24 months of life are more sensitive to the effects of stress and display more behavioural problems compared to children who receive high quality care attributable in part to the structural deficits in the developing brain.

Co-occurrences among developmental risk factors

In addition to a greater variety and prevalence, there are higher levels of co-occurrence among risk factors in LMICs compared to HICs (Panel 1).(49) While such data are not available for estimating risks for the approximately 1 in 10 children living through conflict, crises, and insecure conditions, we estimate higher levels of co-occurrence of risk factors in such situations. Children living in poverty are at greater risk for exposure to disadvantaged social and material environments (50). Young children are particularly vulnerable to the effects of contaminants, household/ambient air pollution, and heavy metals due to the rapid growth and development of their organ and physiological systems (especially the brain), the immature state of their blood-brain barrier, and their increased likelihood of exposure (handling/eating contaminated objects/foods etc.).(50) Our own analysis (see web appendix) of population level data from 52 countries including 99,987 children showed that children from households in the lowest wealth quintile tend to experience more risk and fewer promotive experiences compared to children from households in the highest wealth quintile (Figure 1). Further analyses based on MICS data showed that risks factors in early childhood tend to co-occur; for example, 85% of children aged 3-4 years in West and Central Africa and 56% in East Asia and Pacific experience multiple risks (see web appendix). The findings support the application of combining of interventions, within packages, to reduce exposure to multiple risk factors/increase exposure to multiple protective.

Panel 1: Co-occurrences among bio-ecological and/or contextual risk factors in LMICs(49)

Nutritional deficiencies in infancy and early childhood likely to occur with:

- being born small for gestational age or preterm or both;
- parents who are less involved, sensitive or responsive;
- extreme poverty and food insecurity;
- suboptimal infant and young child feeding practices;
- high burden of infectious disease in infancy and childhood;
- growing up in home environments characterized as less stimulating;
- exposure to domestic violence.

Maternal depression and anxiety likely to coexist with:

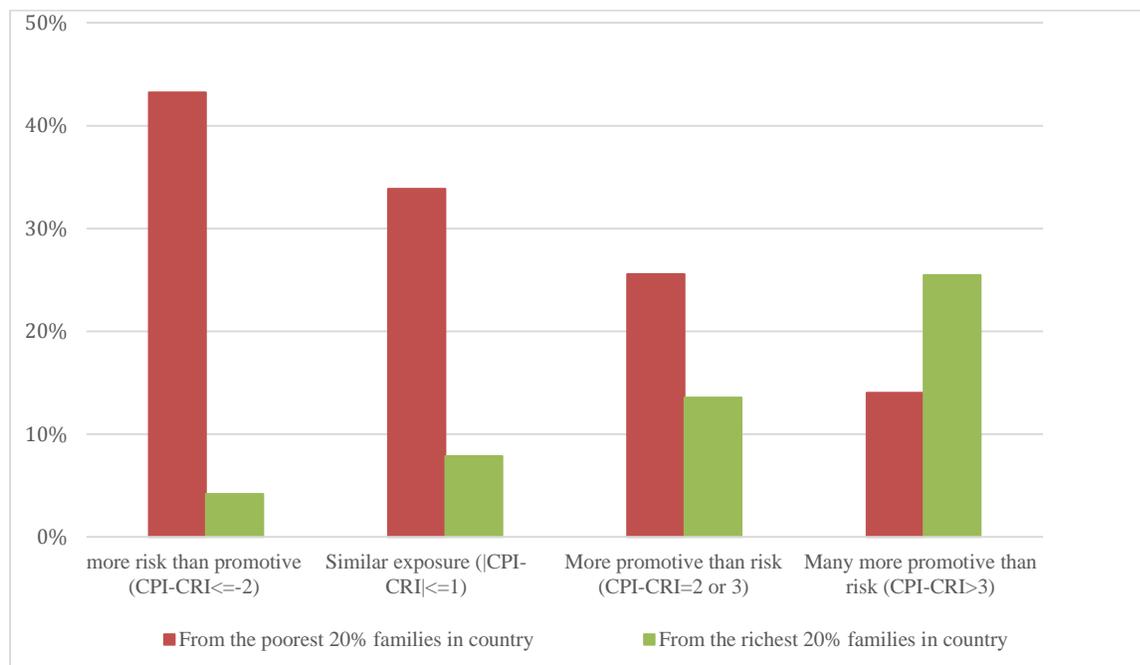
- pre-term birth;
- low birthweight;
- poor infant growth and lowered cognitive development;
- less adequate prenatal care;
- less adequate caregiving including:
 - poor pre-term care;
 - suboptimal infant and child feeding practices;
 - insufficient communication and play;
 - delayed and inappropriate careseeking;
- increased child morbidity;
- increased use of harsh discipline;
- increased family stress.

Exposure to societal violence likely to occur with:

- child abuse and neglectful parenting;
- disruption of family or community support systems;
- child nutritional deficiencies;
- child not being fully immunized.

Growing up in an overcrowded home likely to occur with:

- high burden of infections in infancy or childhood;
- child not getting full course of immunizations;
- infant or child malnutrition;
- spousal violence;
- parental use of harsh physical punishment;
- child ingestion of toxic substances;
- maternal depression.



Data source: Multiple Indicator Cluster Surveys – Round 4 (MICS4), 2009-2012.

Note: (1) Analyses conducted on children aged 3-4 years whose number of calculable risk items are the same as or one less/more than the numbers of calculable promotive items. 99,987 cases are valid for wealth calculation, of which 26,639 children live in the poorest 20% families, and 14,450 live in the richest 20% families. Details are available on <http://mics.unicef.org/tools> (Country-specific statistical syntax is available upon request.). **Risk items** include severe physical punishment, diarrhoea or cough in the last 2 weeks, stunting, wasting or underweight, no improved/treated water or toilet, left with inadequate care, at least one parent away or dead, large household (≥ 9 members) and mom aged < 18 when the child was born. **Protective items** include participation in early childhood education programme, 2 or more types of playthings, 3 or more children's books, adults engaged in 4 or more parenting activities, mom's education \geq primary equivalent, birth registered, received vaccination, vitamin or mineral supplementation and from area with 90% or more coverage of sufficient antenatal care.

Figure 1: Associations between poverty and cumulative exposure to risk and cumulative promotive factors during early childhood (see web appendix for methodology)

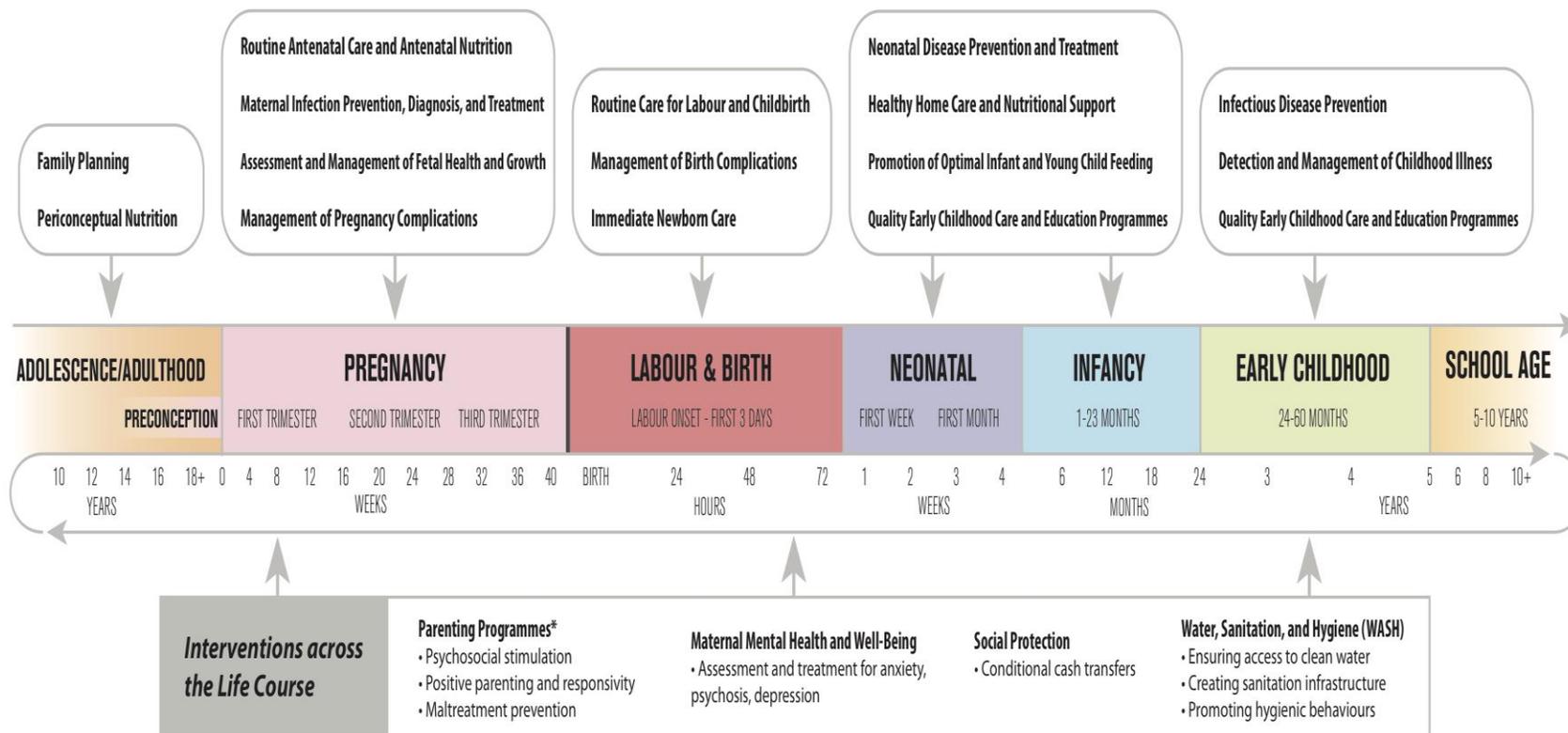
Methodology

The review process began by identifying focal research areas about interventions that promote early child development through aspects of nurturing care and protection. Experts were selected representing research communities in maternal and child health and nutrition, parenting and early learning, maltreatment prevention, and social protection in LMICs and were assembled into five evidence review teams. Each review team conducted a targeted web search of systematic reviews published from 2011 to 2015 and, where available, reviews were identified from the reference lists of recent overviews. (31, 51-54) For interventions where a relevant systematic review was unavailable, a *de novo* review was undertaken of existing trials. Details of the search methods used for screening reviews are described in Panel 2.

Panel 2: Methods and search strategy for selection of interventions for review

This article is based on systematic reviews that were published and peer reviewed. All reviews used established guidelines to search, evaluate and synthesize the results of relevant research; Cochrane and Campbell reviews are included, where available. The search focused on research conducted in LMICs, but studies from HICs were included where evidence from LMICs was either unavailable or limited or where results of interventions from HICs could be potentially informative for the development of similar interventions in LMICs, based on criteria of implementation in lower resource contexts. Most interventions targeted disadvantaged families and were delivered at critical windows in the lifespan starting from preconception through to the transition to primary school (e.g. ages 6-8, depending on the country). The review teams selected search terms from keywords identified in relevant articles and in consultation with experts in their respective fields. More detailed information on the search terms used for the various databases can be found in the web appendix.

The reviews were double data extracted using a standardized form and pooled estimates and methodological quality of each included review was assessed using the AMSTAR criteria.(55) The outcomes of interest were: child health, growth, behaviour, learning, and psychosocial functioning. For *de novo* reviews, inclusion and exclusion criteria were established by each area of review and data were assessed for bias using the Cochrane tool.(56) The meta-analyses employed a random effects model and the der Simonian and Laird method was used for unexplained heterogeneity. The reported effect sizes for each intervention are standardized mean differences (d) of continuous variables. Although a formal systematic review of individual studies was not conducted, the search strategies were intended to identify and synthesize the evidence base on effective interventions that promote early child development through aspects of nurturing care and protection.



*Starting in infancy and continued through to early childhood.

Figure 3: Evidence-based interventions that affect aspects of nurturing care

Review of Interventions Focused on Aspects of Nurturing Care

The results of the review focus on developmental outcomes and are presented by life course periods given the dramatic changes that occur early in life across domains of development and because challenges and vulnerabilities also differ across these early periods. During the preconception to birth period, the focus of the interventions is primarily on the mother or caregiver. From birth through infancy, interventions typically include both adult and child, and in the age period transitioning into primary school we note a predominantly child-focused set of interventions, although during this period evidence on the importance of a nurturing environment provided by teachers is highlighted (See Figure 3 for evidence-based interventions that affect aspects of nurturing care and protection).

Interventions encompassing the period before conception to birth

In addition to established interventions to reduce adverse birth outcomes (presented in Table 1), the key intervention areas in pregnancy, given their significance for later child developmental outcomes and disability, are: maternal health and infection prevention; improved maternal nutrition;(57) and reduction of maternal stress.

Peri-conceptual interventions	
Folic acid fortification	Reduced neural tube defects by 41% (RR:0.59, 95% CI 0.52-0.68) and 72% (RR:0.28, 95% CI 0.15-0.52) (58)(59), averting a major cause of severe childhood disability.
Interventions during pregnancy	
Iodine supplementation	Reduced cretinism by 73% (RR:0.27, 95% CI 0.12-0.60) and improved cognitive development scores in children by 10-20%. (60)(60)(60)
Multiple micronutrient supplementation (involves delivery of more than one micronutrient through capsules or food fortification, including water and fat soluble vitamins and minerals)	18% reduced odds of underweight (OR: 0.82, 95% CI 0.71-0.94) and 12% reduced odds of stunting (OR: 0.88, 95% CI 0.79-0.99) in children 6-60 months old. (61) The composition of the MNN was different in all included trials.
Micronutrient supplementation	11–13% reduction in low birthweight and SGA births and effects on anaemia and IDA were comparable to those seen with iron and folic acid supplements. (62)
Iron supplementation	23% (RR: 0.77, 95% CI 0.60-1.00) reduction in preterm births, 70% reduction in anaemia at term, a 67% reduction in iron deficiency anaemia (IDA), and 19% (95% CI 0.03-0.32) reduction in the incidence of low birthweight for the infant.(63)
Magnesium sulfate supplementation	Reduced the risk of cerebral palsy by 30% (RR: 0.70, 95%CI 0.55-0.89) if birth is before 32 weeks gestation. (64)
Corticosteroids	46% (RR:0.54, 95% CI 0.43-0.69) reduction in the risk of cerebrotentorial haemorrhage in preterm infants, 51% (RR:0.49, 95% CI 0.24-1.00) reduction in developmental delay in childhood (65), as well as neonatal mortality.(66) There is some concern that multiple courses of steroids during pregnancy can lead to later neurosensory deficits in the children.(67)
Interventions at birth	
Therapeutic hypothermia	Reduced the risk of major developmental disability by 23% (RR: 0.77, 95% CI 0.63-0.94), neuromotor delay by 25% (RR 0.75, 95% CI 0.59-0.94), developmental delay by 26% (RR 0.74, 95% CI 0.58-0.94), and cerebral palsy by 34% (RR 0.66, 95% CI 0.54-0.82).(68)
Topical emollient therapy (preterm newborn infants)	Increased weight at 28 days (MD: 98.04 g, 95% CI: 42.64, 153.45) and reduced the risk of hospital acquired infection by 50% (RR 0.50, 95% CI 0.36-0.71) and neonatal mortality by 27% (RR 0.73, 95% CI 0.56-0.94).(69)

Table 1: Evidence-based interventions to reduce adverse birth outcomes that could be combined with parenting interventions to reduce early vulnerability and stress

Maternal health and infection prevention

During pregnancy, maternal health interventions linked to child development outcomes include infection prevention. Maternal infection and the associated inflammatory response have the potential to alter fetal growth and development, the consequences of which may extend long after birth and are associated with poor development outcomes. Along with routine immunizations, prevention strategies such as early detection, treatment and viral suppression of HIV, and intermittent preventative treatment (IPTp) for pregnant women in malaria endemic regions reduces the risk of low birthweight by 19% (RR: 0.81, 95% CI 0.67-0.99),(70) while insecticide-treated nets (ITN) also have a modest effect on birth weight (MD: 60g, 95% CI 20-90g).(71) Combining these strategies has shown a 35% (RR 0.65, 95% CI 0.55-0.77) reduction in the risk of low birth weight.(72) Maternal vaginal infections (e.g., bacterial vaginosis, trichomonas vaginalis, candidiasis) are associated with adverse pregnancy complications (including preterm birth). Available evidence suggests antibiotic use is only beneficial when used in association with membrane rupture or acute membrane infection(73) that might otherwise lead to brain injury including cerebral palsy.(74) Maternal syphilis can lead to preterm birth, stillbirth, and multiple organ morbidities for babies that survive pregnancy. Detection and treatment of maternal syphilis with Penicillin G is able to reduce devastating fetal and neonatal mortality and morbidity associated with this disease. (75) In HICs, intervention programmes have been successful during pregnancy in smoking and alcohol cessation, and both smoking and alcohol consumption are associated with poor child development outcomes although evidence

Maternal nutrition

A second area of intervention during pregnancy is the reduction of maternal malnutrition. Intrauterine growth restriction (IUGR) influences multiple aspects of child development and has been linked to poorer neurodevelopmental outcomes, reduced school performance, and behavioural problems in children.(76) Maternal malnutrition leading to IUGR has been shown to modify gene expression in the offspring and future generations through epigenetic mechanisms.(44)(77) The provision of balanced energy and protein(78) as well as multiple micronutrients for women of childbearing age(79) and expectant mothers at risk of deficiencies can support optimal child growth and development both in utero, at birth, and post-partum (see Table 1 for a review of nutritional support and micronutrient supplementation before and during pregnancy). Folic acid fortification or supplementation, iron, iodine, and additional micronutrient supplementation during pregnancy have been associated with prevention of neural tube defects, improvement in cognitive development scores for children, reduction in underweight and stunting, and risk of adverse birth outcomes. Several individual studies of multiple micronutrients and iron-folate supplementation show potential benefits in reducing the risk of IUGR and small for gestational age (SGA) births, but the potential benefits for mental and motor development during childhood are mixed.(80) is limited on such interventions in LMICs.

Maternal stress

A third area of intervention during pregnancy is the reduction of maternal stress. Living in poverty is associated with a high degree of stress. Indirect positive benefits of cash transfer programmes were noted for prenatal care.(81) Participation in a conditional cash transfer (CCT) also significantly increased both the probability of in-facility birth and the probability of having a skilled birth attendant. While these conditions were associated with improved birth outcomes and later developmental outcomes, this is not always the case. During labour and childbirth, mothers who have continuous social support (e.g., emotional support, comfort measures, information, advocacy) show significant positive clinical benefits for themselves and for their infants.(82)

Interventions during infancy: birth to two years

Kangaroo mother care

Nurturing care begins to emerge through interventions provided at birth. These include early initiation of breastfeeding, thermal care, Kangaroo Mother Care, infant massage, and skin and cord care.(53) Most notably, skin-to-skin contact at birth through interventions such as Kangaroo Mother Care promotes thermal sufficiency and early bonding. Moreover, Kangaroo Mother Care is associated with increased early and continued breastfeeding which leads to improved child developmental outcomes.(83) For low birthweight infants, kangaroo care has been associated with an increase in bonding indicators such as mother-infant attachment (MD 6.24, 95% CI 5.57-6.91), infant growth, and rates of exclusive breastfeeding (RR: 1.20, 95% CI 1.01-1.43).(84) The trials included in these analyses were undertaken in health facilities. Future research studies should focus on effectiveness of skin-to-skin care when delivered at scale in community settings.(52)

Breastfeeding and infant feeding

A recent review on breastfeeding presents evidence that optimal breastfeeding supports improved performance in intelligence tests in childhood and adolescence, demonstrating an IQ increase of 3.44 points (95% CI 2.30-4.58) (85, 86). Findings from a recent analysis of the Pelotas birth cohort in Brazil also demonstrated a dose-response relationship between breastfeeding duration and increased intelligence, educational attainment, and income. (86) Multiple micronutrient supplementation in children at risk of deficiencies has also been shown to improve academic performance (SMD: 0.30, 95% CI 0.01-0.58) and a single study also found an effect on motor development. (87, 88) Reviews of iron supplementation in children consistently found improvement in psychomotor development, but mixed effects on cognitive development. Some studies found a decrease in IQ (MD: -3.00, 95% CI -5.96 to -0.04) (89) and others an improvement in mental development (SMD: 0.30, 95% CI 0.15-0.46). (90) Programmes that combine nutrition and stimulation have been effective in improving child outcomes. (91) However, the extent to which these combinations result in synergistic outcomes it is not clear. Results from individual studies in Bangladesh (92) and India (93) suggest that responsive feeding and sensitive care are effective in promoting child growth and developmental outcomes. Parents who are supported through coaching and modeling of behaviours tend to remember the information provided to them and engage in better responsive feeding and care practices.

Parenting

Opportunities for stimulation, early learning, and positive parenting within the home environment are crucial for children's development. (94) Parenting programmes are operationally defined as interventions or services aimed at improving parenting interactions, behaviours, knowledge, beliefs, attitudes, and practices. Three recent reviews (95-97) of parenting programmes in LMICs found positive effects on direct measures of children's cognitive and language development across diverse policy, service delivery, and social contexts (95-97). Parenting programmes focused on providing parenting support, including the promotion of child-directed/focused enrichment and early childhood education. For this paper, we updated and expanded on the previous three parenting reviews by including non-cognitive outcomes and concluded that parenting programmes increased scores on measures of psycho-social development (SMD 0.35, 95% CI 0.14-0.56, 13 studies) and motor development (SMD 0.13, 95% CI 0.07-0.19, 9 studies) - in addition to child cognitive development (SMD 0.36, 95% CI 0.22-0.49, 19 studies). The effect on child growth was not statistically significant.

Across the reviews, programme implementation varied in relation to dose of intervention, setting, and curriculum. The total amount of contact with parents, which ranged from less than 10 hours to 120 hours, did not have a clear relationship to the size of effect. (96) Some programme models have used only home visits, e.g., Roving Caregivers in Jamaica, (98) and others have used group sessions, e.g., Pastoral del Nino in Paraguay. (99) Combined group sessions and home visits in Bangladesh (100) and Brazil (101) produced better outcomes than home visits alone (102) but not in Jamaica. (102) The most effective parenting programmes used multiple behaviour change techniques, including small media such as posters and cards that illustrate enrichment practices, opportunities for parental practice with their child, guidance and support for changing practices and problem-solving strategies. (95) One such example, the *Care for Child Development* package developed by UNICEF and WHO, provides opportunities to use multiple strategies to strengthen nurturing care by parents. (103) Other examples include "Reach up and learn." A notable gap in the reviews is the role of fathers in parenting. (104) Taken together, the results suggest that parenting support programmes that promote nurturing care and protection can significantly augment the positive impacts of basic health and nutrition (e.g., breastfeeding, complementary and responsive feeding) interventions on early childhood outcomes. (105)

Maternal depression

Maternal mental health disorders can significantly affect the health of both the mother and the newborn baby. Although the benefit of interventions for women with antenatal depression in LMICs, including inter-personal and cognitive behavioural therapies, is well recognized (42, 106), antidepressants for treatment of antenatal depression have been associated with small but significant increases in preterm birth and reductions in birth weight. (107, 108). (109) A cluster randomized trial of integrating cognitive behavioral therapy with home visits by community health workers for mothers with postpartum depression in rural Pakistan showed that this strategy is both feasible and acceptable, with the intervention group having a 78% reduced odds (adjusted OR: 0.22, 95% CI 0.15-0.36) of major depression after 6 months and non-significant increases in WAZ and HAZ after 12 months. (110) The study also increased rates of immunization, exclusive breastfeeding, and parental play with children. A meta-analysis of 13 studies, primarily in LMICs, concluded that the most effective interventions for mothers with depression included infant massage and support groups. (111) Recent trials from Bangladesh (112) and Uganda (113) suggest that group-

based parenting programmes can improve maternal mental health in community settings; however, more analysis is needed to determine which characteristics of interventions are associated with improved maternal wellbeing.

Protection from violence, abuse, neglect and maltreatment

With respect to protective aspects of positive parenting, we drew on a 2009 review of the evidence for prevention of child maltreatment from HICs. (114) Also in 2009, a systematic review of reviews which synthesized evidence on the effectiveness of interventions to reduce child maltreatment(115) identified seven categories of interventions: home visiting, parent-training programmes, child sexual abuse prevention, abusive head trauma prevention, multi-component interventions, media-based interventions, and support and mutual aid groups. For this paper, we reviewed recent evidence on approaches to reduce child maltreatment based on 14 recent reviews, including ten systematic reviews and three narrative reviews: home visiting (three reviews);(116-118)parenting-training programmes (two reviews);(119, 120) sexual abuse prevention programmes (two reviews);(121) (122) universal campaigns to prevent physical abuse (one review);(123) behavioural and counseling interventions (one review);(124) and detection of child maltreatment (one review).(125) Of three review studies, two included sections on prevention of physical abuse(126) and child maltreatment(127) and one review focused exclusively on prevention of child maltreatment.(128) The maltreatment prevention interventions with the best evidence are selective programmes characterized by intensive visits by professional home visitors for a period of at least one year, but these programmes have not been evaluated in LMICs and the extent to which these findings are generalized beyond the specific HICs where they have been evaluated is not clear. Early intervention that occurs prior to the onset of abusive and neglectful parenting is crucial to preventing maltreatment. Reviews are limited in their coverage of interventions that respond to violence against children, in and out of emergencies, including gender-based violence, prevention of injuries, and harmful practices. More recent reviews of early child development interventions in LMICs are suggesting associations with violence reduction and peace promotion (See Panel 3).

Panel 3: ECD for violence reduction and peace promotion

Exposure to violence in the home environment and other adverse childhood experiences can be extremely detrimental to a child's development and is causally related to a broad range of negative outcomes across a lifespan, including major emotional and behavioral problems as well as increased rates of mortality and morbidity.(129-131) These exposures are also associated with changes in brain structure and function.(131-133) These children are also at an increased risk to become perpetrators of violence as they grow older, so that violence can become self-perpetuating from generation to generation. For children in LMICs, this reality is compounded by the situations of migration, war and conflict, and extreme violence.(134)

The biological underpinnings of these conflict and violence-related phenomena likely involve epigenetic mechanisms.(135-137) Epigenetics is a key mechanism by which environmental circumstances can alter gene expression and how our DNA is read and transcribed. Examples include DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence. Epigenetic modifications occur in the regulatory regions of the genome. Once considered "junk" DNA, it is now clear that these changes in the sequence of the "regulatory" portions of the human genome appear to have led to the creation of new combinatorial expression patterns during development, which in turn may be responsible for uniquely human aspects of brain circuitry and connectome.(138) One plausible hypothesis that is currently being explored maintains that these epigenetic modifications may reflect evolutionarily conserved and broadly represented physiological processes that translate specific environmental information at different stages of development to "programme" gene co-expression networks to adapt to specific external environments.(139-141)

Early parent-child programmes aimed at enhancing responsive parenting and supporting can reduce adverse childhood experiences (poor nutrition, neglect, abuse, and exposure to violence in the home) and can positively impact the child's cognitive and socioemotional development as well as their brain structure and function as well as their physical health.(142, 143) The positive changes are linked with social cohesion and promotion of peace in families and communities. The potential role of early child development programmes in peacebuilding was initiated by the Mother Child Education Foundation (Anne Çocuk Eğitim Vakfı, AÇEV) with their concept paper, "Building a Generation of Reconciliation: The Role of Early Childhood Development in Peace Building". This paper presented and discussed their anecdotal observations that when parents came together in groups they became friends despite their religious and cultural differences. The role of epigenetics in this context was first discussed in 2010 at a meeting of the AÇEV Board of Directors in Istanbul. This, in turn, led to a partnership between AÇEV and Yale University to explore the impact of early child development programmes on brain development and its potential trans-generational consequences. Subsequently, an Ernst Strüngmann Forum was convened in Frankfurt in 2013 to explore this question. More than 40 scientists from diverse backgrounds (basic sciences, early child development, cross-cultural psychology, interfaith dialogue, and peace building) from 15 countries reviewed the available data to identify gaps in knowledge and pose key questions for future research.(144) The results of these deliberations were published in 2014 by the MIT Press in a volume entitled, "Pathways to Peace: The transformative power of children and families." In addition, AÇEV and Yale University in partnership with UNICEF and the Fetzer Institute launched the Early Childhood Peace Consortium in 2013. The launch brought together over 140 partners from multiple sectors (including civil society, the social and mass media [Sesame Workshop], government officials, as well as practitioners and academia), agencies and countries to "create a legacy of sustained peace drawing on the transformative power of early child development."

These initiatives have also generated considerable interest in the scientific community to evaluate changes in the epigenome of individuals who have participated in early child development programmes as well as exploring the impact of these programmes on brain structure and function. But despite an ever-growing body of research, we still have a long way to go before we fully understand the role of the epigenome in shaping human behaviour across generations.(137, 145) If consistent findings emerge, this will provide a solid foundation for the assertion that interventions to strengthen families, promote nurturing care and protection, and to improve the cognitive and socioemotional well-being of children have trans-generational consequences for building a more peaceful world from the bottom-up.

Interventions during the preschool period: from age three to five years

Effects of early learning programmes, including quality childcare, kindergarten, preschool, and pre-primary are well established in LMICs.(94, 146, 147) Therefore, in this paper, we only focus on updates of the evidence of overall impacts, and evidence related to the provision of nurturing environments in early learning programmes. We updated and expanded on an earlier published review(96) and found formal and non-formal or community-based preschools in LMICs improved scores on direct measures of children's cognitive development (SMD 0·67, 95%CI 0·43-0·91, 26 studies) and psychosocial development (SMD 0·23, 95% CI 0·06-0·4, 5 studies). Effects on child growth were non-significant and one study measured motor development showed non-significant effects. The earlier review found effects of non-formal preschools on child outcomes were typically weaker than the effects of formal preschools; some low-cost and innovative programmes such as home-based preschool(148) and a child-to-child approach resulted in better developmental outcomes compared with non-participants.

Programme quality is a key predictor of programme effectiveness.(96) Effective interventions to enhance preschool quality include greater number, variety and challenging play materials,(149) dialogic reading, (150) classroom organization and instructional support.(151) Nurturing environments in the form of care and positive interactions and individualized attention appear to be important in early learning programmes. Observational measures of preschool quality have begun to emphasize the notion of emotional climate, which includes individualized attention, positive affect, and positive reinforcement of children's behaviours. One measure, for example, takes as its conceptual basis attachment theory and applies it to classroom interactions.(152) The emotional climate scale has shown positive associations with children's early-childhood cognitive as well as socioemotional skills in Chile(151) and Ecuador.(153) Two experimental trials in Jamaica and Chile showed that promoting teachers' provision of positive emotional climate and behaviour management also improved children's self-regulation and attention, and reduced aggressive behaviours.(154, 155)

Discussion: Intervention Packages that Integrate Nurturing Care with Sector-Specific Programmes

The review demonstrates that compared to the Lancet ECD series in 2007 and 2011, the literature on early childhood interventions has expanded to include new intervention studies and new longitudinal data (156, 157). Most interventions during the period from preconception to birth focus on the physical and mental health of the mother to support a healthy pregnancy and improve birth outcomes, given the associations between preterm birth, low birth-weight, birth complications and poorer developmental outcomes for young children. At birth is when interventions focusing on nurturing care and protection are noted. During infancy, the synthesis of reviews of interventions indicates that evidence-based interventions combining basic sectoral interventions with nurturing care and protection can synergistically improve child developmental outcomes. For example, inclusion of stimulation in nutrition interventions increases effectiveness, as developmental outcomes cannot be fully promoted through nutrition interventions alone(158, 159) or then holistic interventions, such as breastfeeding, which have strong impact as they combine elements of nutrition with bonding (86).

Some sectoral interventions, such as social protection, are not so differentiated across the life course. However, they could also serve as the basis for delivery of services that link policy level strategies of cash transfer, social policies, and income generation with programmatic interventions (See Panel 4). For other sectors, such as water and sanitation, while the review indicated impact on child's nutritional status, growth, and health (73)(74)(75), further research is needed to examine associations for developmental outcomes.

Panel 4: Social protection across the early life course

Social safety net programmes support vulnerable populations by distributing transfers to low income households to prevent shocks, protect the chronically poor, promote capabilities and opportunities for vulnerable households, and transform systems of power that exclude certain marginalized groups (e.g. women, children). For this review of protection from poverty, effects of social programmes – including conditional cash transfer (CCT) and unconditional cash transfers (UCT) – on children’s growth, health, and development were examined. There are other types of social safety net programmes, such as microcredit, food assistance, voucher schemes, health insurance, and user fee removals, but there was not enough evidence about any one of these types of programmes to include them in the analysis. This review examines five systematic reviews that have been published since 2011.(81, 160-163).

In general, the reviews show positive effects of CCT programmes on some child outcomes, including birth weight and illness or morbidity. CCT participation consistently had no effects on hemoglobin concentration or prevalence of anemia in children. Results were strong and significant for effects of CCT participation on prenatal care, growth monitoring, micronutrient supplementation, and household food consumption. There were mixed effects, however, on the presence of a skilled birth attendant at child birth, and receipt of child vaccinations. It is difficult, however, to compare results across countries and contexts because programmes differ greatly. CCTs generally showed greater effects than UCTs, although there were far fewer UCTs than CCTs reviewed, so it is difficult to generalize. Cash transfer programmes appear to be most effective when the receipt of cash is linked with a specific intervention that can maximize the potential impact of the transfer. There may be a limit to the number of conditionalities that can be addressed because they may lead to unintended exclusion of the most vulnerable families, given the potential confusion in determining eligibility based on too many requirements.(164) The impact of cash transfers on child development can be improved by combining social protection and ECD interventions. Cash transfer programmes try to address many issues at multiple levels (e.g. parental, community) that influence child development, but they do not directly work to change the factors that are linked with improving development outcomes. On the other hand, programmes promoting child development that have an educational or stimulation component have shown larger cognitive effects than cash-only or nutrition-only programmes, both in the US(165) and Latin America.(166, 167) Bringing these two interventions together can address both the direct and indirect factors that impact developmental outcomes and illustrative examples are presented in the discussion section.

Across the review, the degree of effectiveness of health, nutrition, education, and child and social protection interventions varies with respect to improving child development outcomes. The impact of these interventions could be improved by taking into consideration the major insights we have gained over the past decade about how human development is molded by complex and multi-faceted experiences. The scientific understanding of early human development encourages us to conceptualize interventions acting together in a meaningful manner, through a coordinated approach, so as to increase their benefits and address child outcomes more holistically (See Panel 5).

Panel 5: Bringing sectors together to promote ECD

The promotion of ECD requires health, nutrition, protection, responsive caregiving, and early learning interventions. How the sectors come together in a synergistic way to deliver a combination of interventions, in packages, through appropriate delivery platforms (e.g. community platform) needs to be defined.

Multi-sectoral services: describe the combination of interventions within existing delivery platforms with common messages and opportunities for synergy. The combination of stimulation interventions with nutrition interventions in a package, to promote ECD has been widely reviewed.(95) The advantages of such integrated packages from a delivery perspective is that one location for the provision of key services for young children, can be leveraged efficiently. From the scientific perspective, this integrated package is an opportunity for interventions to mitigate shared risks for poor development and growth, a common window period of intervention opportunity in the first 1000 days, and the potential for impacting multiple child health, growth and development outcomes. The strategy selected to deliver a package of interventions might be determined by the age group being targeted, the expertise of the sector, coverage, and an analysis of the most efficient and effective use of resources within a service for a particular context. More evaluations are needed to assess effectiveness, implementation quality and cost-benefits of integrated, inter-sectoral and multi-sectoral approaches for child health, growth and development packages.

Inter-sectoral collaboration: Inter-sectoral collaboration is defined as “collaboration between part or parts of one sector with part or parts of another sector which has been formed to take action on an issue to achieve specified outcomes ... in a way that is more effective, efficient or sustainable than could be achieved by a sector alone.” (WHO International Conference on Inter-Sectoral Action for Health, 1997).(168) Inter-sectoral collaboration is especially relevant given the range of inputs needed to support healthy development because it brings together services and organizations from different sectors for the common purpose of promoting developmental outcomes. Successful inter-sectoral collaboration requires a shared vision, leadership, clear communication, defined roles and responsibilities, and relationships of trust between partners across sectors.(168) An example of inter-sectoral collaboration is the *Chile Crece Contigo* programme (see Paper 3 case study). Coordination and governance at the national and local levels are crucial to the success of inter-sectoral collaborations, but are not always considered.(169)

In instances where sectoral interventions were combined with elements of nurturing care and protection, the impact of the intervention on child outcomes increased significantly (See webappendix for Landmark studies of ECD). Combining interventions with elements of nurturing care and protection allows us to support families as the most proximal environment for early development by intervening with the family as a unit, as opposed to addressing the child as an isolated beneficiary. Further, the established and emerging science continues to offer opportunities to improve and better target interventions to improve their efficacy by combining them with nurturing care and protection, through parenting support and skills programmes.

- Integrating nurturing care for the parents involves support of health and well-being even before conception by addressing adolescent and young adulthood nutrition as well as stresses related to poverty and other sources of adversity.
- Integrating nurturing care, through breastfeeding support, responsive feeding and sensitive care, and positive parenting in interventions from birth through infancy can substantially augment positive effects on children’s learning, health, and development.
- Integrating nurturing care in early care and education can take two forms. First, the addition of an emphasis on parenting support can augment the cognitive benefits of early care and education(170) Second, teachers, when supported to provide nurturing and supportive climates in classrooms, can enhance children’s socioemotional as well as cognitive development.(154, 155)

Previous attempts at creating packages of effective interventions have focused either on the temporal relevance of the interventions, i.e., packaging interventions that co-occur during the same age period of the child (e.g., World Bank), or then are delivered through the same system (e.g., RMNCH). In conceptualizing the integration of interventions, for holistic ECD, in addition to taking into consideration the temporal relevance to the age of the child, any consensus on the effectiveness of the intervention, quality of the intervention, and feasibility of delivery at scale, we need to incorporate nurturing care and protection and tailor the packages to unique sets of risks and adversities that characterize complex environments. (See Panel 6 for illustrative packages combining key

interventions). Finally, platforms, at community, clinic and school levels, need to be identified to coordinate the delivery of the packages targeting population segments and families in greatest need. For example, community platforms that mobilize antenatal and postnatal home visits by community health workers complement facility-based care and promote family contact with the health system at crucial times. Social protection platforms could also serve as the basis for delivery of packages of services that link policy level strategies of cash transfer, social policies and income generation with programmatic interventions.

Panel 6: Illustrative ECD packages of essential ECD interventions

1. *Early Care & Nutrition Package: a Multi-Generational Approach to Nurturing Care.* This set of interventions emphasize care and protection of the mother's and father's physical health and well-being while enhancing her capacity to provide nurturing care. This set of essential interventions integrates key elements across adolescent health, preconception, pregnancy, childbirth, post-natal and newborn health. These interventions are primarily driven by the health system with a focus on health and nutrition services and skills. The main recipient of the services and skills is the parent, or adolescent as defined above. However, starting at childbirth, service involves two generations. As per the findings of the review, a package combining preconception and pregnancy nutrition and health care, nutrition supplementation where necessary and support for breastfeeding, support for maternal mental health, skin-to-skin care, stimulation, and coaching and modeling for parenting behaviours could lead to improved developmental outcomes. This package can be further strengthened with parental leave policies as discussed in Richter et al, this series.
2. *Family Support and Strengthening Package:* Three elements of family strengthening: (i) access to quality services (e.g., antenatal care, immunization); (ii) skills building (e.g., positive parenting to reduce harsh discipline and promote stimulation); and (iii) support (e.g., social protection, safety networks, enabling policies) increase the likelihood that families are better able to provide nurturing care for their children. As presented in the review, each of these elements, services, skills and support (Panel 5) tend to operate independently. As indicated in the review of the social protection interventions, significant positive effects are seen when they are combined with programmatic interventions. By creating a package of the 3 elements of Services, Support and Skill building, based on the age of the child and nature of risks, developmental outcomes could be substantially improved.
3. *Early Learning Package:* This set of interventions integrates support of parents in learning programmes, as well as teachers' and caregivers' ability to create a nurturing environment in centers, classrooms and community settings for learning. For young child health, learning and development, the existing set of services typically includes community-based child care, preschool, kindergarten and other early learning programmes. However, the package of interventions should include nurturing care and protection by enhancing teachers' capacities to providing a nurturing, safe and positive emotional climate and should include greater attention to parental support. As noted in Panel 3, the ACEV programme has demonstrated long-term gain when early learning packages have included both the child and the parent as target beneficiaries. This package needs a clear emphasis on quality and family support through parental empowerment, guidance on nutrition, child protection and nurturing care.
4. *ECD Family Support Package in Humanitarian Crises:* Conflict, violence and insecurity present a complex array of adversities. Families, parent and children require a package of services that addresses both the immediate needs and also long-term nutrition, health care and psycho-social support. While the reviews did not specifically cover situations of conflict and violence, Panel 3 presents a series of effective interventions for maternal (and paternal) mental health, skills building and psychosocial support to improve development outcomes linked to prosocial development, citizenship, social cohesion, and promotion of peace.

While we have made progress in our understanding of “what works”, we also note gaps in our knowledge. The particular set of risks faced by children in conflict are not well understood. Notable gaps in our understanding are evaluations and reviews of early childhood interventions operating in conflict-affected and fragile country contexts. A recent set of reviews examining the association between preschool-aged interventions in LMICs and high income

countries and reduction of violence, note that while there are gaps in our knowledge, the trends noting the association between early care and later positive social outcomes for children are positive.(144, 171). While we know that makes more sense to combine interventions, because of holistic development and the opportunity to provide multiple services, in one instance, to a family, a gap in our knowledge is that most interventions are still delivered through single sector approaches. We need to understand how to better combine interventions, through evaluations of integrated parenting, responsive care, stimulation, mental health, and protection interventions that could be delivered through community platforms. We also need to understand better how to use technology based platforms to deliver effective interventions (See Panel 7). We also need a range of evaluations, in addition to outcome evaluation, that focus on implementation evaluations to inform scale-up. Another set of gaps notes in the review was that further research is also needed to establish the validity of child-development measures in LMICs.(172)

Panel 7: Technology delivery platforms for ECD

The rise of mobile communications technology in LMICs is creating new opportunities to expand access to reproductive, maternal, newborn, and child health (RMNCH) information and services using cell phones and other devices. Mobile health (mHealth) innovations support health service functions such as health promotion, emergency medical response, data collection, point-of-care diagnostics, and clinical guidance.(173) Delivery modes include short-message-service (SMS), voice calls, and smartphone applications equipped with audiovisual tools. Most RMNCH interventions have focused on the antenatal period, although mHealth innovations are relevant across the continuum of care.(173-175)

mHealth is based on strong indications of the clear potential diversity in delivery modes, intended beneficiaries, target health outcomes, and intervention contexts. A systematic review of mHealth interventions for RMNCH found 15 relevant effectiveness studies representing a variety of intervention foci and contexts.(182) One trial of SMS support for pregnant women reported significantly decreased risk of subsequent perinatal mortality in the intervention group,(183) and preliminary indications from other trials of mHealth interventions in pregnancy reported positive effects on antenatal care uptake and skilled birth attendance.(184-186) A meta-analysis of three interventions targeting improved infant feeding showed positive effects on breastfeeding practices.(182) Provision of mobile-phone-based support for frontline health workers can improve adherence to clinical protocols for malaria treatment(187) and quality of antenatal care and management of childhood illness.(188, 189)

Despite a burgeoning of pilot projects, the evidence base to support broad application of mHealth for improving RMNCH outcomes remains limited (176, 177) Implementation and ethnographic research is needed to elucidate contextual factors and impact pathways through which mHealth innovations can contribute to improved health outcomes.(178, 179) It is widely accepted that mHealth innovations are not stand-alone solutions but rather complementary tools to be integrated within broader health system strengthening and behaviour change communication frameworks.(173, 175, 180, 181) Currently, the breadth of potential applications makes it a challenge to identify clearly effective and feasible mHealth approaches.(190) Future studies are needed to clarify which mHealth interventions can realistically target RMNCH and ECD outcomes, which outcomes are most amenable to influence, and under what conditions. Research on the cost-effectiveness, sustainability, and scalability of mHealth interventions will inform global policy and programming.(177) The design, implementation, and evaluation of mHealth interventions should also consider equity issues; those most in need of RMNCH interventions – specifically disadvantaged and vulnerable women and children - are less likely to have access to mobile phones.(191, 192)

Conclusion

We have reviewed the scientific basis for interventions to improve the health and well-being of our world's most valuable asset – our children. We have documented the effectiveness of interventions across domains of health and nutrition, care and nurturing, and protection from violence, maltreatment, and poverty. The results of the review suggest that “smart and sustainable” interventions to improve developmental outcomes need to: (i) include nurturing care and protection behaviours; (ii) be implemented as packages that target multiple risks; (iii) be applied at

developmentally appropriate times during the life course; (iv) promote quality; and (v) build on existing delivery platforms to enhance feasibility of scaling-up and sustainability. We have proposed illustrative packages that meet these requirements. The nature of these interventions will continue to be improved as new understanding of early human development emerges (Panel 8). However, we are now at a juncture where the evidence is clear about what needs to be done to improve the future health and well-being of future generations. The question remains about the means to scale-up interventions at a population level and the commitment of nations to enable all children everywhere to reach their developmental potential (See Richter et al., this series). In this paper we call for greater integration between sectoral interventions and those that promote nurturing care and protection to improve developmental outcomes. The science is clear and the evidence convincing that our earliest experiences matter. Let us draw on this knowledge to take action to support parents, caregivers, and families in providing the nurturing care and protection that young children deserve.

Panel 8: Emerging research

Microbiome: role in metabolic function and energy absorption

The human body contains many times more bacterial cells (notably in the gut, skin and urogenital tract) than human cells. These bacteria have co-evolved with us and are fully integrated into our biology including our brain and immune functions. Assembly of the infant microbiome is defined by exchange of microbiota between mother and infant.(193) Breastfeeding introduces new microbiota and is known to be important in the development of the neonatal gut microbiome.(23, 194, 195) Human breast milk also contains prebiotic human milk oligosaccharides that act to encourage bacterial colonies that can protect against colonization by harmful pathogenic organisms.(196) In this regard, use of infant formula rather than breastfeeding has been shown to negatively influence the neonatal immune system, as well as modify metabolism in later life.(197, 198) New data indicate that malnutrition damages the development of the child's gut microbiome and reduces its ability to absorb nutrients (194). Antibiotics can profoundly influence the maternal and infant microbiomes, increased the risk for childhood asthma and obesity (193), and in mouse models impair cognitive function, reduce anxiety and impact gut-brain communication.(139) Damaged microbiomes may not only adversely impact child growth and development, but reduce the effectiveness of nutritional interventions. The use of probiotics and fecal transplants to "repair" the microbiome is gaining increasing interest and represents an important target for future interventions. (195, 196)

Paternal impact on child development

Recent studies in rodents have shown that paternal chronic stress prior to breeding results in offspring that exhibit dysregulated HPA function and behaviours.(39) Similar associations are beginning to be observed in humans. Individuals born to fathers with PTSD exhibited increased glucocorticoid receptor methylation in peripheral blood mononuclear cells.(199) Strong evidence is also emerging that indicates paternal body composition and nutrient intake can profoundly influence health of offspring across the life-course.(200)(201) Paternal obesity in humans has been linked to increased BMI and body fat in pre-pubertal children, however it is difficult to factor out the potential genetic component.(25) In rats, paternal obesity is linked to increased adiposity, insulin resistance and beta-cell dysfunction in female offspring; effects that were associated with epigenetic changes in glucose regulating genes in pancreatic islet cells. (200). At the level of potential interventions, in mice, preconception diet or exercise in obese fathers normalizes the sperm miRNA profile and prevents metabolic syndrome in female offspring.(202)

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