Global Network for Women's and Children's Health Research: Achievements at the 5-Year Mark

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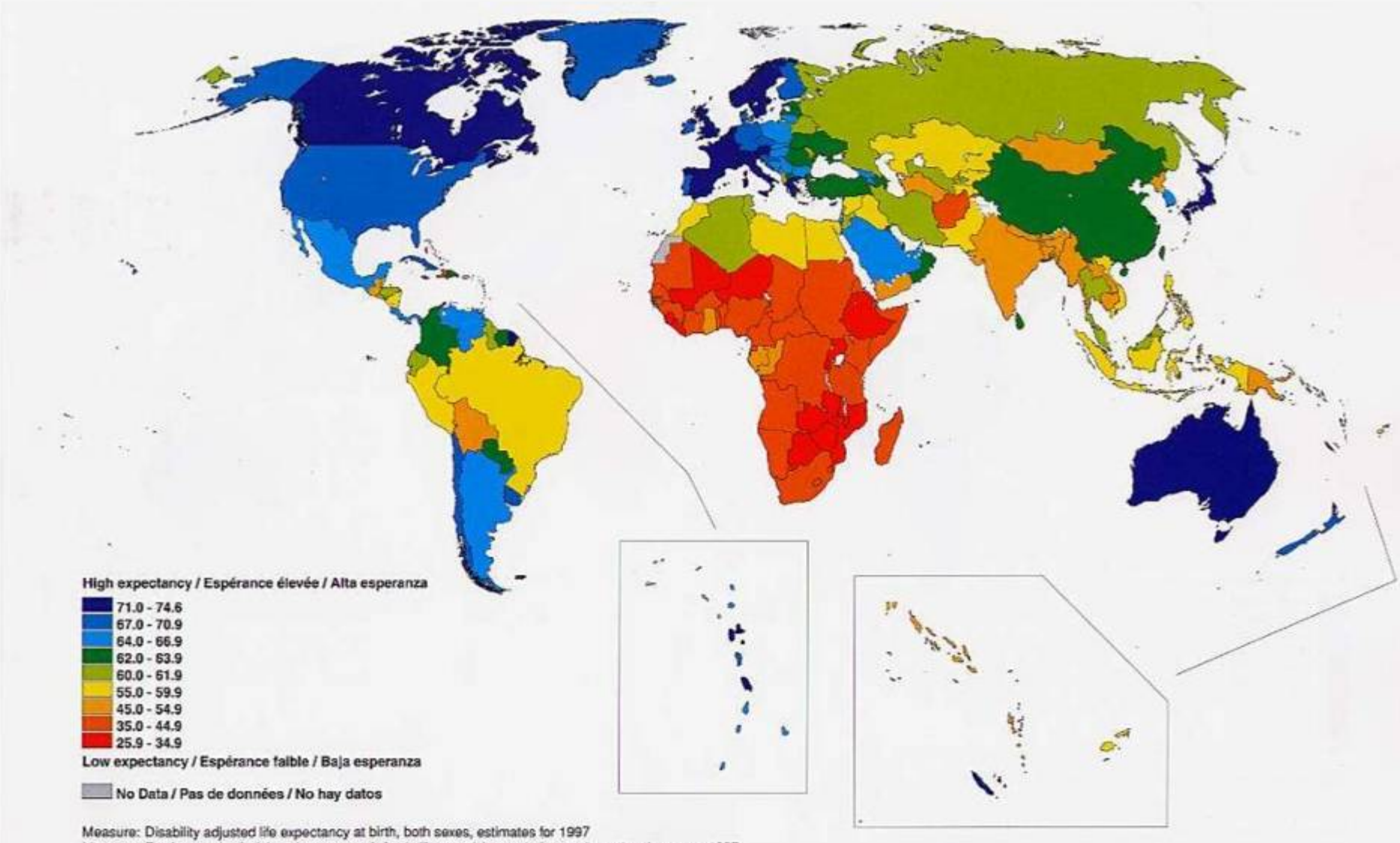
Scope of the Larger Problem

Over 1.3 billion people live in dire poverty

- **They survive on $1 or less/day/person**
- **Poorest countries spend $5-$10/person/yr**
- **Systems are poor, logistics are worse, and services and competence suffer**
- **Nearly 99% of maternal and infant deaths worldwide occur in low and middle income countries**

Healthy Life Expectancy



Leading Causes of Death Among Pregnant Women and Neonates

Women

- Hemorrhage
- Malaria and anemia
- Sepsis/unsafe abortion
- Eclampsia

Neonates

- Asphyxia
- Low birth weight
- Infection

International Research Status

- Many interventions that save maternal/ newborn lives are well known
- The challenge is to take them into the community in an affordable, sustainable manner
- Lack of epidemiologic data and communication between research groups seriously hampers research efforts

NIH and Gates Foundation

Unique private-public sector collaboration to build maternal and child health capacity in the developing world through research partnerships

Jointly established the Global Network for Women's and Children's Health Research in 2001after applications rated by competitive peer review

10 Research Units
1 Data Center (RTI)
NIH scientific staff

Global Network Partners

- NIH Partners: NICHD, FIC, NCCAM, NCI, NCRR, NIDCR, ODS, OAR, ORWH
- Non NIH Partners: PAHO, USAID, WHO, MMV, CDC
- Advisory Board for First Breath: AAP, IAP, ILCOR, Gates Foundation, MOD, PAHO, SNL, USAID, WHO

Global Network Goals

- To address important perinatal public health problems to improve the outcome of mothers and children in the developing world
- To build sustainable public health and research infrastructures
- To build scientific capacity
- To provide multidisciplinary, multi-level training opportunities

Global Network Key Principles

- Collaborative partnerships and activities
- Broad-based capacity and infrastructure building: scientific, technical, clinical, institutional, field research
- Feasible, sustainable, cost-effective, community-based interventions
- Geographic and program balance
- Potential for common protocols

Where is the Global Network?

Global Network Structure

- Multi-disciplinary research units led by a US Principal Investigator and a Senior Foreign Investigator
- A Data Coordinating Center to provide research support services
- A senior NICHD trialist to provide oversight with staff scientists assigned to individual projects to provide logistical support
- A Data Monitoring Committee and Advisory Group to provide oversight

Building a Foundation (1)

Initially:

- State Department clearance
- Federal Wide Assurance
- Institutional Review Boards
- Assistance with the foreign investigator's research administration/management system

Building a Foundation (2)

On site collaboration:

- Meet with foreign site team members
- Meet with ministries of health, government officials and community leaders
- Refine study design issues
- Assess needs for all aspects of study
- Identify training needs

Building a Foundation (3)

- Protocol development including formative research
- Manual of operations
- Data forms
- Information technology plan
- Data management system plan
- Training plan
- Pre-testing and piloting

Information Technology

- Standard hardware provided to GN Research Units through DCC
- Custom data management software; local data entry; weekly data download
- Land lines, satellite, internet access
- Local IT staff hired by DCC; training of all staff (data collection, entry, reports)

Common Hurdles

- Global Network model
  - Long term commitment
  - Foreign sites expected to bring something to the table
  - Collaborative model
  - Lack of infrastructure—grants management, computers, staff with clinical research experience

Common Hurdles

- Cultural issues
  - Very diverse sites
  - Concept of informed consent
  - Adverse event reporting
  - Systematic thinking (QC) and work ethic
- Sustainability issues
  - Maintaining local standard of care
  - Providing too much advanced technology (EpiInfo)
  - IT/DMS sophistication vs. schedule demands

Common Hurdles

Delays associated with

- Constituting IRBs; obtaining FWA; IRB clearance
- Drafting study protocols, manuals, and data forms
- Translation
- Training
- Cost of drugs, equipment, shipping (customs)
- Regulatory issues (data, contracts, imports, indemnification)
- Overly ambitious designs
- Changing political environments

Global Network Trials

- Preventing postpartum hemorrhage
- Preventing preeclampsia
- Preventing asphyxia
- Reducing infection-related perinatal mortality
- Tibetan child birth practices
- Preventing neonatal sepsis
- Decreasing LBW
- Preventing cleft lip and palate

Global Network Trials

Reducing deaths from postpartum hemorrhage

1. RCT of misoprostol to reduce PPH (n=1620) given by ANMs in Indian clinics; calibrated drape to measure blood loss
2. RCT of behavioral interventions to increase 2 evidence-based birth practices in 19 hospitals: (2 in Uruguay; 17 in Argentina):
   - selective use of episiotomies
   - oxytocin in 3rd stage of labor to prevent PPH
3. RCT of ZB11 vs. misoprostol in TAR to prevent PPH (n=800); blood collection drape to measure blood loss

Reducing deaths from preeclampsia

1. RCT of vitamin C and E to reduce incidence and severity of preeclampsia in 4 Brazilian university clinics

Global Network Trials

Reducing infection-related perinatal mortality

1. Risk factors for poor perinatal outcome (observational);
2. RCT of chlorhexidine (CHX) vaginal and infant wash to reduce perinatal mortality and morbidity

Reducing neonatal sepsis deaths

1. Prospective epi study of infants with suspected sepsis (>200 Indian villages); identify sources of organisms causing neonatal sepsis
2. Hospital RCT of safety/colonizing ability of a probiotic (n=330)
3. Community-based RCT of a probiotic to reduce neonatal sepsis

Treating malaria in pregnant women

1. 1st PK/PD study of artestunate in pregnant women

Global Network Trials

Preventing cleft lip and palate

1. Case-control study of intense management in 1st 28 days (A) followed by RCT (B) of two levels of care in a subset of isolated CLP to 2 yrs
2. RCT of 4 mg vs. 0.4 mg folate to moms with CLP or previous child with CLP to decrease recurrence

Decreasing LBW/prematurity

1. Nested RCT to test the effect of:
   - High vs. low phytate maize in 600 maternal/ infant pairs on birth weight
   - Nested RCT of Zn supplementation on infant growth
   - Metabolic study of Zn metabolism

Global Network Studies

Epidemiology of monkeypox in the DRC

1. Population-based prospective study to define the incidence, clinical, epidemiologic, ecologic characteristics of MPX in a high-risk population

Improving Tibetan child birth practices

1. Training of OBs and TBAs in western OB care
2. Ethnographic study of childbirth practices/beliefs

Global Network Tobacco Study

A 9-site survey to investigate:

- Tobacco use in 9,000 pregnant women
- Environmental tobacco smoke exposure
- Knowledge of attitudes toward health hazards of tobacco use
- Help inform and guide interventions to reduce women's tobacco use
- Serve as a "baseline" to measure the impact of future work (baby step toward maternal GDB)

Global Network Trials

Reducing mortality due to asphyxia

1. Pre-post study comparing effects on mortality of two neonatal resuscitation training programs in clinics in Lusaka/Ndola (WHO Essential Newborn Care vs. ENC + AAP Neonatal Resuscitation Program)
2. Common GN cluster randomized trial to compare the effects on mortality of two resuscitation training methods
   - all birth attendants in >80 communities of at least 500 births/yr and >4,000 birth attendants trained
   - baseline data, 6 mos of ENC, 12 mo ENC + NRP
3. Validation of community workers' verbal autopsy
4. Parent early infant stimulation trial planned in 3 cos.

Global Network Successes

1. Indian community RCT of misoprostol decreased PPH by ~50% (*Lancet* Oct 7, 2006)
2. Guidelines trial increased oxytocin use by 90% and decreased episiotomies by 30%
3. Indian sepsis surveillance decreased NMR by >20%
4. First research done in Tibet
5. 7 sites have Global Scholars projects
6. FIRST BREATH Zambian pilot scaled up at 7 sites
   - birth registries established
   - stillbirths differentiated from early neonatal deaths
   - preliminary Zm clinic data showed 50% decrease 7-day mortality with ENC

Reducing Neonatal Sepsis Deaths

- 33% of the 4 million neonatal deaths per year occur in India
- Majority of births and neonatal deaths in India take place at home in the villages
- Indian babies born in the village die in the village

Reducing Neonatal Sepsis Deaths

Evaluate the effects of a community-based educational intervention on infant and neonatal mortality

Community Educational Intervention

- 223 study villages; 254 control villages in the State of Orissa
- AWNs registered women in 7th month of pregnancy; monitored wkly
- Monitor newborns daily for 60-days after birth for signs of sepsis
- “Suspect” sepsis cases referred to local hospitals for evaluation/treatment

Impact of AWW Education on IMR and NMR One Year Later

- 25 % reduction in IMR
- 20% reduction in NMR

Conclusions

- Mothers in rural Indian villages can be educated easily re neonatal ailments
- Once informed, mothers will continue to bring their babies to local hospitals for treatment
- Reductions in IMR and NMR are sustainable using the existing facilities

Global Network's Dilemma/ Opportunity

- How to fulfill our mission more rapidly and cost effectively?
- How to simultaneously build scientific capacity?
- How to do this in such diverse countries?
- How to ensure dissemination?
- How to obtain funding?

Our Approach

To transform the Global Network from a group of ambitious individual projects into an international resource that can perform several simultaneous common trials and studies

Future Directions

- Re-issue RFA to start in April 2008
- Multiple concurrent common protocols
- Increase collaboration with other funding agencies, NGOs, and industry
- Improve in-country research capacity
- Simplify/improve efficiency
  - Ethics training
  - Good Clinical, Good Lab Practices
  - Quality improvement efforts
- Intervention packages: ANS/KMC & EBF/CF

Thanks

- To the wonderful Global Network investigators
- To the mothers and children of the developing world that are struggling against terrible odds to survive and thrive
- To all the individuals who are working on their behalf

The Global Network

- **US PI Carl Bose,** MD, UNC; **SFI Antoinette Tshefu**, Sch of Public Health, DRC
- **US PI Pierre Buekens**, MD/ PhD, Tulane Sch of Public Health; **SFI: Jose Belizan**, MD Instit for Clinical Effectiveness & Health Policy, Univ of Buenos Aires
- **US PI Waldemar Carlo**, MD, UAB; **SFI Elwyn Chomba**, Univ Teaching Hosp ZM
- **US PI Richard Derman**, MD, MPH, University of MO, KC; **SFI Bhalchandra Kodkany**, MD, MBBS, Jawaharal Nehru Medical College
- **US PI Robert Goldenberg**, MD, UAB; **SFI Omrana Pasha**, MD, Aga Khan Univ
- **US PI Michael Hambidge**, MD, University of Colorado; **SFI Manolo Mariegos**, MD, CESSIAM, Guatemala
- **US PI Jeff Murray**, MD, University of Iowa; **SFI Eduardo Castilla**, MD, ECLAMC & Danilo Moretti, MD, Centrinho
- **US PI Pinaki Panigrahi**, MD/PhD, Univ of Maryland; **SFI SN Parida**, MD, SCB Medical College, Orissa
- **US PI Joseph Spinnato II**, MD, Univ of Cincinnati; **SFI Salvio Freire**, MD, PhD, Univ of Pernambuco
- **US PI Michael Varner**, MD, University of Utah; **SFI Dr. Tudeng**, TAR Health Bur
- **US PI Ty Hartwell,** PhD; Co-PI **Beth McClure**, Research Triangle Instit Internatl
- **NICHD Yvonne Maddox**, PhD**; Anne Willoughby**, MD; **Linda L. Wright**, M.D.; **Macaya Douoguih**, M.D., **Lorette Javois**, PhD; **Nancy Moss**, PhD

Global Network for Women's and Children's Health Research

http://gn.rti.org
http://www.globalhealthreporting.org
http://ClinicalTrials.gov

Prevention of Postpartum Hemorrhage

U.S. PI	Richard Derman, MD, MPH, University of MO, KC
SFI	Bhalchandra Kodkany, MD, MBBS, Jawaharal Nehru Medical College
Locations	Village health posts of 4 primary health centers
Design	RCT placebo-controlled trial of misoprostol administered by auxiliary nurse midwives to reduce postpartum hemorrhage; calibrated drape to measure blood loss

Tibetan Childbirth Practices

U.S. PI	Michael Varner, MD, University of Utah
SFI	Dr. Tudeng, Director TAR Health Bureau
Locations	Lhasa: Tibet
Design	Training of OBs and TBAs in western OB care Ethnographic study of childbirth practices/beliefs Pilot study of use of blood collection drape Pilot RCT of ZB11 vs. misoprostol for PPH

Cleft Lip and Palate

U.S. PI	Jeff Murray, MD, University of Iowa
SFI	Eduardo Castilla, MD, ECLAMC & Danilo Moretti, MD, Centrinho
Locations	Maternity hospitals (Argentina, Bolivia, Brazil, Chile, Columbia, Ecuador & Venezuela) Centrinho Hospital (Brazil)
Design	Case-control study of intense management in 1st 28 days (A) followed by randomized trial (B) of two care levels in a subset of isolated CLP to 2 yrs RCT of 4 mg vs. 0.4 mg folate supplementation to decrease recurrence in high-risk moms (mom has CLP or previous child with CLP)

Preeclampsia

U.S. PI	Joseph Spinnato II, MD, Univ of Cincinnati
SFI	Salvio Freire, MD, PhD, Univ of Pernambuco
Locations	4 Brazilian university hospital clinics (Recife, Botucatu, Porto Alegre, Campinas)
Design	RCT of antioxidant therapy (C and E) to reduce incidence and severity of preeclampsia

Improving Management of Labor

U.S. PI	Pierre Buekens, MD, PhD, UNC/Tulane
SFI	Jose Belizan, MD Institute for Clinical Effectiveness and Health Policy, University of Buenos Aires
Location	19 hospitals (Argentina-17; Uruguay-2)
Design	RCT of behavioral interventions to increase two evidence-based birth practices: • selective use of episiotomies • oxytocin in 3rd stage of labor to prevent PPH

Reducing Low Birth Weight

U.S. PI	Michael Hambidge, MD, University of Colorado
SFI	Manolo Mariegos, MD, CESSIAM, Guatemala
Locations	Comalapa, Western Highlands of Guatemala
Design	Nested RCT to test the effect of:

High vs. low phytate maize in 600 maternal/ infant pairs on birth weight

Nested RCT of zinc supplementation on infant growth

Metabolic study of Zn metabolism

Preventing Neonatal Sepsis

U.S. PI	Pinaki Panigrahi, MD, PhD, Univ of Maryland
SFI	SN Parida, MD, SCB Medical College, Orissa
Locations	200+ matched villages in the State of Orissa Hospitals in Mumbai, Rourkela, Bhubaneswar New Delhi
Design	Prospective epi study of infants with suspected sepsis; identify sources of organisms causing neonatal sepsis Phase I hospital pilot (n=30) Phase II hospital pilot (n=300) Community-based RCT of probiotics to reduce neonatal sepsis Phase III probiotic community RCT

Reducing Infection-Related Perinatal Mortality

U.S. PI	Robert Goldenberg, MD, UAB
SFI	Omrana Pasha, MD, The Aga Khan University
Locations	Aga Khan University; Civil Hospital, Karachi Hyderabad (clinics)
Design	Observational study of risk factors for poor perinatal outcome Feasibility pilot RCT of chlorhexidine (CHX) vaginal and infant wash

Management of Malaria in Pregnant Women

U.S. PI Robert Ryder, MD, UNC at Chapel Hill
SFI Antoinette Tshefu, School of Public Health, DRC

Location Kinshasa

Design 1) Pilot of STIs and malaria (n=2108)
Prevalence of HIV: 2%
Prevalence of malaria: 34%
Prevalence of SP-resistance: 4%
2) PK/PD study of artesunate in pregnancy (IND)

Monkeypox Study

U.S. PI	Robert Ryder, MD, UNC at Chapel Hill
SFI	Jean Muyembe, MD NIBMR, DRC Dr. Okitolanda, KSPH, DRC **Dr. Anne Rimoin, NICHD/UCLA**
Location	Kasai Province
Design	Population-based prospective study to define the incidence, clinical, epidemiologic, ecologic characteristics of MPX in population at high risk for MPX

Neonatal Resuscitation

U.S. PI	Waldemar Carlo, MD, UAB at Birmingham
SFI	Elwyn Chomba, Univ Teaching Hospital, ZM
Location	19 community-based birth clinics in Lusaka/Ndola
Design	Cluster RCT to compare effect of two neonatal resuscitation programs on mortality Midwives trained to resuscitate asphyxiated newborns using the new WHO Essential Neonatal Care (ENC) vs. Neonatal Resuscitation Program + ENC

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Neonatal Resuscitation

Revised design

Location	18 community-based birth clinics	
Design	Pre-post study to compare effects of two neonatal resuscitation programs on mortality	
Status	Aug 2004	Trained 40 NMW in data collection
	Jan 2005	Trained NMW on WHO ENC
	Dec 2005	Trained NMW in NRP
	Feb 2005	7,230 enrolled in 3 mos
		5,561 7d FU (78%)

Misoprostol Trial: PPH Rates

Primary Outcome	Misoprostol (N= 812*) N (%)	Placebo (N=805) N (%)	
Postpartum Hemorrhage (≥ 500 ml)	53 (6.5)	97 (12.0)	0.0001
Severe Postpartum Hemorrhage (≥ 1,000 ml)	2 (0.2)	10 (1.2)	

Global Network Results

- Guidelines Trial in So America increased oxytocin use and decreased episiotomies
- Community misoprostol RCT in India decreased PPH
- Indian sepsis surveillance study decreased NMR
- 7 sites have Global Scholars projects
- We introduced ethnographic, consent, RCTs to TAR
- FIRST BREATH Zambian pilot scaled up to test WHO ENC vs. AAP NRP at 7 sites

International Research Status

- Many interventions that save maternal/ newborn lives are well known
- The challenge is to take them into the community in an affordable, sustainable manner
- Lack of epidemiologic data and communication between research groups seriously hampers research efforts

Bhubaneswar ,India

Global Network for Women's and Children's Health Research

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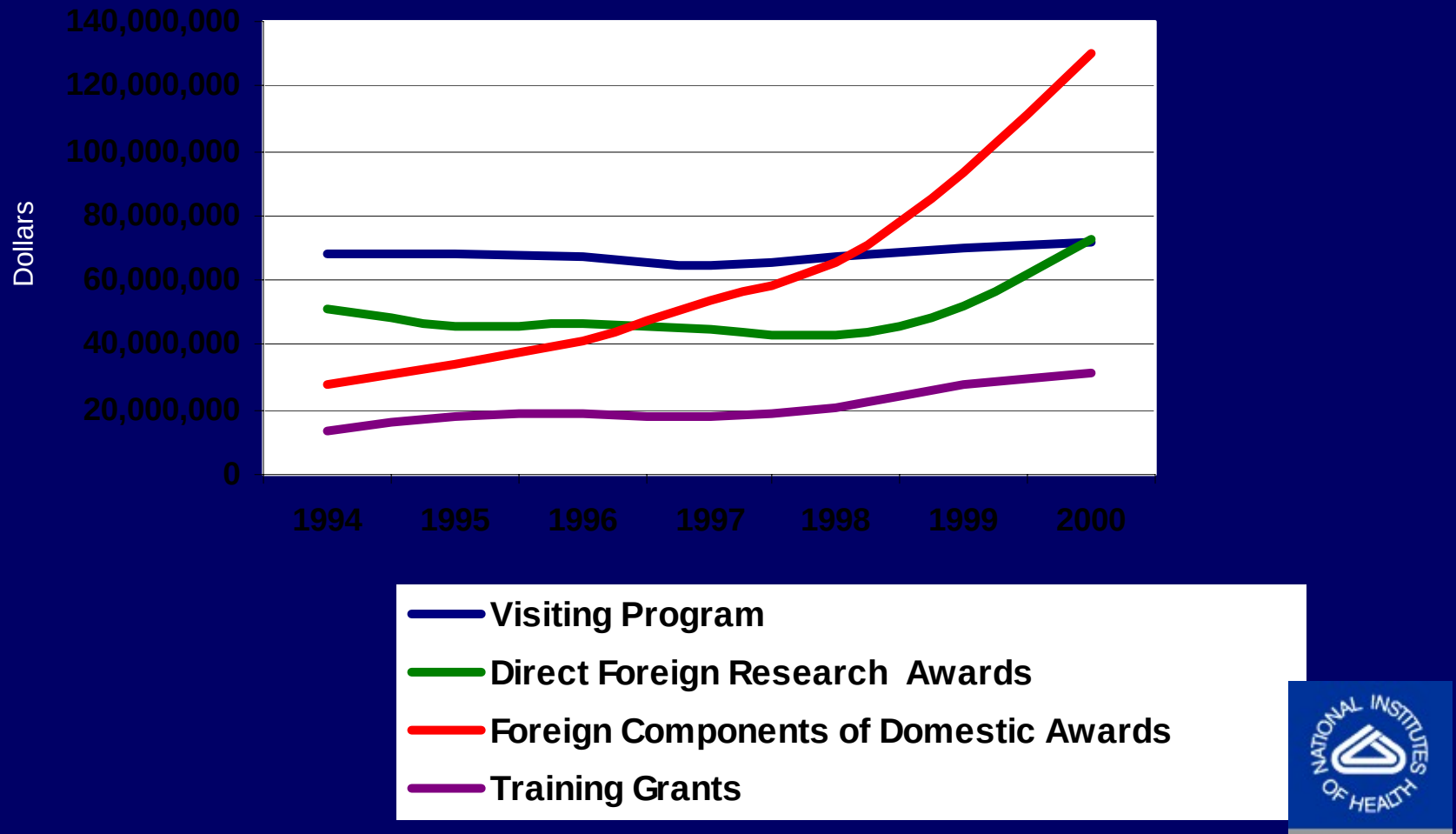
NIH International Research Expenditures

Fiscal Years 1994 to 2000



FIC-NICHD Collaborations in Global Health

Research and Training

Bioethics; Maternal and Child Health; Population and Health; International Clinical/Operational/Health Services Research and Training Award for AIDS/TB

Building U.S. Capacity in International Research

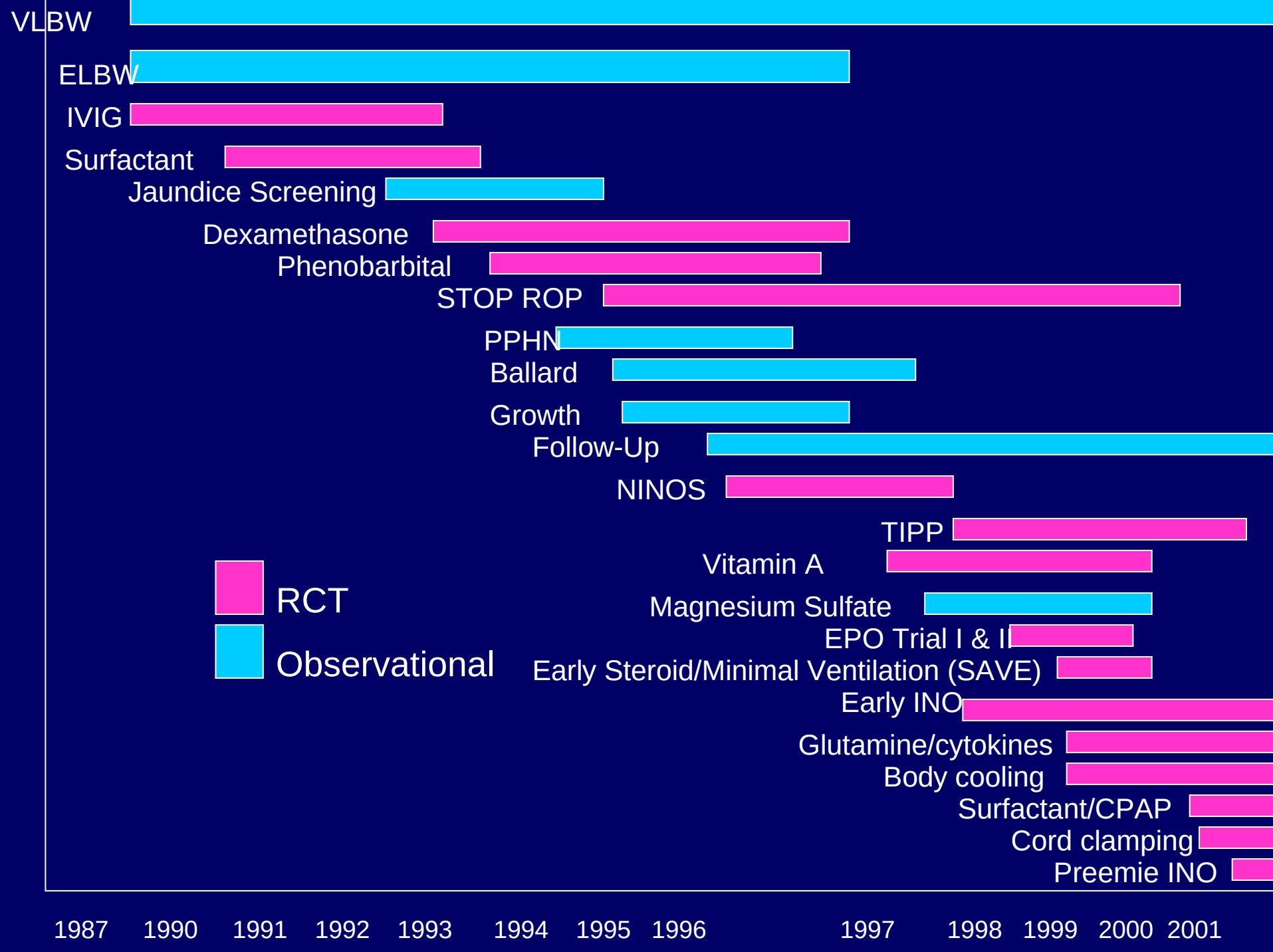
International Research Scholar Development Award

RO1/R21 Awards

Tobacco and Health; Brain Disorders in the Developing World; Health and Economic Development; Health, Environment and Economic Development; International Collaborative Biodiversity Groups

All programs evaluated by rigorous competitive NIH review

JOHN E. FOGARTY INTERNATIONAL CENTER


VLBW
ELBW
IVIG
Surfactant
Jaundice Screening
Dexamethasone
Phenobarbital
STOP ROP
PPHN
Ballard
Growth
Follow-Up
NINOS
TIPP
Vitamin A
Magnesium Sulfate
EPO Trial I & II
Early Steroid/Minimal Ventilation (SAVE)
Early INO
Glutamine/cytokines
Body cooling
Surfactant/CPAP
Cord clamping
Preemie INO
RCT
Observational
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Guidelines Trial: Summary of Results

	RR (95% CI)	RRR
• Episiotomy (all)	0.72 (0.64-0.82)	28%
– Primips	0.77 (0.62-0.94)	23%
– Multips	0.64 (0.45-0.89)	36%
• 3rd – 4th degree tears	1.15 (0.38-3.47)	-15%
• Perineal sutures	0.89 (0.79-1.01)	11%
• No active management	0.10 (0.09-0.36)	90%
• PPH ≥ 500	0.51 (0.33-0.78)	49%
• PPH ≥ 1000	0.32 (0.16-0.63)	68%
• Mean blood loss	- -73 ml	
• Manual extraction of placenta	2.10 (0.57-7.66)	- 110%

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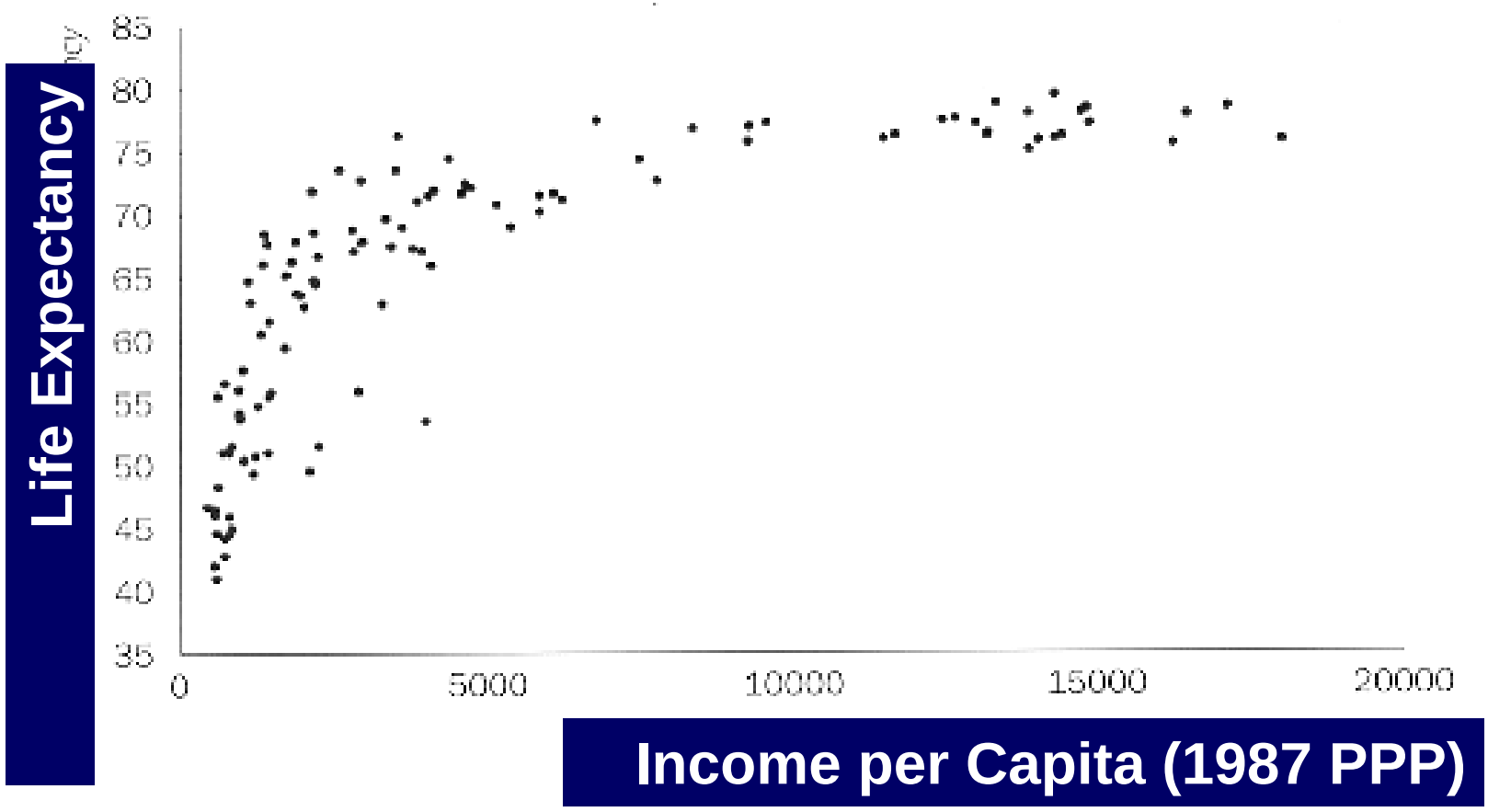
Global Network Organization

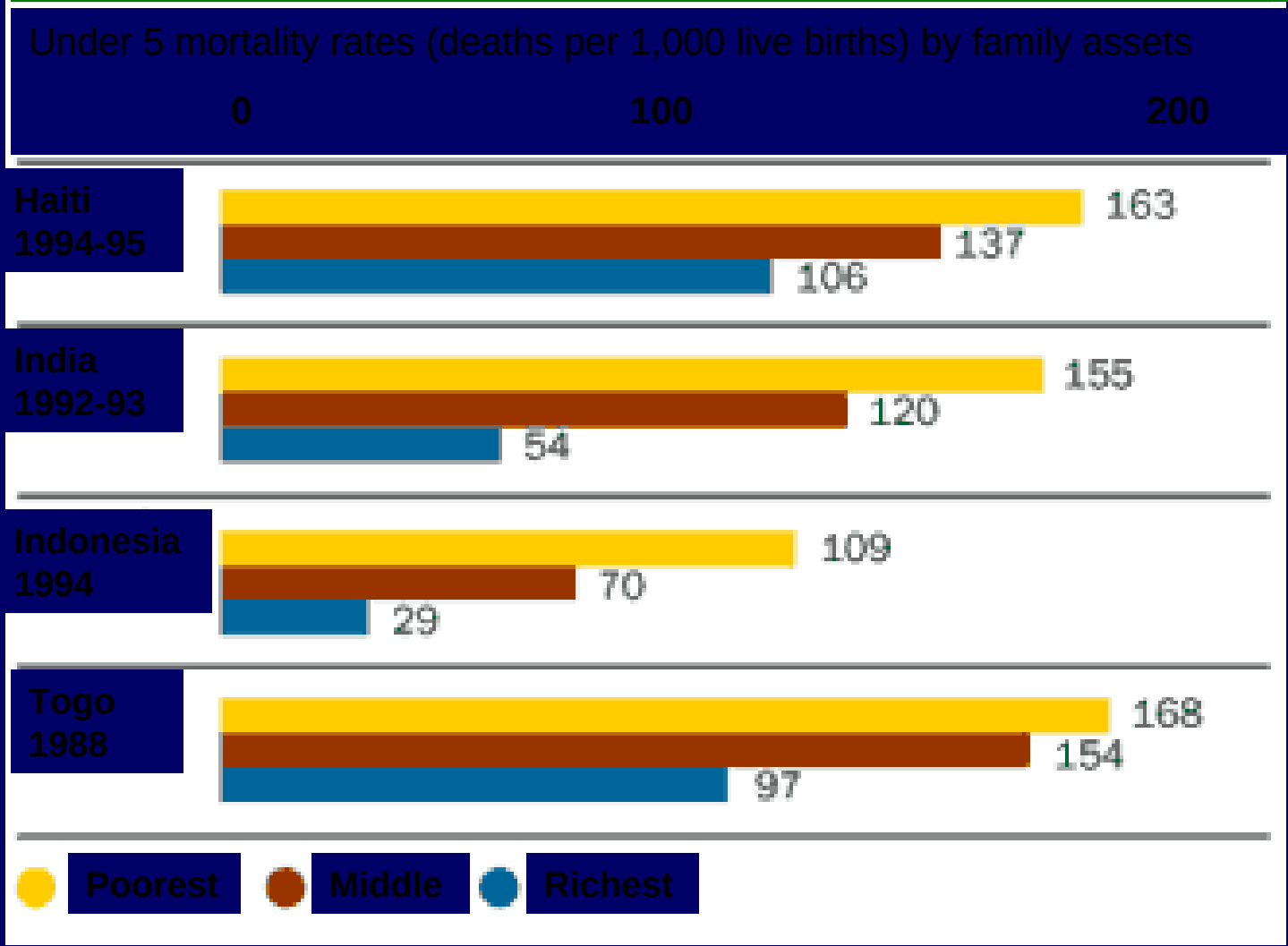
Kinshasa Pilot Results

- Prevalence of STIs (based on first 524)
  - Chlamydia: <2
  - Gonorrhea: <1%
  - Trichomonas: <8%
  - Syphilis: <1%
  - BV: 35%
- Prevalence of HIV: 2%
- Prevalence of malaria: 34%
- Prevalence of SP-resistance: 4%

Income is Highly Correlated with Life Expectancy



More Poor Children Die



Causes of Death Differ with State of Development

- In the high income countries, chronic non-communicable diseases are the major cause of death
- In the low income countries, infectious diseases account for 3/4 of the mortality in the under 5 year old group and up to half the mortality in adults
- As countries develop, there is a shift from communicable to non-communicable disease burdens

Fogarty International Center

What Can NIH and US Scientists Do?

- More research relevant to the problems: basic, translational, operational, health care delivery
- "Grand Challenges in Global Health Initiative", a new $200M program from the Gates Foundation
- Improve access to information globally – Harold Varmus' "Public Library of Science"
- Transfer technology to developing nations and create opportunities for local research using national resources
- Advocate to increase effective first world spending to improve third world health