Early Life Determinants: Can Advocacy Make a Difference?

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Protecting Children From NCDS: Leadership Advocacy Workshop
Kenya Paediatric Association Scientific Conference
Eldoret, Kenya | April 26-27, 2016
Session Objectives

- Objective 1
  - Participant will understand effects of early determinants on adult disease

- Objective 2
  - Participant will recognize how investment in advocacy can influence change
Linking Childhood Experiences and Adult Outcomes

Childhood Adversity → ? → Poor Adult Outcomes

ACEs, POVERTY

POOR HEALTH, EXECUTIVE FUNCTION
The Basic Science of Pediatrics

Biology
- Physiological Adaptations and Disruptions

Ecology
- Epigenetics

Health & Development
- Life Course Sciences
- Learning, Behavior, and Physical & Mental Well-being

Neuroscience

The Social and Physical Environment
Genetics, Genomics and Epigenetics
Definitions from the Epigenetics Leadership Group

- **Genetics:**
  The study of inherited variability and transmission of traits

- **Genomics:**
  The study of the entire complement of genetic information in an organism

- **Epigenetics**
  The study of changes in gene expression without alteration of the DNA sequence
Why Learn Epigenetics?

- “Epigenetic diseases are rare”
  - It is far more common than you think
  - It plays a major role in development

- “It’s like genetics, we can’t change it anyway”
  - By definition, epigenetics is modifiable, prospects for treatment are far greater than for genetic engineering.
Epigenetics

“The study of changes in gene function that occur without a change in DNA sequence”
Epigenetic Influences Across Generations

- Epigenetic changes can occur in utero.
- Changes affect postnatal development of infant/child and occur in germ cells (sperm or ovum).
- Changes can be secondary to environmental influence and passed on to subsequent generations.
- Trans-generational effects may emerge in 1-2 generations.
Key Factors Leading to Epigenetic Changes

- Asthma
- Chemical Exposures
- Diet during SGP
- Endocrine disrupting compounds (BPA)
- Hypoxia
- Maternal Diabetes
- Maternal habitus, maternal age, placenta size
- Maternal smoking
- Psychosocial stress
- Psychological trauma
Non-chemical Toxicants-Psychological Stress

- Psychological stress – activates HPA axis
  - Increases cortisol

- Hippocampus – highest density of glucocorticoid receptors
  - Modulate neuro and synaptogenesis
  - Acutely, stress enhances memory formation
  - Chronic stress appears to inhibit it
Example: Handling Paradigm

- Licking/grooming in mothers is stimulated by human handling of pups

- Maternal LG and Arch back nursing behaviors program more appropriate long term HPA axis response to stress

- Maternal LG/ABN clusters in family lines
  - Is it genetic?
Effects of Cross-Fostering

low LG and ABN mothers

Fearful offspring with brisk HPA stress response

high LG and ABN mothers

Less fearful offspring with more modest HPA stress response

Weaver et al. Epigenetic programming by maternal behavior
Nature Neuroscience | Volume 7 | Number 8 | August 2004
Handling Paradigm

- Weaver et al
  - Glucocorticoid receptor expression is more active in offspring of high-LG mothers compared with low-LG mothers
  - Effect inversely correlated with methylation across Glucocorticoid
  - Receptor promoter sequence in the hippocampus
  - REGARDLESS OF GENETIC BACKGROUND
Monozygotic (MZ) Twins and Epigenetics

- Epigenetic difference negligible at birth
- Differences increase over their lifetimes
- One-third (1/3) have epigenetic differences (methylation and histone modification)
- Affect disease susceptibilities?
Adverse Childhood Experiences (ACEs)

Experiences in childhood (both good and bad) are strongly associated with behaviors, health and economic productivity . . . . . . DECADES LATER!
Ecobiodevelopmental Framework
Neuroendocrine Responses

Adverse Childhood Experiences Study

- **Risk factors**
  - Child abuse/neglect
  - Household members with substance abuse
  - Mentally ill, suicidal or imprisoned
  - Violence against mother

- **Health Outcomes**
  - 1.4 – 12 ↑ in alcoholism, drug abuse, depression, ischemic heart disease, cancer, chronic lung disease

- Strong guided relationship between exposure to childhood adverse events and multiple health risk factors as adults

- ACE categories linking childhood experiences and adult outcomes

CDC.gov
BMJ 11  13,494 adults, standardized medical evaluation
Bull, Marilyn J., 4/16/2015

BMJ 12  7 childhoos exposures:
Bull, Marilyn J., 4/16/2015

BMJ 13  1/2 - at least 1 and 25%  2 or more
Bull, Marilyn J., 4/16/2015

BMJ 14  # of categories of ACE had graded relationship to presence of adult disease (4 or more compared to none had 4-12 fold increase for alcoholism, drug abuse, depression and suicide. 1.4-1.6 -fold increase in physical inactivity and obesity
Bull, Marilyn J., 4/16/2015
You see patients everyday whose health may be affected now and throughout their life by epigenetic changes.

There are opportunities for pediatricians, patients and families to intervene.
Summary

- Epigenetics represents a look into further complexities of hereditary material.
- Understanding epigenetic marks will provide clues into the interaction between genetic material and environment.
- Epigenetic changes will provide clues into common health conditions in population.
Prevention

- Opportunity to impact disease prevention!
  - Multiple factors early in life affect the onset of adult diseases and degree of severity
  - Knowledge expected to grow as influences on DNA methylation, histone modification, and micro-RNA are delineated

- Track factors occurring in prenatal, perinatal, or early infancy period over the health care trajectory
“The time has come to expand the public’s understanding of brain development and shine a bright light on its relation to the early childhood roots of adult disease...."
Human Brain Development is Greatest at Very Young Ages

[Diagram showing development curves for Synapse Formation and Retraction, Sensory Pathways (Vision, Hearing), Language, and Higher Cognitive Function, with age in months and years marked.]
90% of Brain Growth Occurs Before Age 5

Neuron connections are forming at 700 per second . . .

shaping executive capabilities such as patience and persistence for life
Malnutrition and Neurodevelopmental Effect

- Dutch hunger winter October 1944 – May 1945
- Increase in congenital neural defects – spina bifida and anencephaly – conceived during famine
- Twofold greater cumulative risk of schizophrenia as adults in persons conceived at height of famine months
- Twofold increase in schizoid personality disorder in exposed cohort

Natural experiment, carefully recorded food rations, health outcomes, immediate relief with lifting of embargo.

6 West coast cities
Fetal Undernutrition and Health

- Dutch Famine Study
- Increased incidence central obesity in women
- Double rates of coronary heart disease
- Increased risk metabolic disease and breast cancer – 5X
- Possible accelerated cognitive aging
- Direct evidence of epigenetic programming through prenatal famine

Roseboom et al. Maturitas. 2011
Assesses transgeneration effects of famine exposure. Grandmaternal exposure to famine for brief period during gestation did not affect birthweights nor rates of cardiovascular disease. It was associated with increased neonatal adiposity and poorer health of women who themselves were exposed to famine in utero suggesting that poor maternal nutrition during gestation on health in later life pass down to subsequent generations.

Bull, Marilyn J., 4/17/2015
Malnutrition and Development

National Nutrition Center Barbados

- 129 children hospitalized with protein energy malnutrition (marasmus) in 1st year of life
- 109 children (85%) evaluated ages 9 – 15
  107 well nourished comparison children
- Delayed sexual maturation in girls and reduced physical growth in boys and girls
- Behavioral deficits (attention deficits, reduced social skills, emotional instability) independent of IQ
- Slight correlation with socioeconomic factors and conditions in home

Galler et al. Pediatr Res. 1985
Well Water Arsenic and Child IQ

- 272 children grades 3-5 where water arsenic known above EPA guideline (10 ug/l)
- Families resided in home average 7.3 years
- Water samples taken and WISC-IV administered
- Adjusted for HOME scores, maternal education and IQ, and number of children in home
- WA significantly negatively associated with FSIQ and Working Memory, Perceptual Reasoning and Verbal Comprehension (FSIQ 4.5 – 6.5 point reductions)

Wasserman, A cross-sectional study of well water arsenic and child IQ, Environmental Health. 2014
BMJ 20  1/3 of water supplies were >EPA standard of 10 microgm/L (high of 115)
Bull, Marilyn J., 4/16/2015

BMJ 21  Studies in bangladesh had similar results but variables of school attendance, test instruments, blood lead and nutritional status are confounders difficult to eliminate.
Bull, Marilyn J., 4/16/2015

BMJ 22  Laci hi end lead in Me study and lack low lead in Bangladesh study
Bull, Marilyn J., 4/16/2015

BMJ 23  Did not correct for amount of water consumed.
Bull, Marilyn J., 4/16/2015
Low Level Environmental Lead Exposure and Children’s Intellectual Function: International Pooled Analyses

- Longitudinal Cohort studies birth to 5 – 10 years

- Outcome measures
  - Full scale IQ
  - Covariants assessed: Home Inventory, sex, BW, BO, maternal education and maternal IQ
  - Lead associated intellectual decrement greater from maximal Pb < 7.5 ug/dl than Pb > 7.5
  - No evidence of threshold for adverse consequences of Pb exposure

Lanphear, Low-level environmental lead exposure and children’s intellectual function, Environ Health Perspect. 2005 Jul
True Grit

Pediatrician proves Michigan community's water was poisoning children

by Madeline Sturgeon • Editorial intern

Although the residents of Flint, Mich., had been complaining for months about the color, smell and taste of the community's water, state and local officials maintained the water supply was safe.

Mona Hanna-Attisha, M.D., M.P.H., FAAP, however, was not convinced.

A dinner party conversation with a water-quality expert stoked the Flint pediatrician's curiosity and compelled her to seek evidence that would prove the water supply was toxic.

"As the stewards of these children, it is our responsibility to

"Nobody listened to the mom, to the activist, to the water expert. But when the pediatrician spoke, that's when the game changed," said Mona Hanna-Attisha, M.D., M.P.H., FAAP, after convincing state officials to remedy the toxic water supply poisoning children in her community."
Fruits and berries have vitamin C and natural sugars.

We built our mike up high so babies cannot crawl into the fire.
Helping Babies Survive (HBS) is a suite of three educational programs designed to improve neonatal survival in resource-limited areas:

- Helping Babies Breathe (HBB)
- Essential Care for Every Baby (ECEB)
- Essential Care for Small Babies (ECSB)
Launched in 2010, Helping Babies Breathe® is an evidence-based educational program to train birth attendants in the essential skills of newborn resuscitation, with the goal of having at least one person who is skilled in neonatal resuscitation at the birth of every baby.
Asphyxia accounts for nearly a quarter newborn mortalities. Among these are babies who are not breathing well at birth, and who could be helped with simple measures.

The key concept of HBB is The Golden Minute®: Within one minute of birth, a baby should be breathing well or should be ventilated with a bag and mask. The Golden Minute® identifies the steps that birth attendants must take immediately after birth to evaluate the baby and stimulate breathing.
Fantastic Success in Just Five Years!

After Nation-wide Implementation of HBB, Neonatal mortality in Tanzania dropped by 47%
The success of HBB in lowering the risk of death due to asphyxia at birth led to the development of the ECEB and ECSB training modules, which address other common causes of neonatal mortality.

Collectively these three initiatives are called *Helping Babies Survive*
Trends in Occupant Fatality Rates Per 100,000 Population

NHTSA
Figure 2: Child road deaths in world regions

- Sub-Saharan Africa
- South-Eastern Asia
- Southern Asia
- Latin America and the Caribbean
- Caucasus and Central Asia
- North Africa
- Eastern Asia
- Western Asia
- Developed regions
- Oceania

Road deaths /100,000 people aged 0-19
Figure 15: Correlation between regional pedestrian injury death rates and total road injury death rates
Children on their daily journey to school across the Thika Road in Nairobi, Kenya

Photo: Georgia Goodwin/FIA Foundation
http://www.theguardian.com/global-development-professionals
network/2015/may/07/road-fatalities-deaths-safety-sustainable-development-goals
“Never believe that a few caring people can't change the world. For, indeed, that's all who ever have.”

~ Margaret Mead
AAP Agenda for Children 2013-2014
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Poverty and Child Health
- Epigenetics
- Early Brain and Child Development
- Children, Adolescents, and Media

Access | Quality | Finance

ADVANCES IN BASIC SCIENCE

HOW DO WE APPLY THIS SCIENCE?

CONTEXT: HEALTHCARE UPHEAVAL!
Leading causes of death globally by age group, 2010 – Males

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>0-1 years Cause</th>
<th>1-4 years Cause</th>
<th>5-14 years Cause</th>
<th>15-59 years Cause</th>
<th>60-64 years Cause</th>
<th>65-74 years Cause</th>
<th>75+ years Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Premature birth complications</td>
<td>Malaria</td>
<td>ROAD INJURY</td>
<td>ROAD INJURY</td>
<td>HIV/AIDS</td>
<td>Ischemic heart disease</td>
<td>Ischemic heart disease</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>Lower respiratory infections</td>
<td>Lower respiratory infections</td>
<td>HIV/AIDS</td>
<td>Interpersonal violence</td>
<td>ROAD INJURY</td>
<td>Stroke</td>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td>3</td>
<td>Neonatal encephalopathy</td>
<td>Diarrhea</td>
<td>Diarrhea</td>
<td>Self-harm</td>
<td>Ischemic heart disease</td>
<td>Cirrhosis</td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>4</td>
<td>Neonatal sepsis</td>
<td>Protein-energy malnutrition</td>
<td>Lower respiratory infections</td>
<td>HIV/AIDS</td>
<td>Tuberculosis</td>
<td>Lung cancer</td>
<td>Lung cancer</td>
<td>Lower respiratory infections</td>
</tr>
<tr>
<td>5</td>
<td>Diarrhea diseases</td>
<td>HIV/AIDS</td>
<td>Malaria</td>
<td>Tuberculosis</td>
<td>Self-harm</td>
<td>Tuberculosis</td>
<td>Lower respiratory infections</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>6</td>
<td>Congenital anomalies</td>
<td>Drowning</td>
<td>Drowning</td>
<td>Interpersonal violence</td>
<td>ROAD INJURY</td>
<td>Diabetes</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Malaria</td>
<td>Meningitis</td>
<td>Typhoid Fever</td>
<td>Malaria</td>
<td>Cirrhosis</td>
<td>HIV/AIDS</td>
<td>Tuberculosis</td>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>8</td>
<td>Meningitis</td>
<td>ROAD INJURY</td>
<td>Meningitis</td>
<td>Lower respiratory infections</td>
<td>Stroke</td>
<td>Liver cancer</td>
<td>Cirrhosis</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>9</td>
<td>Protein-energy malnutrition</td>
<td>Measles</td>
<td>Congenital anomalies</td>
<td>Mechanical forces</td>
<td>Lower respiratory infections</td>
<td>COPD</td>
<td>Stomach cancer</td>
<td>Other circulatory &amp; metabolic disease</td>
</tr>
<tr>
<td>10</td>
<td>Syphilis</td>
<td>Fire</td>
<td>Forces of nature</td>
<td>Diarrhea</td>
<td>Liver cancer</td>
<td>Self-harm</td>
<td>Liver cancer</td>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>
Leading causes of death globally by age group, 2010 – Females

<table>
<thead>
<tr>
<th>Females</th>
<th>Under 1 Cause</th>
<th>1-4 years Cause</th>
<th>5-9 years Cause</th>
<th>15-29 years Cause</th>
<th>30-44 years Cause</th>
<th>45-59 years Cause</th>
<th>60-71 years Cause</th>
<th>75+ years Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preterm birth complications</td>
<td>Malaria</td>
<td>Diarrheal diseases</td>
<td>HIV/AIDS</td>
<td>HIV/AIDS</td>
<td>Ischemic heart disease</td>
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</tr>
<tr>
<td>2</td>
<td>Lower respiratory infections</td>
<td>Diarrheal diseases</td>
<td>HIV/AIDS</td>
<td>Maternal disorders</td>
<td>Maternal disorders</td>
<td>Stroke</td>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td>3</td>
<td>Neonatal encephalopathy</td>
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<td>Malaria</td>
<td>Self-harm</td>
<td>Tuberculosis</td>
<td>Breast cancer</td>
<td>COPD</td>
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</tr>
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<td>4</td>
<td>Neonatal sepsis</td>
<td>Proven-energy malnutrition</td>
<td>Lower respiratory infections</td>
<td>ROAD INJURY</td>
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</tr>
<tr>
<td>7</td>
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<td>Measles</td>
<td>Drowning</td>
<td>Fire</td>
<td>ROAD INJURY</td>
<td>Lung cancer</td>
<td>Breast cancer</td>
<td>Alzheimer's disease</td>
</tr>
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<td>Cirrhosis</td>
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</tr>
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<td>Diarrheal diseases</td>
<td>Cervical cancer</td>
<td>Cirrhosis</td>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>

Transport for Health, the global burden of disease from motorized road transport World Bank, IHME 2014
## ACE Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Women (n=9,367)</th>
<th>Men (n=7,970)</th>
<th>Total (n=17,337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abuse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>13.1%</td>
<td>7.6%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Physical</td>
<td>27.0%</td>
<td>29.9%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Sexual</td>
<td>24.7%</td>
<td>16.0%</td>
<td>20.7%</td>
</tr>
<tr>
<td><strong>Household Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother Treated Violently</td>
<td>13.7%</td>
<td>11.5%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Household Substance Abuse</td>
<td>29.5%</td>
<td>23.8%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Household Mental Illness</td>
<td>23.3%</td>
<td>14.8%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Parental Separation or Divorce</td>
<td>24.5%</td>
<td>21.8%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Incarcerated Household Member</td>
<td>5.2%</td>
<td>4.1%</td>
<td>4.7%</td>
</tr>
<tr>
<td><strong>Neglect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>16.7%</td>
<td>12.4%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Physical</td>
<td>9.2%</td>
<td>10.7%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

* Wave 2 data only (n=8,667)  
Data from [www.cdc.gov/nccdphp/ace/demographics](http://www.cdc.gov/nccdphp/ace/demographics)
Figure 15 illustrates that regional pedestrian death rates are strongly associated with overall road injury death rates and differ greatly across regions. Rates of death due to pedestrian injury vary by almost an order of magnitude. They are highest in the three sub-Saharan Africa regions and lowest in Western Europe and Australasia. Total road injury death rates in these regions mirror trends in death rates from pedestrian injury. In addition to being a key part of reducing road injuries, ensuring the safety of pedestrians is essential for reducing emissions from vehicles and increasing physical activity. Promoting active transport by protecting vulnerable road users can reduce the burden of non-communicable diseases, including ischemic heart disease, stroke, lower respiratory infections, COPD, and lung cancer. Research shows that the provision of safety infrastructure for walking and biking is among the most important ways to encourage these active modes of transport. Such infrastructure includes traffic calming measures to reduce vehicle speeds, such as the use of speed bumps, curb extensions, chicanes, and roundabouts, and the provision of separated sidewalks and bicycle lanes to reduce exposure to motor vehicles.
Overview

- Epigenetic mechanisms and modifications
  - DNA Methylation
  - Histone modifications
  - microRNA
  - Retrotransposons

- Imprinted genes
Treatments based on epigenetic changes have not yet been established.

Dietary intervention studies have not shown significant results.

Future treatments possible:

- Altering epigenetic marks: gene expression, subsequent protein expression, and phenotype.
- Delineate more precisely epigenetic mechanisms that affect DNA: methylation, histone modification and microRNAs.
Rural water solution, local shallow well as raw water source

Turkan children in NW Kenya getting water from a shallow well water pump
Christine Ntahe is a children’s advocate and radio broadcaster in Burundi known as “Mama Dimanche” (“Mama Sunday”). Every Sunday, she opens her house to the homeless street children of Bujumbura, the capital of Burundi, providing them with free meal.
From here to the end of PP are things you told me to hold for Kenya talks – just in case you need them to finish other talks 😊
Helping Babies Survive (HBS) is a suite of three educational programs designed to improve neonatal survival in resource-limited areas:

- Helping Babies Breathe (HBB)
- Essential Care for Every Baby (ECEB)
- Essential Care for Small Babies (ECSB)
The HBS Curricula address 3 major causes of neonatal mortality:

- **HBB: Intrapartum-related complications**
- **ECEB: Severe Infections**
- **ECSB: Complications from preterm birth**
Launched in 2010, Helping Babies Breathe® is an evidence-based educational program to train birth attendants in the essential skills of newborn resuscitation, with the goal of having at least one person who is skilled in neonatal resuscitation at the birth of every baby.
Asphyxia accounts for nearly a quarter newborn mortalities. Among these are babies who are not breathing well at birth, and who could be helped with simple measures.

The key concept of HBB is The Golden Minute®: Within one minute of birth, a baby should be breathing well or should be ventilated with a bag and mask. The Golden Minute® identifies the steps that birth attendants must take immediately after birth to evaluate the baby and stimulate breathing.
Fantastic Success in Just Five Years!

After Nation-wide Implementation of HBB, Neonatal mortality in Tanzania dropped by 47%
The success of HBB in lowering the risk of death due to asphyxia at birth led to the development of the ECEB and ECSB training modules, which address other common causes of neonatal mortality.

Collectively these three initiatives are called *Helping Babies Survive*
Essential Care for Every Baby is a user-friendly newborn care training module designed to equip care providers with essential newborn care skills.

The curriculum covers the period after birth throughout the first day of the newborn’s life, until the time of discharge.
Up to two thirds of newborn deaths could be prevented if skilled health workers perform effective health measures at birth and during the first week of life.

The ECEB curriculum focuses on a variety of newborn care practices that can save infant lives:
• Supporting breastfeeding
• Preventing infection
• Maintaining normal temperature
• Recognizing danger signs
Essential Care for Small Babies focuses on premature and low birthweight (under 2,000 grams) infants and builds on ECEB and HBB.

The objective of ECSB is to provide birth attendants with the skills necessary to care for small babies.
An estimated 35% of neonatal deaths globally can be attributed to low birthweight or complications from preterm birth. ECSB provides education on the essential care practices that help small babies remain well and thrive:

- Supporting warmth and feeding
- Preventing infection
- Recognizing and responding promptly to problems
- Preparing a family to care for their baby
The HBS training modules may be used as stand-alone programs, integrated with one another, or integrated within a country’s existing health infrastructure.
HBS programs have been implemented in 70+ countries, and more than 300,000 health workers have been trained worldwide!
To facilitate implementation, HBS training resources have been translated into many languages. These materials are conveniently available for free access and download by visiting the AAP International Resources site:

http://internationalresources.aap.org
Want to know more?

Visit our website
helpingbabiesbreathe.org

Find us on Facebook
Facebook.com/HelpingBabiesBreathe

Follow us on Twitter
@AAPGlobalHealth

Email us
hbs@aap.org