

New evidence on intervention efficacy & effectiveness

Betty Kirkwood

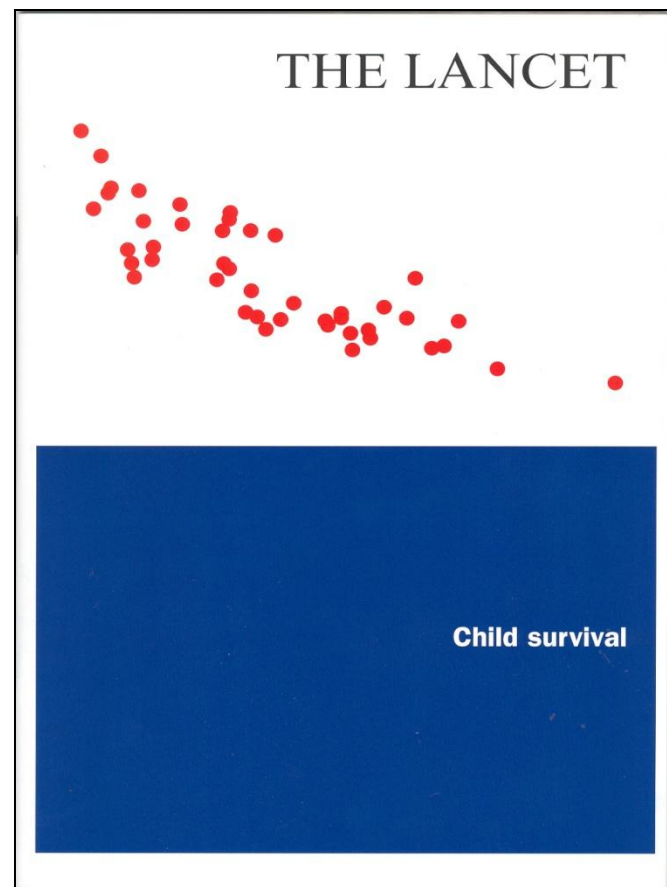
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New research evidence

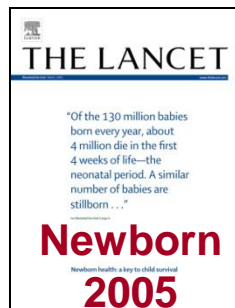
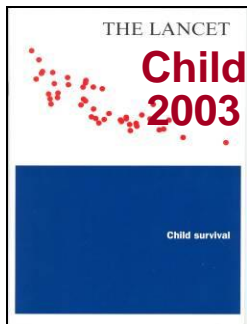
- Introduction
- What's new since Countdown 2008
 - Child survival (Betty Kirkwood)
 - Newborn survival (Joy Lawn)
 - Maternal survival (Fernando Althabe)
 - Implementation (Anuraj Shankar)
- What's on the horizon
- Major gaps

The beginning!

- **Lancet Child Survival Series 2003**
- **23 effective affordable interventions**
 - 15 preventive (9 child, 6 newborn)
 - 8 case-management (6 child, 2 newborn)
- **Could save 6.6m of 10.6m deaths**
- **Call to action: child survival fallen off the agenda**



**About 200
interventions**



- 15 effective child survival interventions + RUTF for SAM
- 6 to watch

New Evidence

- Promoted interventions
 - Challenging current thinking
 - PMNCH review
- Interventions “on watch”
 - Accumulating evidence base
- New interventions
- Good ideas that don’t work
- Delivery strategies
- Implementation

Thanks to

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New evidence: adapting existing intervention

Severe pneumonia: Amoxycillin & task shifting

- Pakistan Randomised Open-label Equivalency Trial:
 - Home treatment with high-dose oral amoxicillin equivalent to hospitalisation and parenteral ampicillin
 - Treatment failure at day 6: 7.5% vs 8.6%; $P > 0.05$
- Observational cohort study Bangladesh:
 - CFR reduced from 1.1% (when cases referred) to 0.6% (treatment at 1st level facilities introduced); $P = 0.39$
- Pakistan cluster RCT of home management of severe pneumonia by Lady Health Workers:
 - Encouraging preliminary findings

New evidence: adapting existing intervention

HIV+ mothers: BF then Abrupt weaning

- RCT Lusaka Zambia
 - Counseling encouraged abrupt weaning at 4 months
 - encouraged continued BF for as long as women chose.
- The primary outcome was either HIV infection or death of the child by 24 months.
- No difference in rate of HIV-free survival at 24 months; 68.4% vs 64.0% survived ($P=0.13$)
- Higher mortality among children HIV+ by 4 months in intervention group; 73.6% vs. 54.8% ($P = 0.007$)

New evidence: “on watch” intervention

HIV+ infants: Early ARVs reduce mortality

- RCT South Africa: HIV+ infants 6-12 weeks
 - Immediate ARVs
 - Deferred: CD4 <20% (25% aged < 1 year) or clinical criteria
- Early ARVs reduced:
 - Early infant mortality by 76% (49%-89%, $P < 0.001$); 4% vs 16%
 - HIV progression by 75% (59%-85%, $P < 0.001$); 6% vs 26%
 - Stopped by DSMB (average 40 weeks followup)

Violari et al, NEJM 2008

New intervention “to watch”: “old” intervention, new outcome

Antenatal iron & Child mortality

- RCT Nepal; 7 year follow-up; 3761 children

	Deaths/1000 child years	HR (95% CI)
VA (control)	15.2	1
VA+Folic acid	13.4	0.90 (0.65,1.22)
VA+Folic acid+IRON	10.3	0.69 (0.49,0.99)
VA+Folic acid+IRON+zinc	12.0	0.80 (0.58,1.11)
MMN (above + 11 others)	14.0	0.93 (0.66,1.31)

New intervention: rediscovery of old intervention

Indoor residual spraying (IRS)

- WHO Position Paper 2006; recommends IRS as a major means of malaria vector control
- New systematic review; Evidence gaps
- Bioko, Equatorial Guinea: intensive malaria control
 - IRS all houses; ACT (oral artesunate with SP) free of charge to children < 15 years and pregnant women as the first-line treatment, IPTp (2004-2008)
 - Under-5 mortality fell from 152 to 55 per 1,000
 - 66% reduction [95% CI = 51%–77%]

Pluess et al, Cochrane Review 2010
Kleinschmidt et al, AJTMH 2009

“On watch” vaccines

New evidence

■ **Rotavirus Vaccine:**

- High efficacy: LA/US
- New RCT South Africa & Malawi
- VE 61.2% (44.0%, 73.2%); lower in Malawi than SA

■ **Pneumococcal conjugate 11 valent vaccine:**

- RCT Philippines; VE 22.9% (-1.1%, 41.2%) Xray Pn
- No impact on clinical pneumonia

■ **PCV7:**

- Trend data (USA) suggest 64% reduction in meningitis in those aged < 2 years

Madhi et al, NEJM 2010

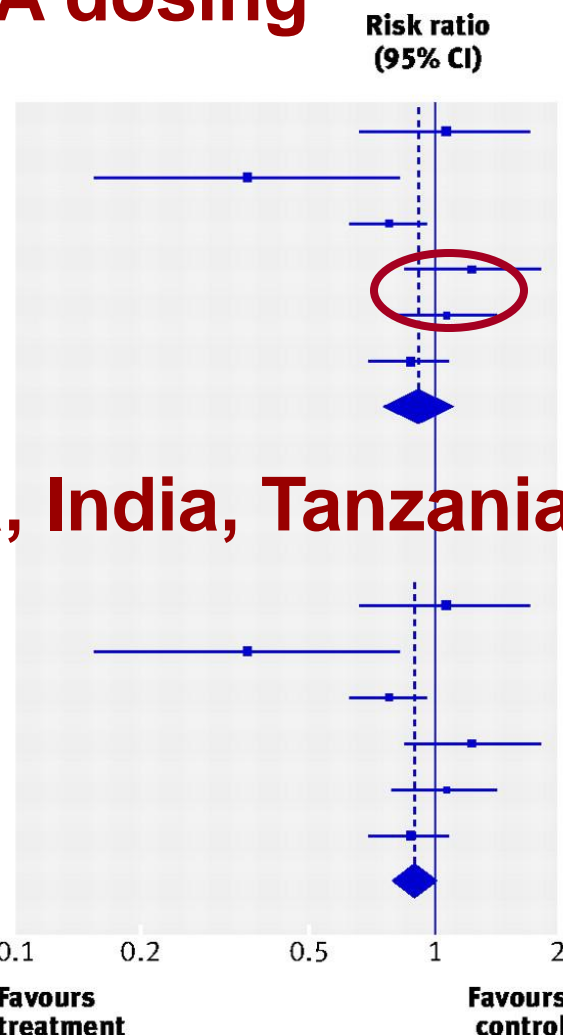
Lucero et al, PIDJ 2009; Hsu et al NEJM 2009

Accumulating evidence: intervention “to watch”

Newborn vitamin A dosing

Random effects model

West (0-1 mo) 1995
Humphrey 1996
Rahmathullah 2003
Malaba 2005
Benn 2008
Klemm 2008
Overall ($I^2=54.1\%$, $P=0.053$)



Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
11.48	11.48	1.07 (0.66 to 1.73)
4.77	4.77	0.36 (0.15 to 0.84)
24.70	24.70	0.78 (0.63 to 0.96)
15.61	15.61	1.24 (0.85 to 1.79)
19.23	19.23	1.07 (0.79 to 1.44)
24.21	24.21	0.88 (0.71 to 1.10)
100.00	100.00	0.92 (0.75 to 1.12)

New trials: Ghana, India, Tanzania

Fixed effects model

West (0-1 mo) 1995
Humphrey 1996
Rahmathullah 2003
Malaba 2005
Benn 2008
Klemm 2008
Overall ($I^2=54.1\%$, $P=0.053$)

Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
6.44	6.44	1.07 (0.66 to 1.73)
2.06	2.06	0.36 (0.15 to 0.84)
33.33	33.33	0.78 (0.63 to 0.96)
10.71	10.71	1.24 (0.85 to 1.79)
16.40	16.40	1.07 (0.79 to 1.44)
31.05	31.05	0.88 (0.71 to 1.10)
100.00	100.00	0.90 (0.80 to 1.02)

Accumulating evidence: intervention “to watch”

Home fortification: complementary foods

- Systematic review and meta-analysis:
 - Micronutrient powders (e.g. Sprinkles®), crushable tablets and lipid-based or soy-based products.
 - 16 trials (5 anaemia treatment, 11 prevention)
- Home fortification highly effective for prevention of iron deficiency and iron deficiency anaemia.
- Products that contain both micronutrients and a small amount of energy (mainly from fat and protein) can have positive effects on child growth & development.
- Acceptability high by caregivers and young children.

On the horizon: New child survival intervention?

Mass distribution of oral azithromycin

- Cluster RCT Ethiopia: Mass distribution for trachoma control
- Reduced mortality among children aged 1-9 years:
 - 18,415 children; 48 clusters
 - 4.1 vs 8.3 per 1000 child years
 - $RR = 0.51$ (0.29-0.90); $P=.02$

- RSV & malaria vaccines
- Lab on a chip diagnostic tools
- Sound wave analysis for auscultation of pneumonia
- Improved stoves that dramatically reduce IAP & cost <\$30
- Low cost micronutrient fortified, lipid-based supplements for home fortification (maternal diets, complementary foods)
- Maternal depression; Domestic violence

Interventions to improve nutrition in 1st 2 years: window of opportunity

- Growth faltering occurs in the first 2 years and increases short-term mortality
- The timing of weight gain affects the future risk of chronic diseases
 - Early weight gain is neutral or even protective
 - Later weight gain is consistently detrimental
- The worst possible combination seems to be early undernutrition followed by later rapid weight gain

Major gaps

Evidence-based implementation

- Delivering interventions effectively and equitably. And at scale. And with an impact.
- Bridging trial impact – programme delivery gap:
Mortality impact in routine implementation