

INSTITUTE FOR DISEASE MODELING

INTELLECTUAL VENTURES®

Keeping the Promise of Child Mortality Reduction Strategies: Initial Models and Thoughts

Assaf Oron, IDM, April 2018

Acknowledgments and Talk Topics

I joined IDM's Epidemiology team in December, recruited specifically to help IDM's expanding work on general maternal and childhood mortality and morbidity.

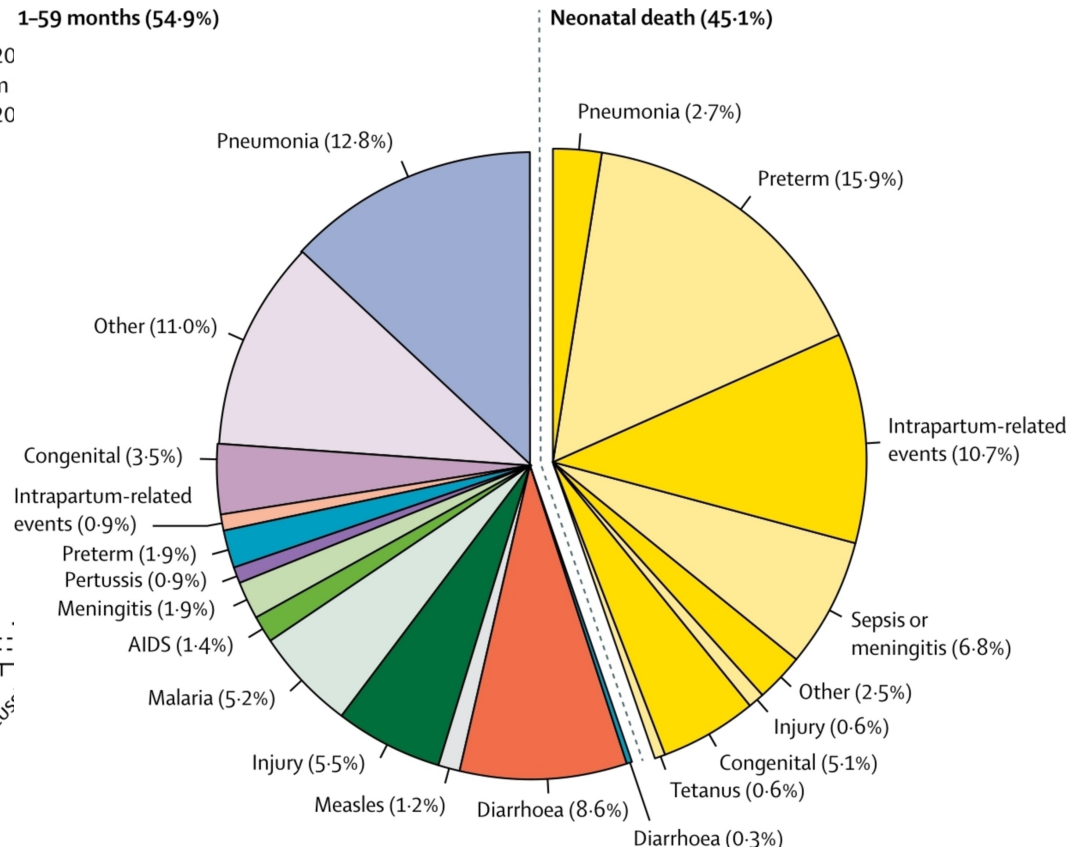
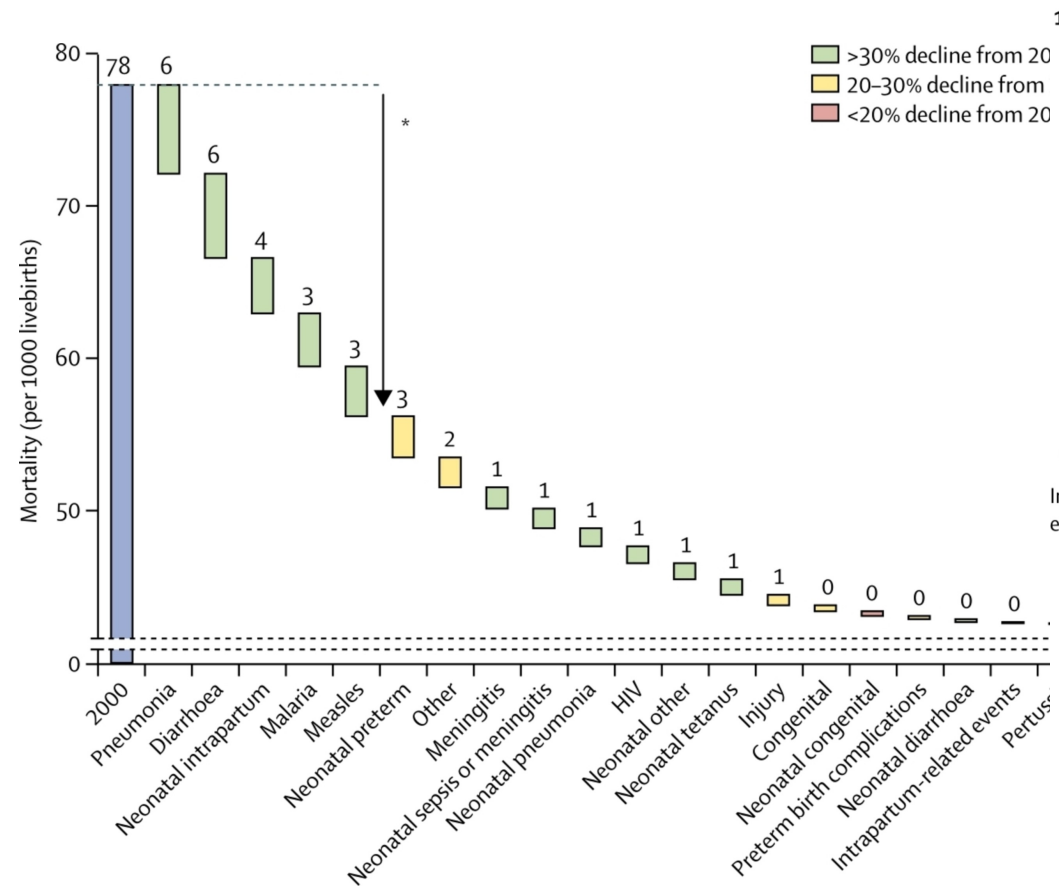
Acknowledgments (partial list): Hao Hu, Edward Wenger, Philip Welkhoff, Dennis Chao and the rest of the Epi team, Kevin McCarthy and the Measles team, Anna Bershteyn, Laina Mercer, Hil Lyons, Rasa Izadnegahdar, Laura Lamberti, Travis Porco, Roy Burstein, Amelie von St.Andre – von Arnim

I will present two work-in-progress topics, and an inkling of directions on a third topic. All input welcome, to aoron@idmod.org.

- **Nonspecific mortality-reduction effect of the Measles Vaccine**
- **Simulating future mass Azithromycin MDA impact (REACH)**
- ✓ Access, delivery, and care improvements

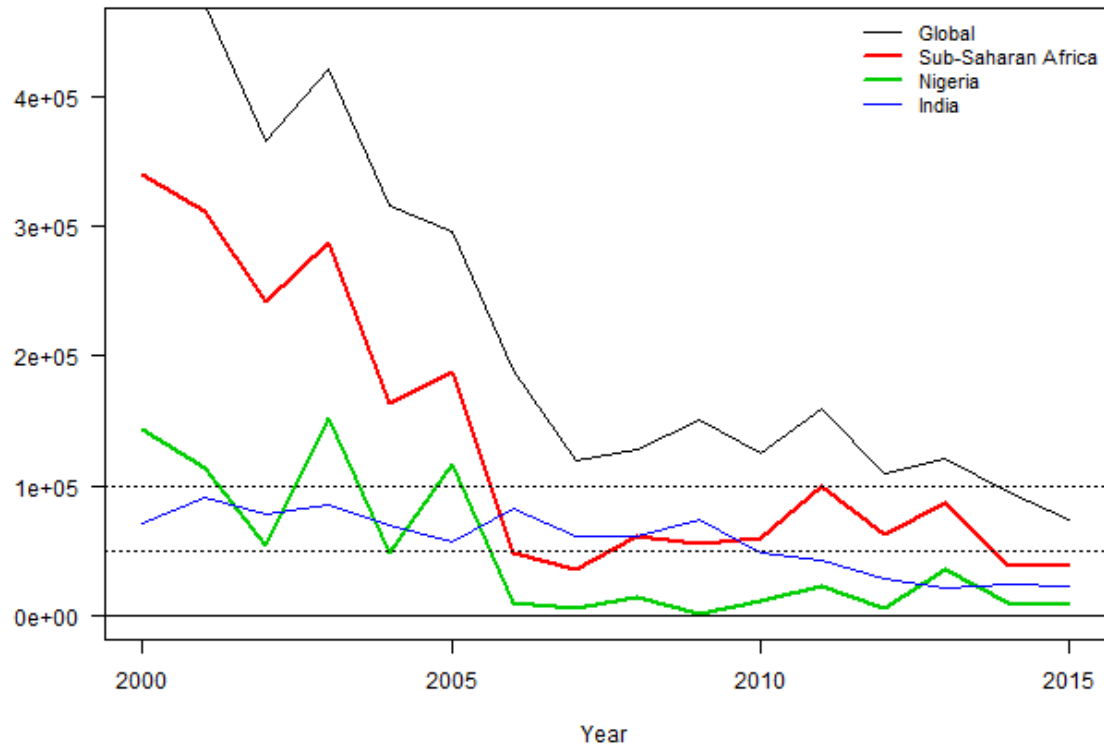
The Riddle of Measles Impact

- Work with the IDM Measles team: Kevin McCarthy, Niket Thakkar and Kurt Frey
(Unfortunately the Measles session is right now – so I can't be there and they can't be here.)
- First, a reminder that unlike other leading child-mortality causes (malaria/AIDS/enteric/respiratory/neonatal), for measles we have an intervention – measles-containing-vaccine (MCV) – that ticks all boxes:
 - ✓ **Highly effective with a proven track-record**
 - ✓ **Safe**
 - ✓ **Cheap**
 - ✓ **Already in every country's standard program.**

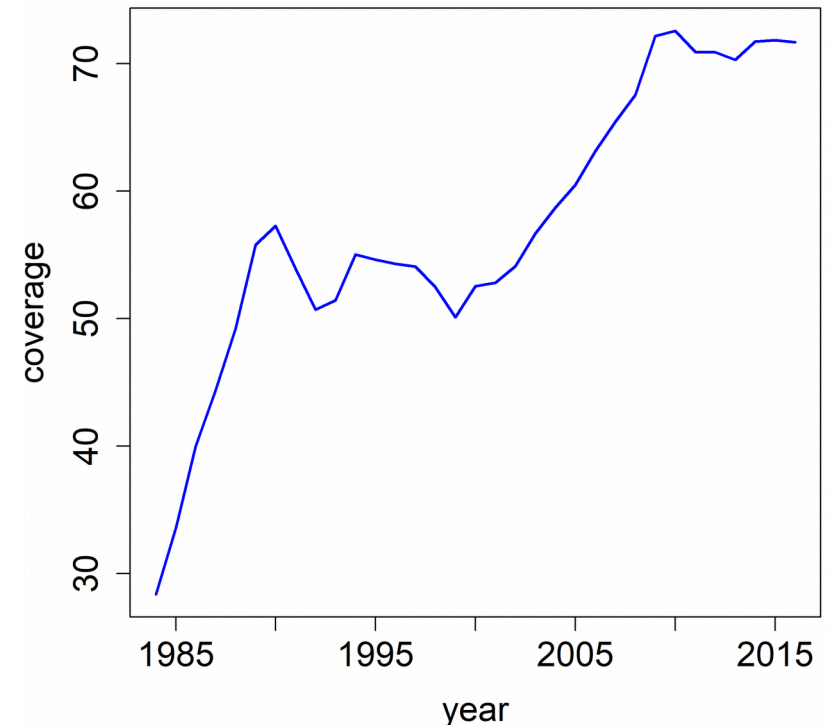


Liu et al. (2016) place measles in the top tier of U5M **reduction** in 2000-2015, equal to malaria in magnitude. However, going forward (*right*) measles is way down the list, barely second-tier at 1.2% of U5M deaths. **So has measles been largely resolved in high-mortality regions??**

Liu et al. Annual Measles Child Death Estimates



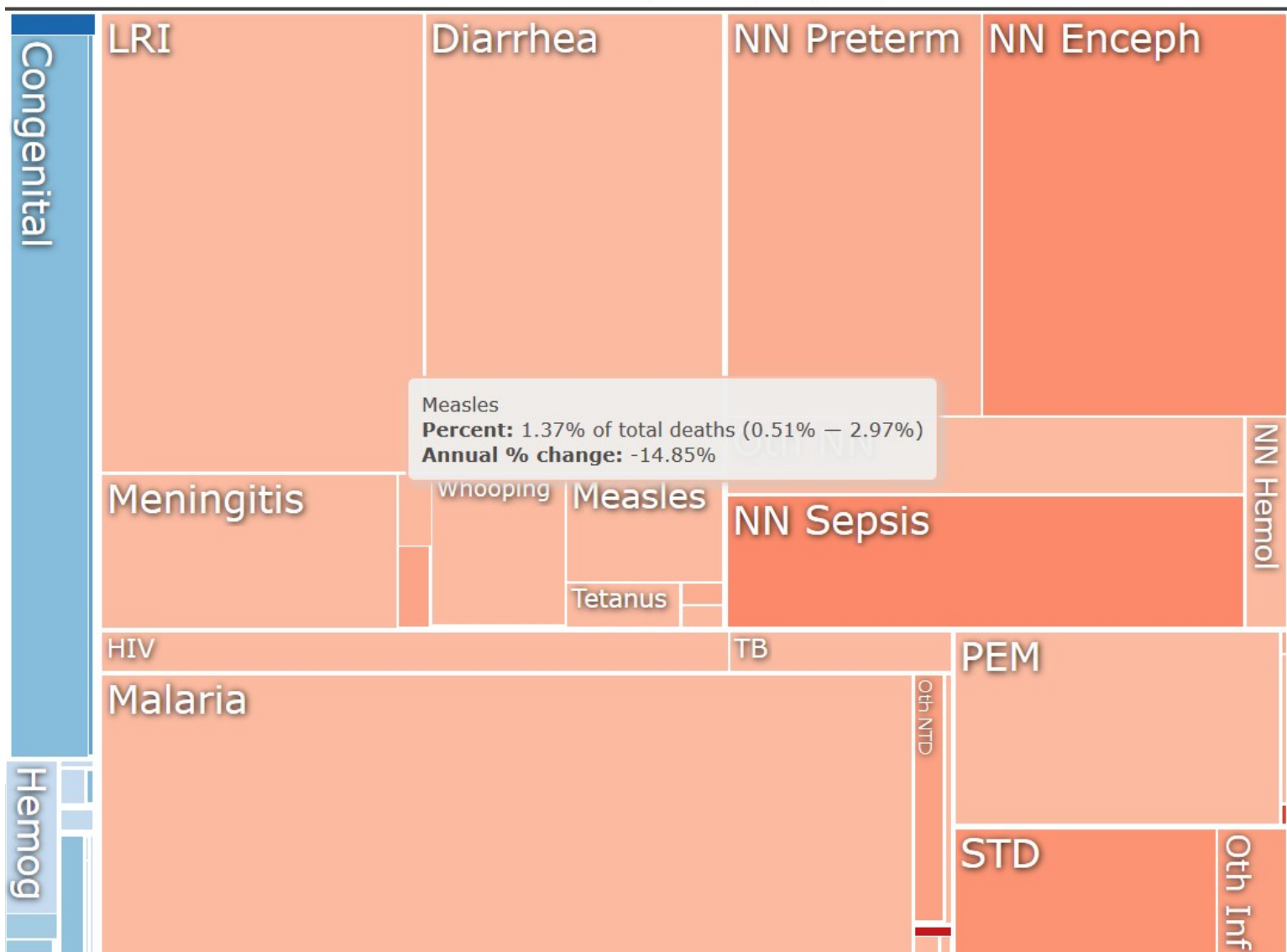
Sub-Saharan Africa MCV1 Coverage



According to Liu et al. global measles deaths dropped 6.5x in 2000-2015, led by SSA (9x) and in particular Nigeria (15x). These estimates are driven mostly by one-time mass immunization campaigns (SIAs), in particular Nigeria 2005 (*apparently coupled with a reporting-system change*).

These drill-down details reinforce the impression that **since ~2006, measles has supposedly become a second-tier child mortality cause in the region. Note however that even with SIAs, overall MCV1 coverage in SSA has increased only moderately (right).**

Sub-Saharan Africa
Both sexes, Under 5 years, 2016, Deaths



Measles
Percent: 1.37% of total deaths (0.51% – 2.97%)
Annual % change: -14.85%

Looking at estimates produced by another leading group, their measles numbers are very similar.

So there seems to be a consensus. Leaving aside the question-mark regarding mediocre/poor MCV immunization levels (<30% in northern Nigeria), is there any other reason to doubt this consensus?

Nonspecific Measles Mortality Evidence

- Epidemiological studies and a few RCTs in West Africa (Nigeria 1961 and 3 Guinea-Bissau RCTs 1989-2008) suggested short-term reductions of 10%-50% in overall child mortality – not only measles deaths - after MCV1 introduction.
- A WHO-commissioned review (Higgins et al. 2016) found the epi studies at high risk of bias, and the RCTs with an aggregate 0.74 relative risk but shy of significant (95% CI: 0.51,1.07).
- Recently, Mina et al. (2015) found that the mass introduction of MCV in the US, UK and Denmark, was associated with a rapid and irreversible ~2x drop in infectious-disease childhood mortality in each country. Again, multiple times above and beyond the count of narrowly-attributed measles deaths.

InDepth to the Rescue!

Mina et al. examined wealthy, lower-mortality countries.

Most higher-mortality studies were in the context of MCV introduction to a vaccine-naive population.

This is not where we're at now.

Following a tip from IDM's HIV/TB manager Anna Bershteyn, I downloaded the multi-site mortality dataset from **InDepth Network:**

- ✓ A setting close to present-day
- ✓ Represents millions of lives
- ✓ Multi-country, urban/rural, high/medium mortality mix



*INDEPTH Network. **INDEPTH Network Cause-Specific Mortality - Release 2014.** Oct 2014. Provided by the INDEPTH Network Data Repository. www.indepth-network.org .10.7796/INDEPTH.GH003.COD2014.v1*

InDepth to the Rescue!

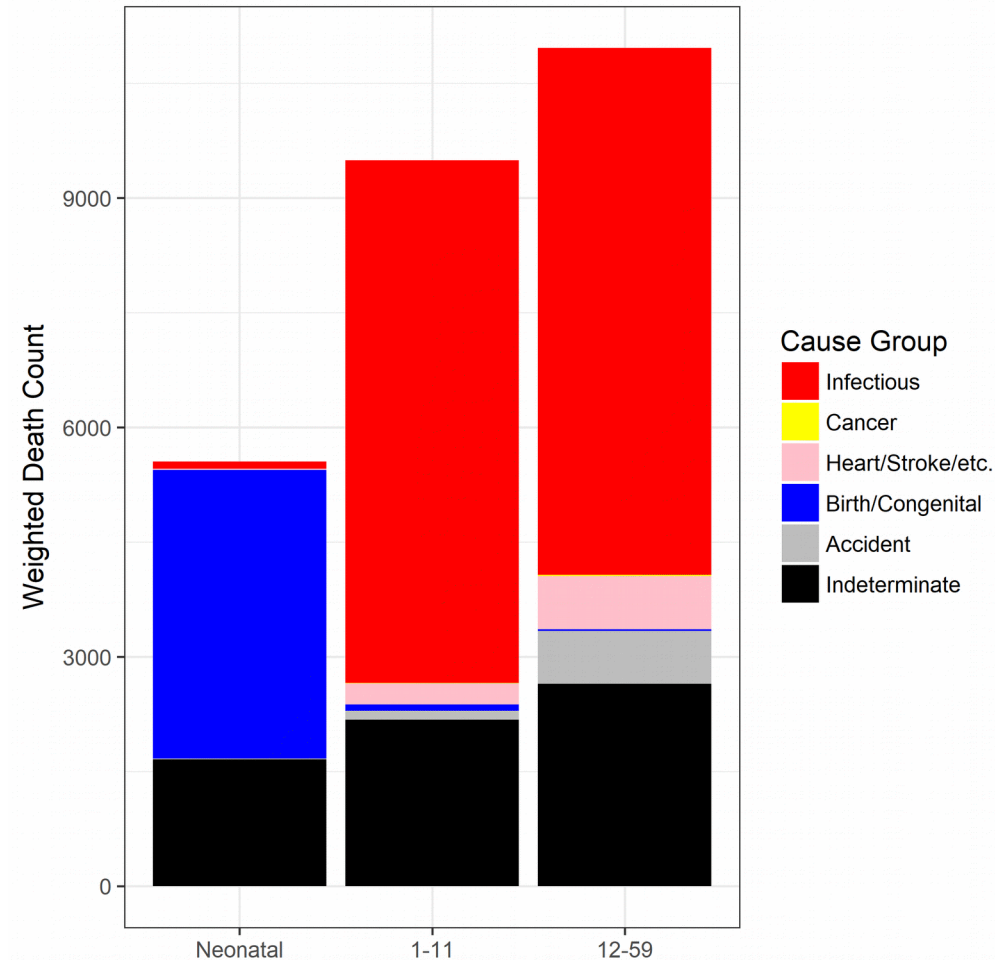
- ✓ Records of individual deaths, with standard verbal autopsy (VA) and survey weights
- ✓ Descriptors binned into site, age group, sex and year resolution
- ✓ Denominator person-years for each bin

✓ **Since MCV1 is usually administered at 9-12 months of age in these countries, analysis focused on the 12-59 month age group only.**

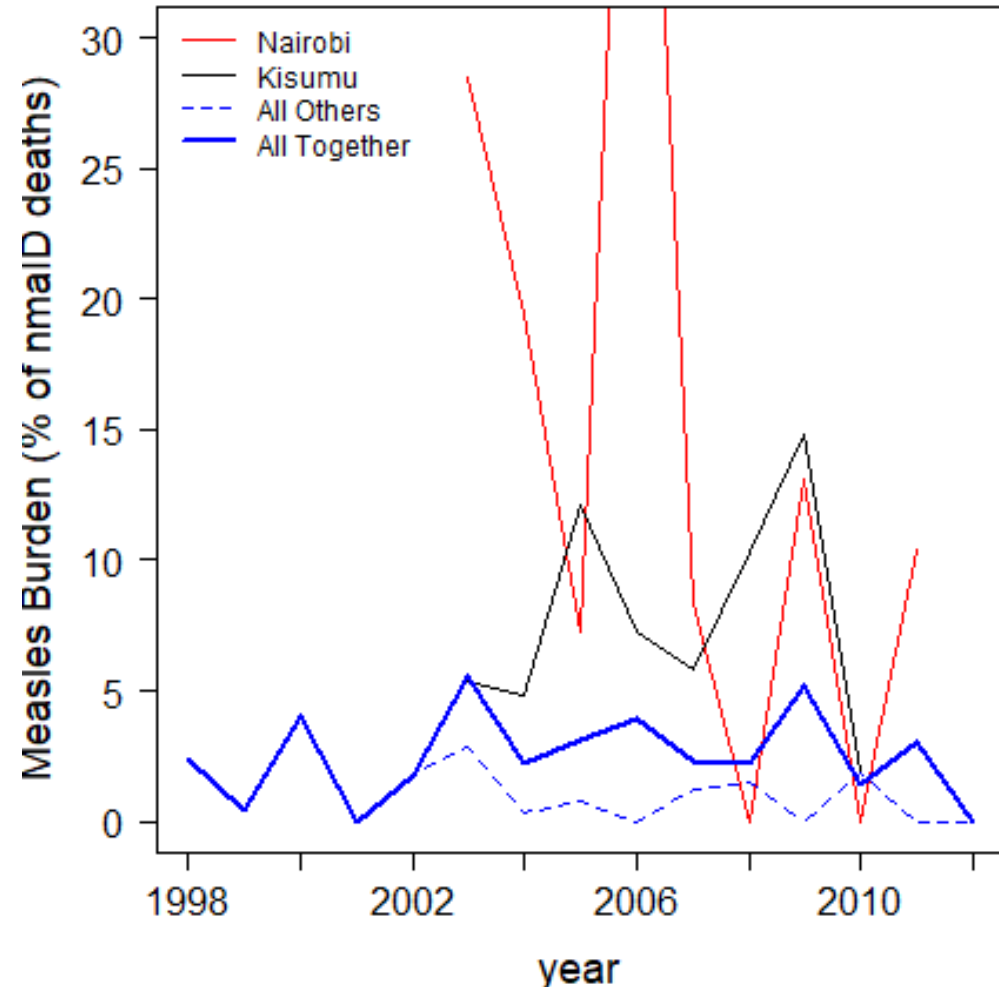
✓ **Endpoint: infectious-disease mortality, excluding malaria and AIDS (hereafter: nmaID mortality)**

✓ Years modeled: 1998-2012.

✓ Main analysis dataset has 112 site-years from 16 sites in 9 countries, representing **1.2 million person-years** (~80% from Africa).



Measles in the InDepth Dataset



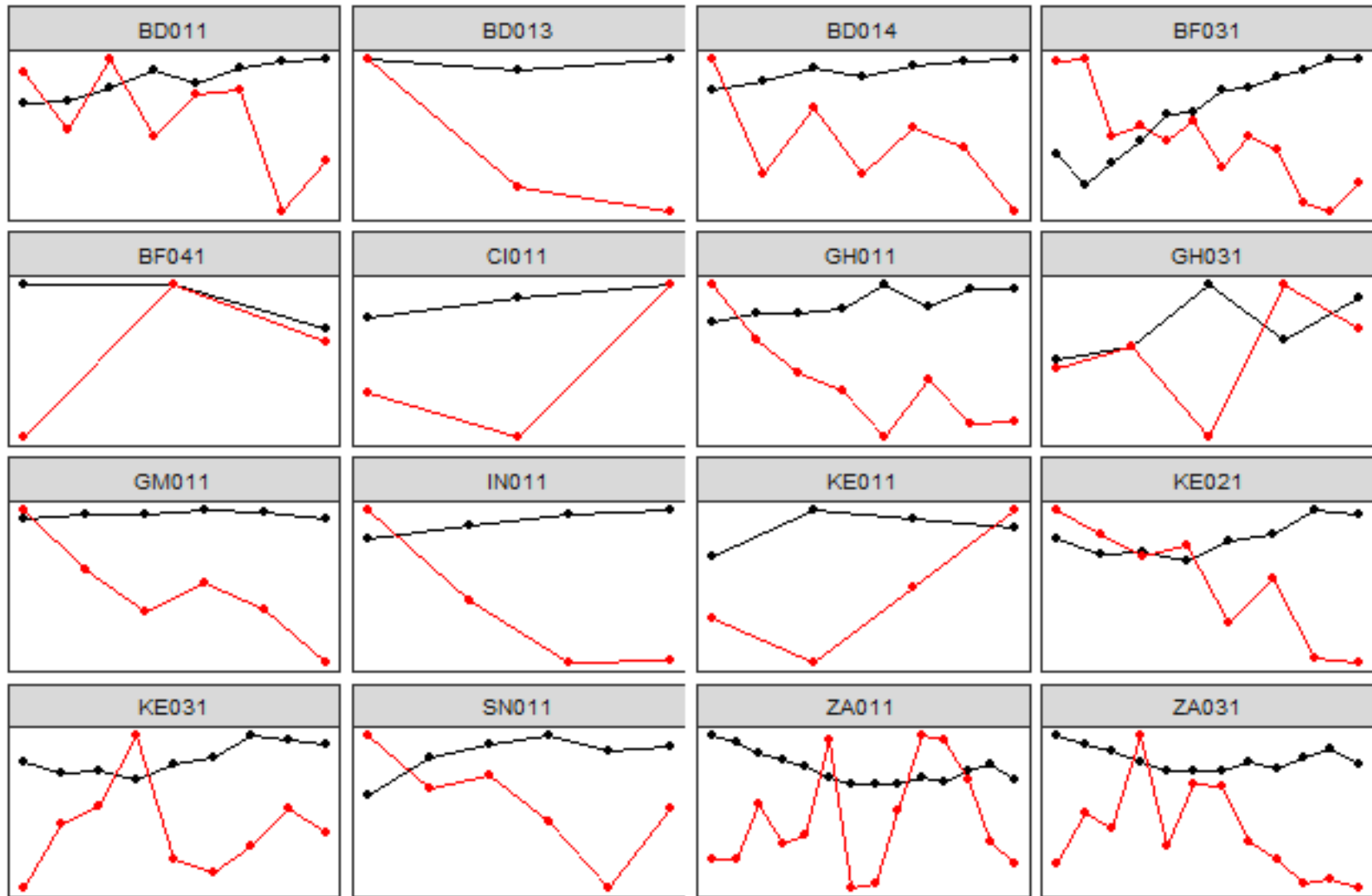
- ✓ **Nominally, measles accounted for 3% of weighted nmaID deaths among 12-59 month old children in the dataset. The proportion never exceeded 5.5% in any single year.**

- ✓ *(Outside of 2 Kenyan sites, this drops to 1%.)*

- ✓ **In other words, official InDepth measles deaths are in the same ballpark as the Hopkins/IHME numbers.**

- ✓ *(except that the sharp, quasi-permanent 2003-2006 drop is not reflected in InDepth; could be site location, or actual negative evidence)*

Infectious Death Risk (excl. malaria/AIDS; site-normalized scale)

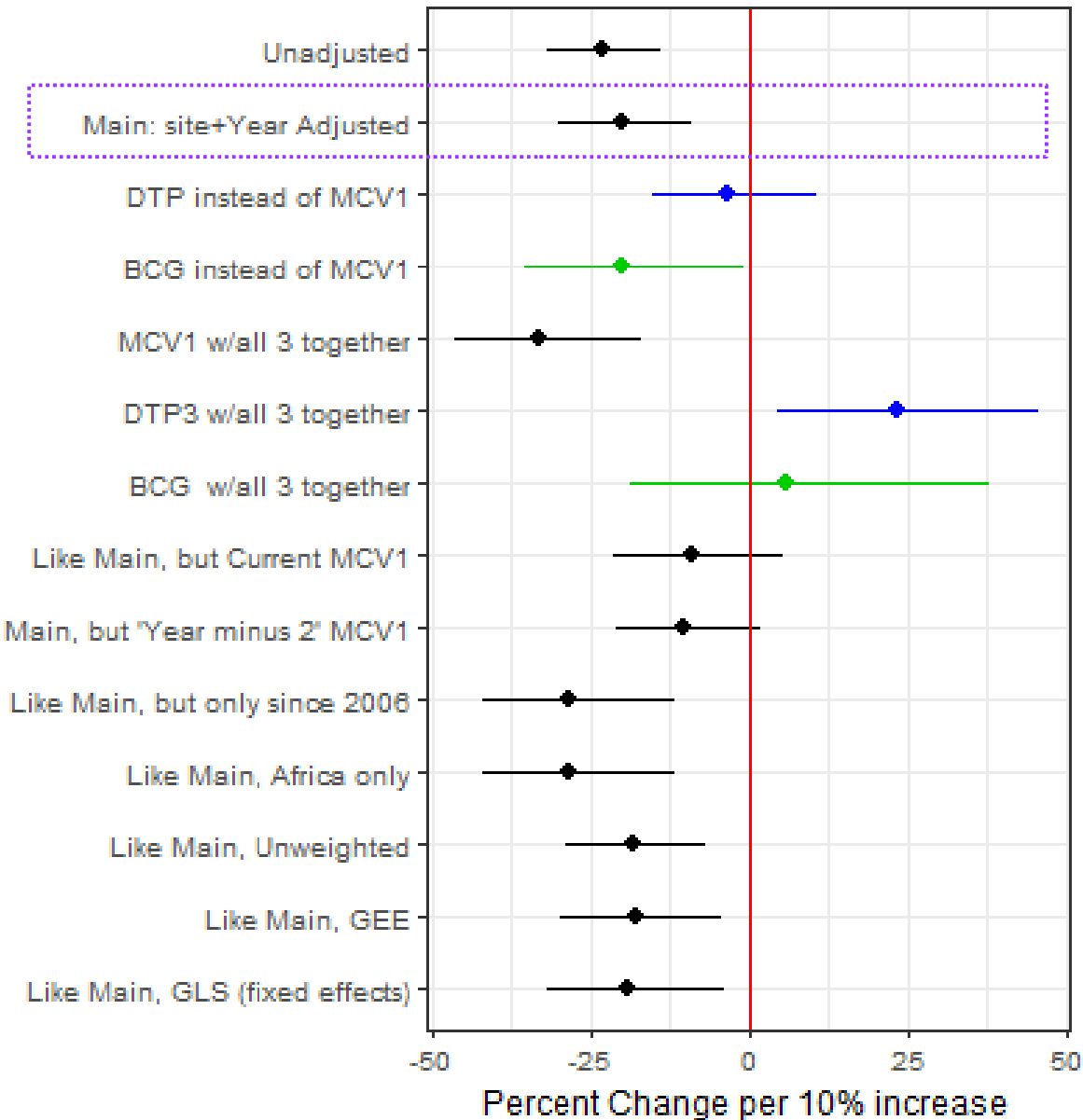


Black:
previous-year
national MCV1
coverage

Red: nmaID
mortality
among 12-59
month olds

Both normalized
within each site

MCV1 nmaID Mortality Effect

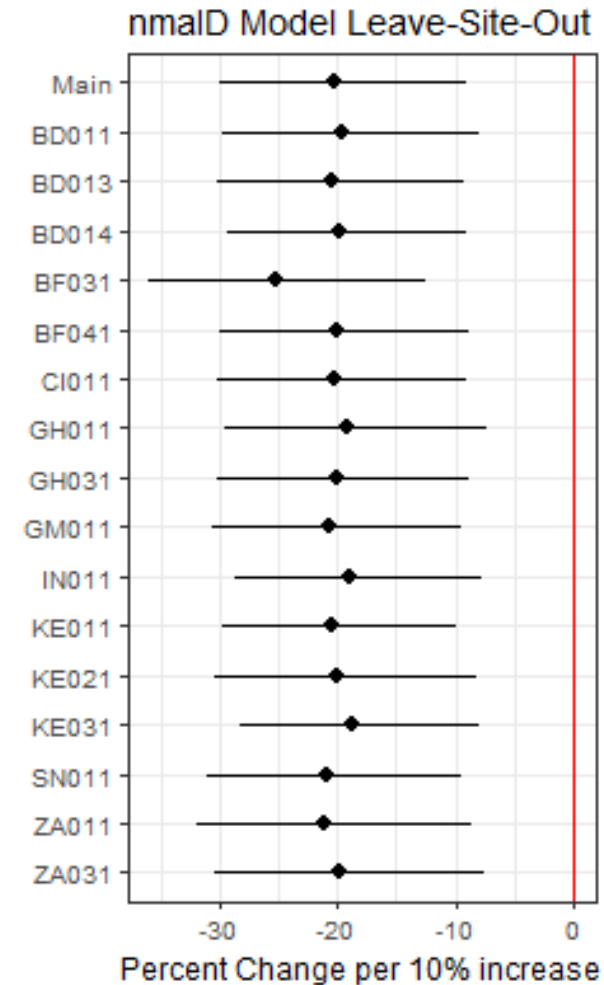


- ✓ **Predictor variable: national MCV1 coverage in the year immediately prior, per WHO/Unicef.**
- ✓ *(MCV1 coverage increased 1.5% per year on average in this dataset)*
- ✓ Adjusted for site-specific secular mortality trend, via random slope.
- ✓ Both time and MCV1 coverage site-indexed.
- ✓ **Estimated effect: ~20% nmaID mortality reduction per 10% MCV1 coverage increase.**

MCV Impact: Tentative Projections

The usual limitations and disclaimers apply. In particular, the fidelity of MCV1 coverage estimates. However:

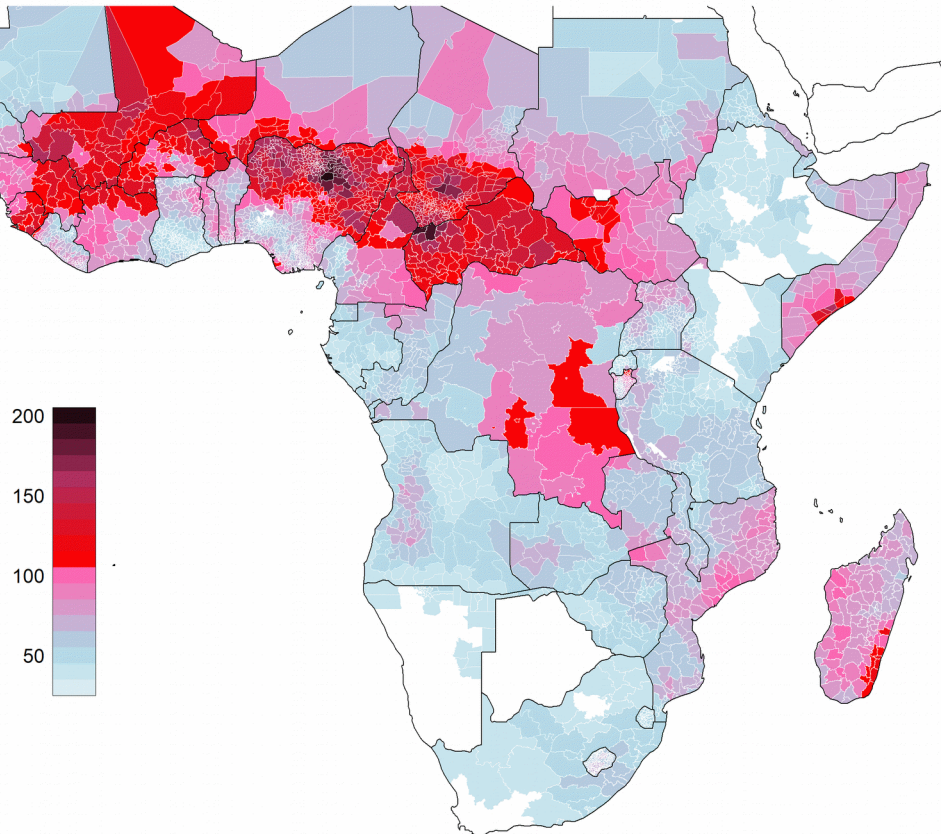
- ✓ Estimated effect is broad-based, robust to sensitivity analyses, and not dominated by individual sites (*right*).
- ✓ Can potentially provide a projected effect size for present-day high/medium mortality, non-vaccine-naive settings.
- ✓ This projection is work-in-progress. However, compared to the nominal measles count in InDepth, **the average nonspecific MCV1 effect would be at least ~5x-20x that.**
- ✓ **Rule-of-thumb population extrapolation: an across-the-board rise from 70% to 90% in sub-Saharan MCV1 may reduce nmalD deaths by 20%-50% among 9-59 month olds. This translates roughly to ~4%-15% reduction in total under-5 deaths, or 3x-10x the current nominal measles burden.**



Azithromycin MDA

And now, to a completely different non-specific intervention... preventative, regular mass distribution (MDA) of azithromycin. *Acknowledgments: Laura Lamberti and Rasa Izadnegahdar (BMGF), Travis Porco (UCSF), Hao Hu and Dennis Chao (IDM).*

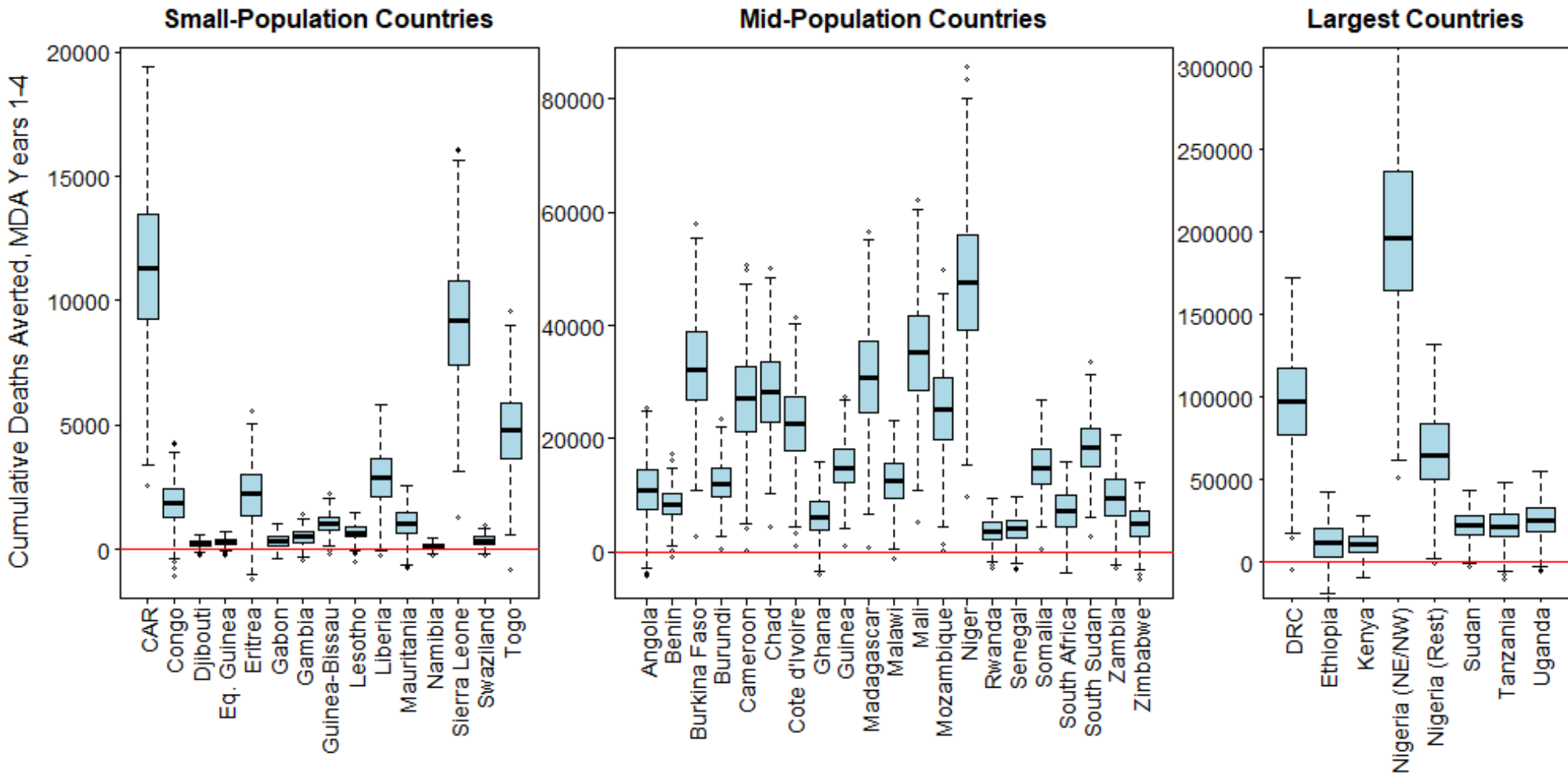
IHME 2019 U5MR Projections



- ✓ IDM was asked to help produce model-informed projections for future MDAs.
- ✓ **Focus: African regions that might miss the U5MR<25 Sustainable Development Goal.**
- ✓ See et al. (2015) report a “TANA Posterior/ MORDOR Prior” distribution of the population mortality-reduction impact of a twice-yearly azithromycin MDA.
- ✓ Here I use those estimates in lieu of the not-yet-public MORDOR study numbers (*which will be published very soon*).

Azithromycin MDA: Assumptions

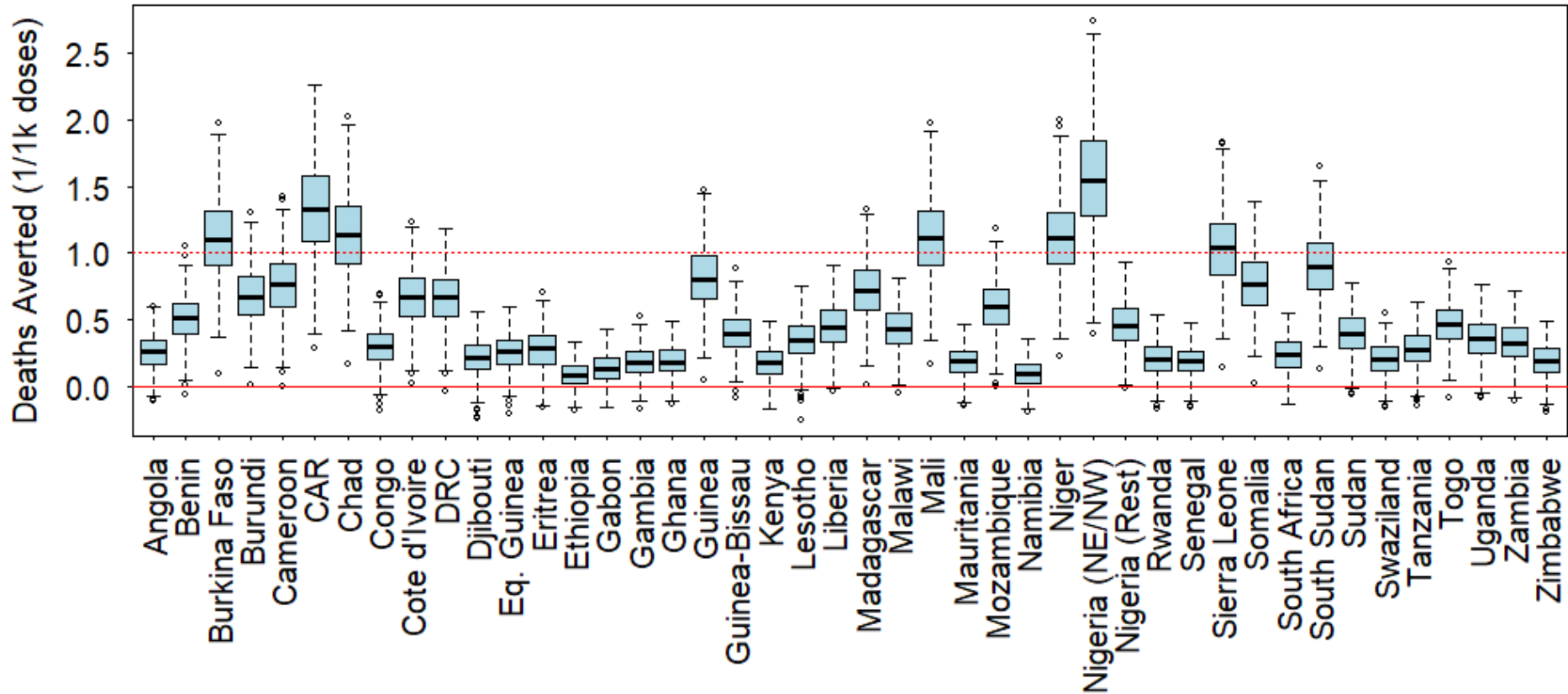
- ✓ **MDA given to 1-59 month olds, 2x annually for 4 years.**
- ✓ Loosely based on See et al. (2015) “Prior/posterior effect size guesstimate”: **about 20% mortality reduction (95% CI 4%,36%)**.
- ✓ Simulation resolution: Admin-2 units. Uncertainty distributed hierarchically between global/national/Adm1/2 levels, plus an additional “out-of-sample implementation noise”.
- ✓ IHME’s Roy Burstein kindly provided U5MR estimates for 2019-2021 (broken into neonate, 1-11m, 12-59m) and population projections, both based on Golding, Burstein et al. (2017). **Uncertainty reported with IHME estimates also propagated into effect and into deaths-averted count estimates.**
- ✓ No effect modification by baseline mortality rate, except some tapering off at the low end (approximately around U5MR<50).
- ✓ Effect increases gradually cycle-to-cycle, until reaching full strength towards the end of Year 2. Then continues at that strength in Years 3-4 (*alternate versions wane or further potentiate it*).



Projections of country-aggregate averted U5 deaths, from 500 simulations.

Note the different vertical scales for the country-size groups.
 Nigeria split into NE/NW and all the rest.

Overall Average MDA Impact Per 1000 Doses, Years 1-4



Same results, normalized as deaths-averted per 1000 doses (averaged across the 4 years).

Some top-impact countries are unfortunately (*and not coincidentally*) fragile states where universal access may be risky to infeasible: e.g., CAR, DRC, Lake Chad region, South Sudan, Somalia.

Note the large uncertainty, particularly in those countries.

Azithromycin MDA and Trachoma

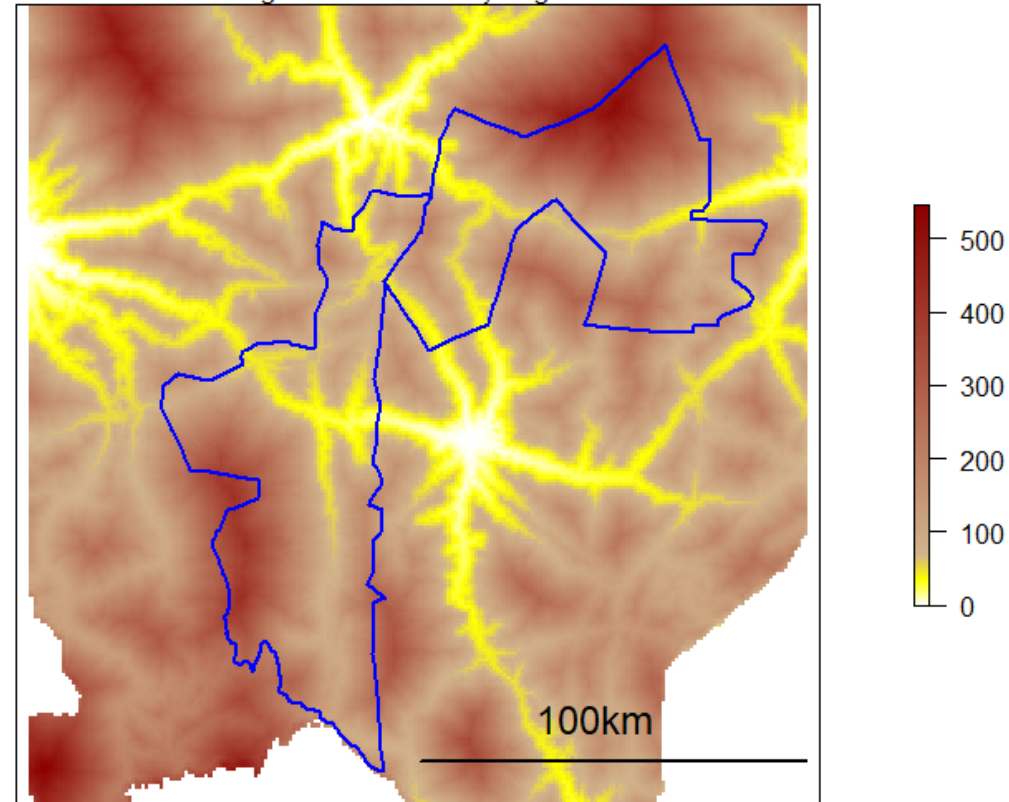
- ✓ While a mass “prophylactic Abx” may seem problematic, azithromycin MDA is already a WHO-endorsed treatment for trachoma elimination. In fact, in light of results on mortality reduction, all regions with 5%+ endemic trachoma prevalence were recently approved to increase from 1x to 2x annual MDAs.
- ✓ Only partial overlap with potential mortality-MDA targets: e.g., the top trachoma-burden country (Ethiopia) is not a promising mortality-MDA target. *Perhaps not a coincidence, as Ethiopia has had the longest-running MDA programs?*
- ✓ Good overlap in parts of West Africa (Niger, Burkina Faso, Mali, Guinea), and partially in far northern Nigeria, CAR, South Sudan and Chad.
- ✓ Some high-mortality countries have no trachoma program to speak of: e.g. DRC, Madagascar, Sierra Leone, Somalia, Angola.
- ✓ IMHO, a key question is **contingency strategy**. Unlike vaccination, which is sustainable and recommended until eradication, Abx MDA should be viewed as temporary, and buying us time (and access?) until more sustainable mortality-reduction solutions are in place.

Access to/of Treatment

- Anywhere in the world, travel time to the nearest city or care facility can vary greatly over relatively short distances.
- However in low-resource settings, a substantial proportion of the population actually lives in those difficult-reach regions – and lacks the means for quick shortcuts (e.g., an airlift).
- Andre Lin Ouedraogo, Dennis Chao and myself were asked to start an IDM effort focusing on this issue. IDM is also hiring a dedicated health delivery analyst, initially focusing on Nigeria.

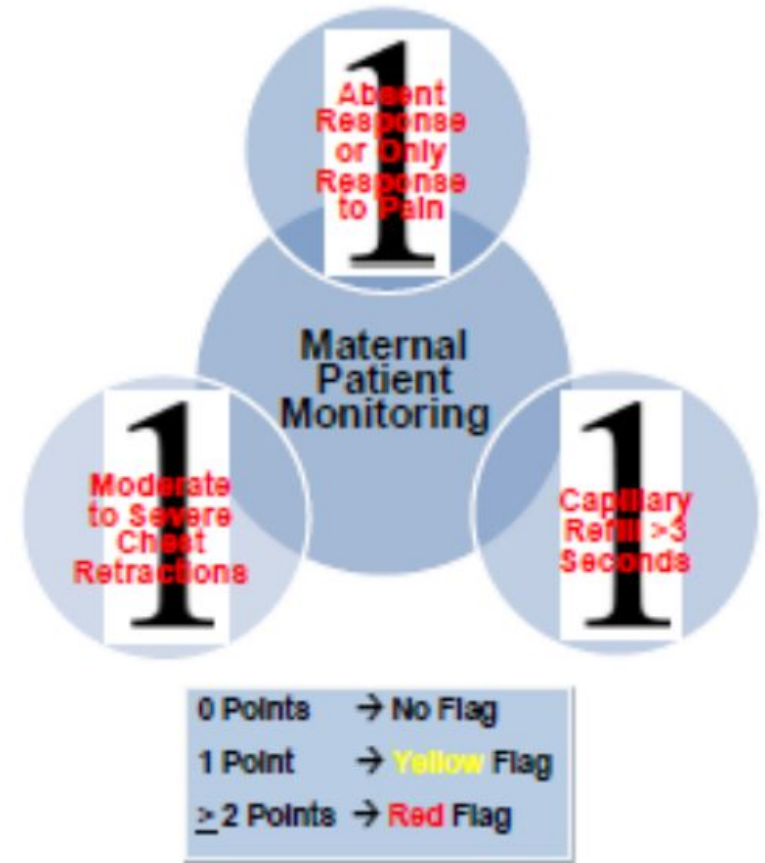
Estimated Travel Time to Nearest City (minutes)

Niger MORDOR Study Regions



Access and Care: FASTER

- **Even after reaching hospital, case fatality rates can be unacceptably high.**
- Some is due to understaffing and overwhelm.
- Amelie von St. Andre – von Arnim (UW and Seattle Children's) has initiated and led the FASTER study, which I designed and continue to support (with Nancy Gove).
- The goal: leveraging and empowering caregivers (usually moms) in continuous triage of their children who are admitted with febrile illness.
- Pilot study (Kenyatta Hospital) currently in analysis: success in caregiver training, but on average the intervention had no effect upon provider care patterns.
- **Case fatality during the trial itself was >10%.**



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Again, I'm new at this. Apologies for any inaccuracies.
Input and ideas welcome, to aaron@idmod.org.

Thank you.