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Benefits and Costs of the Malaria Targets
for the Post-2015 Development Agenda

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Post-2015 Consensus

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HIGHLIGHTS

In the area of malaria the following two targets have very high benefit cost ratios and should be included in a post-2015 agenda:

1. *Delay emergence of artemisinin resistance greater than 1% until 2025* which has a benefit-to-cost ratio of 94-470 when done through the use of quality ACTs and MFTs.

2. *Reduce malaria incidence by 50% between 2015 and 2025* which has a benefit-to-cost ratio of 39-194 when done *through mass distribution of long lasting insecticide treated bed nets (LLITNs).*

Introduction

Despite a 42% decrease in global malaria mortality since 2000, the disease was estimated to cause 627,000 estimated deaths worldwide in 2012. According to WHO's Global Health Observatory, 90% percent of all estimated deaths occurred in Sub-Saharan Africa and 77% were in children under five. Most malaria deaths can be avoided by a combination of measures to prevent and treat the disease. In addition to the obvious health consequences, malaria has societal economic consequences beyond the direct costs of prevention and treatment, and loss of earnings to patients and caregivers.

Malaria-endemic countries also bear considerable indirect long-term costs associated with physical and cognitive retardation in children, resulting in poor educational performance and reduced job prospects in adulthood; malnutrition; anemia; and increased susceptibility to other infectious diseases. Macroeconomic non-health costs to the economy result from reduced labor market productivity, and loss of tourism and business investment, in addition to lost capital and purchasing power (Mills and Shillcutt 2004). Malaria is estimated to dampen a country's annual per capita GNP growth rate by 0.25% and 1.30% after controlling for other factors known to influence economic growth (Guerin et al. 2002; Sachs and Malaney 2002). This loss of economic growth is particularly costly for malaria-endemic countries, which are among the world's poorest.

The world has long recognized that malaria exercises a drag on global human development. Millennium Development Goal (MDG) 6 sets a target of halting and beginning to reverse malaria incidence by 2015. MDG 4, reducing childhood deaths by two-thirds from the 1990 level, cannot be achieved by 2015 without a major reduction in deaths of malaria. In addition, malaria control is also expected to contribute to achievement of other MDGs related to eradication of poverty and hunger (MDG 1), universal primary education (MDG 2), gender equality and empowerment (MDG 3), maternal health (MDG 5), and global partnership for development (MDG 8) (WHO 2012). In 2007, the World Health Assembly passed a resolution calling for a 75% reduction in the global malaria burden by 2015. Between 2000 and 2010, the substantial expansion of malaria interventions has led to a 26% decline in malaria-specific mortality rates globally while the estimated global incidence of malaria declined by 17%. In the decade since 2000, 1.1 million deaths from malaria were averted and reported malaria cases reduced by more than 50% in 43 of the 99 countries with ongoing transmission (WHO 2012).

The past decade of malaria control has seen significant changes in antimalarial drug policies, mass distribution of insecticide-treated bed nets, and corresponding declines in the incidence of malaria (Fegan et al. 2007). A big push is being contemplated to eliminate malaria in areas of unstable transmission, with the eventual goal of global elimination (Smith et al. 2013). Interest in malaria elimination has been stimulated by investment in new technologies and newly proven tools for vector control, individual protection, and malaria treatment, and by the availability of funding from the Bill & Melinda Gates Foundation, the World Bank Malaria Booster Program, the President's Malaria Initiative, and the Global Fund for AIDS, TB and Malaria. Interest has also been fueled by successes in South Africa, Vietnam, Brazil, and more recently Ethiopia, Ghana, Rwanda, Zambia, and

Zanzibar (Barnes et al. 2005; Barat 2006; Bhattarai et al. 2007; WHO 2008). Recent studies report that malaria deaths in children admitted to inpatient facilities declined by 62% in Ethiopia and 67% Rwanda (Otten et al. 2009). In Zambia, high malaria prevention coverage was associated with a 38% reduction in post-neonatal infant mortality and 36% reduction in 1-4 years of age child mortality (Chizema-Kawesha et al. 2010).

Despite these impressive gains, potential resistance to the first line drug, artemisinin, looms large; besides declining financial support for malaria control, it is likely one of the greatest threats to the gains made globally in rolling back malaria, while long lasting LLITNs have yet to be fully deployed in some parts of the world where they could be useful. In this perspective paper, we discuss two targets and corresponding potential sets of interventions to address the threat of resistance to artemisinin and reduced malaria incidence. These should form part of an overall strategy that includes expansion of indoor residual spraying programs and larval control (where appropriate) to reduce malaria prevalence.

A. Delay artemisinin resistance greater than 1% until 2025 through a combination of quality artemisinin combination therapies (ACTs), multiple first-line therapies (MFTs) and resistance containment efforts

B. Reduce malaria incidence by 50% between 2015 and 2025 through mass distribution of long lasting insecticide treated bed nets (LLITNs)

The following sections present the context for the goals and corresponding strategies, followed by estimates of their cost effectiveness and discussion of the challenges in implementing them.

A. Delay emergence of artemisinin resistance greater than 1% until 2025 through the use of quality ACTs and MFTs

Artemisinin resistance is the one of the greatest threats to global malaria control efforts today. Although full resistance has not yet been detected, reduce susceptibility to artemisinins has been observed in the Greater Mekong Subregion (GMS). Early containment efforts did not stop an increase in resistance, but tools for malarial prevention may be effective in eliminating the disease and containing resistance.

Artemisinins have been responsible for averting millions of deaths from falciparum malaria and there are no other drugs available today or in the late stages of development that are nearly as effective. Artemisinins entered into routine use in the GMS much earlier than in other regions, mainly as monotherapy. Those facts alone might be enough to explain why resistance also arose there first, but other factors may be at play. Resistance to the last mainstay of treatment, chloroquine, also arose in the region (and was not first used there), as did resistance to pyrimethamine.

Factors that promote the emergence and spread of drug resistance include certain pharmacokinetic properties of a drug, such as a long terminal elimination plasma half-life

(the case of mefloquine, for instance), a shallow concentration-effect relationship, and other factors, such as resistance being conferred by a single-point mutation in the parasite (White 1999). Moreover, indiscriminate use of drugs at high intensity increases drug pressure and increases the chances of selection of resistant parasite populations. Combination therapies delay the emergence of resistance to antimalarial drugs and also halt the spread and further increase of established resistance.

Increase in disease burden from rising drug resistance to conventional antimalarials in endemic countries prompted the WHO in 2001 to recommend the use of ACTs as first line therapy for uncomplicated cases of *P. falciparum* malaria (Bosman and Mendis 2007). In the last decade, an increasing number of endemic countries have deployed highly effective ACTs to delay the evolution of drug resistance. National malaria control policies of several countries, especially in Africa, recommend the use of a single first-line therapy or drug for treatment of uncomplicated malaria and, when resistance to the officially recommended drug emerges and spreads, switching over to a new drug for which there is no evidence of resistance.

MFTs simulate the idea of combinations, but at the population scale. Boni et al. (2008), use a mathematical simulation model to show that a "wait-and-switch" sequential policy leads to suboptimal reductions in mortality and morbidity levels besides burdening public health systems in endemic countries. Instead, population-wide use of MFTs, where several different therapies are made available to both public and private health service providers is shown to delay the emergence and evolution of resistance compared to using a single drug for the entire population and lowers the total clinical burden of malaria. In the context of multiple ACTs, the model suggests that the optimal strategy would be to deploy all available ACTs to reduce selection pressure on the partner drugs. The short half-life of artemisinin may make it possible to use multiple ACTs and reduce the selection pressure on the partner drugs, thus extending the useful therapeutic lives of all ACTs. Smith et al. (2010) illustrates that in the wake of high levels of uncertainty regarding the waiting time to the emergence of artemisinin resistance, deploying MFTs on a population-wide scale would reduce the fitness of resistant parasites and guard against early drug failure. An MFT strategy, deploying more than one first line therapy at a population level, would marginally increase program implementation, procurement and inventory costs.

As of 2014, no country has implemented a national MFT strategy, although a *de facto* MFT strategy is operational in many countries. Using a diversity of combinations could be a significant operational challenge for distribution and access. However, the underlying ecological argument for use of MFTs is strong and MFTs could be an important complement to the use of combinations in delay in resistance. An important challenge in delaying resistance is the assessment and surveillance of antimalarial drug susceptibility in parasites. In the absence of a validated molecular marker (Bacon et al. 2007) and a sensitive acceptable in vitro test for drug susceptibility that can be comparable across geographically distinct laboratories (Lourens et al. 2010), the World Wide Antimalarial Resistance Network (WWARN) was established to accurately assess the spread of artemisinin resistance through a worldwide system for collating information on antimalarial resistance and standardizing key parameters of in vitro tests to overcome

inter and inta-laboratory variability. In this paper, we recommend a target of delaying, until 2025, the spread of artemisinin resistance by greater than 1% (as measured by the WWARN) through the use of ACTs and MFTs.

B. Reduce malaria incidence by 50% between 2015 and 2025 through mass distribution of long lasting insecticide treated bed nets (LLITNs). LLITNs have been proven to prevent malaria transmission. LLITNs, mostly impregnated with a pyrethroid insecticide, physically reduce human vector contact and reduce the vector population by killing the mosquitoes that come into contact with the nets. Use of LLITNs by a majority of a target community provides protection even to those who do not sleep under LLITNs (Hawley et al. 2003). A review of LLITN randomized trials estimates that they reduce the incidence of uncomplicated malaria by 50% compared to no use of nets at all and by 39% compared to the use of untreated nets (Lengeler 2009). LLITNs have been shown to be more cost-effective than other vector control tools, such as indoor residual spraying (IRS), especially when targeting children under five years who bear the majority of the malaria disease burden (WHO 2007). Use of LLITNs has also shown to reduce deaths attributed to non-malarial causes such as acute respiratory infections, acute gastro-enteritis, and malnutrition in Gambia (Alonso et al. 1993). Pyrethroid impregnated bed nets and indoor DDT spraying have also shown to provide effective protection against other vector-borne diseases such as Japanese encephalitis in China (Dapeng et al. 1994) thus increasing the overall cost-effectiveness of LLITNs.

Scaling up of LLITN distribution by providing them free of charge or at highly subsidized rates has led to a substantial increase in coverage in several endemic areas (Cohen and Dupas 2010)[1]. This has been achieved through the public sector (using cost-sharing strategies), private sector (mostly in urban areas), as well as through public-private partnerships, mainly targeting pregnant women and children under five years in high transmission areas. Delivery strategies have included provision of LLITNs through existing routine health services, such as antenatal care visits of pregnant mothers (in Tanzania), and immunization programs (e.g., measles vaccination in Togo) to reach the most vulnerable population (Breman et al. 2006).

Although a powerful and accessible intervention, LLITNs requires coverage of a large proportion of the at-risk population to produce larger community-wide effects (Hawley et al. 2003). While initial distribution of LLITNs can be achieved through mass campaigns and free or highly subsidized provision (either through direct provision of nets or through a voucher system), maintaining near full coverage of LLITNs as a long-term intervention requires routine redistribution and replacement of nets, and behavior change communication regarding proper use and maintenance of the nets. Currently available LLITNs typically last for less than 5 years and are subject to tearing, and unintended uses due to lack of user information (WHO 2007). Therefore, if LLITNs were to be delivered through antenatal care visits and immunization programs that typically have low coverage

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[1] Cohen and Dupas (2010) find that while subsidies through cost-sharing arrangements may increase usage intensity relative to free distribution, it may also reduce program uptake by dampening demand. They argue that free distribution of ITNs could save many more lives and at a lower cost per life saved (due to large externality effects) compared to cost-sharing programs.

in the malaria endemic regions of the world, achieving full or near full coverage for LLITNs use will be challenging in the absence of their mass production, provision through additional delivery mechanisms, mass distribution campaigns and awareness programs that generate sustained demand for LLITNs and promote proper and consistent use. Additionally, millions of vulnerable people still continue to use untreated or conventionally-treated bed nets, which need to be replaced by LLITNs for effective protection against malaria. Lastly, pyrethroid resistance is a serious threat to the sustained effectiveness of LLITNs. There have been ongoing efforts to treat LLITNs with a combination of pyrethroid and non-pyrethroid insecticides to improve their efficacy as well as delay the emergence and spread of insecticide resistance (Guillet et al. 2008). New (or existing alternative) insecticides are needed to sustain the effectiveness of LLITNs in halting malaria transmission. In this paper, we recommend a target of halving malaria incidence by 50% through the mass distribution of LLITNs by 2025. In the following section, we present cost effectiveness of a combination of interventions that can help achieve these two targets.

Cost Benefit Estimates

Morel et al. (2005) evaluated the cost effectiveness of combinations of selected malaria control interventions[2] separately for two sub-regions of Sub-Saharan Africa, both of which have high transmission rates but differ in disease burden, mainly because of different urbanization patterns and elevations.[3] The interventions were evaluated at differing target coverage rates (50%, 80%, and 95%) to allow unit costs and effectiveness to vary with coverage. Costs include the value of resources needed to implement the interventions over a 10-year horizon and human resource training costs. Effects were measured as disability-adjusted life years (DALYs) averted by an intervention program of 10 years. In Western Africa, the region with a greater at-risk population, case management including treatment with ACTs at 80% target coverage is the most cost effective intervention (Int$9 per DALY averted). In Southern and Eastern Africa, for this intervention to be the most cost effective, the target coverage needed is 95%. In both regions, use of ITNs plus case management with ACTs is the next most cost-effective intervention. In Western Africa (with a larger at-risk population), adding presumptive treatment with SP during pregnancy is also cost-effective. The cost effectiveness ratios for these two sets of interventions are presented below.

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[2] Interventions evaluated were combinations of: ITNs, indoor residual spraying, case management with ACTs, case management with chloroquine, case management with SP, case management with non-artemisinin based combination treatment and intermittent presumptive treatment with SP in pregnancy.
[3] For a systematic review of studies on cost effectiveness analysis of malaria interventions, see White et al. 2011. Also see Mills and Shillcutt (2004) for a summary of benefit cost ratios of three interventions and of scaling up ACTs coverage in Sub-Saharan Africa.

Western Africa: 98% of the population at risk			
Interventions	Average yearly DALYs averted	Average yearly costs (2000 Int$)	Average cost effectiveness (Int$/DALY averted)
Case management with ACTs (80% coverage)	7,771,018	72,386,626	9
ITNs + case management with ACTs+ intermittent presumptive treatment with SP during pregnancy (95% coverage)	12,972,791	315,546,119	24

In Southern and Eastern Africa: 69% of the population at risk			
Interventions	Average yearly DALYs averted	Average yearly costs (2000 Int$)	Average cost effectiveness (Int$/DALY averted)
Case management with ACTs (95% coverage)	5,886,159	73,000,256	12
ITNs + case management with ACTs (95% coverage)	9,138,452	254,755,715	28

To the best of our knowledge, there have been no cost effectiveness studies on the use of MFTs as a potential intervention. To calculate the benefit-cost ratios of the recommended targets, we therefore rely on the cost effectiveness ratios in Morel et al. (2005) for the African region presented above. Assuming DALY values of $1000 and $5000, and mapping interventions to our proposed targets we can calculate the combined benefit-cost ratios for the most cost-effective interventions in SSA. To convert the average cost effectiveness ratios into discounted benefit-cost ratios, we assume a life expectancy at birth of 68 years and average ages of death from malaria in high transmission areas of SSA to be 2 years among under-five children and 20 years among the rest of the population (Goodman et al. 1997). Further, there is evidence that 77% of all malaria deaths are among under-five children (WHO Global Health Observatory). Using these parameters, we compute the weighted average years gained from surviving malaria which are then discounted at 3% and 5% to arrive at the discounted annual benefits of the two recommended interventions for DALY values of $1000 and $5000. In results not shown here, the undiscounted benefit-cost ratio for delaying artemisisn resistance through case management with ACTs ranges between 94 and 470 for DALY values of $1000 and $5000 respectively. The corresponding (undiscounted) ratio for use of ITNs to reduce malaria incidence ranges from 39 to 194 for DALY values of $1000 and $5000 respectively. The discounted benefit-cost ratios are presented below.

Value of a Life: 1000 USD/DALY	3% discount rate			5% discount rate		
	Annual Benefits ($m)	Annual Costs ($m)	BCR	Annual Benefits ($m)	Annual Costs ($m)	BCR
Delay artemisinin resistance greater than 1% until 2025 in SSA	5844	145	40	3878	145	27
Delay artemisinin resistance and reduce malaria incidence by 50% between 2015 and 2025 in SSA	9461	570	17	6279	570	11

Value of a Life: 5000 USD/DALY	3% discount rate			5% discount rate		
	Annual Benefits ($m)	Annual Costs ($m)	BCR	Annual Benefits ($m)	Annual Costs ($m)	BCR
Delay artemisinin resistance greater than 1% until 2025 in SSA	29220	145	201	19391	145	133
Delay artemisinin resistance and reduce malaria incidence by 50% between 2015 and 2025 in SSA	47307	570	83	31394	570	55

Delaying artemisinin resistance through case management with ACTs results in a higher benefit-cost ratio compared to a combination of ITNs and case management with ACTs, although this excludes the benefits and costs of providing MFTs due to lack of information on these. In comparison, Mills and Shillcutt (2004) present benefit-cost ratios (in Int$2003) in annual terms for various malaria control measures for SSA and find that switching from SP to ACT has the highest benefit-cost ratio (38.6), followed by scaling up ACTs (19.1). The benefit-cost ratio of using ITNs alone is 10.4.

Although these interventions focus on Africa, these are a good approximation of the more generalized non-region specific targets since Africa accounts for a large majority of global malaria morbidity and mortality.

Although the study by Morel and colleagues evaluates multiple combinations of antimalarial interventions, it is non-dynamic in nature and does not account for local malaria transmission patterns and their evolution over time. The model assumes a fixed number of cases or deaths averted per unit of service provided. However, in a more realistic setting, externality effects play a big role in determining the future path of malaria infection. Computing the size of the externality is difficult without an understanding of the dynamics of malaria transmission and consequences such as drug resistance. Smith et al. (2006) and Tediosi et al. (2006) have developed mathematical models that incorporate malarial transmission dynamics into cost-effectiveness models to evaluate a malaria vaccine. Ross et al. (2011) extends this to evaluate cost-effectiveness of intermittent preventive treatment with SP or artesunate-amodiaquine for infants and children.

These types of models are ideally suited for evaluating the cost-effectiveness of malaria interventions compared to a static model. However, they are specific to preventive interventions and are not directly applicable to ACTs treatment, for which no dynamic model has yet been developed.

Morel and colleagues' model also does not include the costs of comorbidities such as anemia and low birth weight among young children, which are indirectly linked to malarial infections and further increase the susceptibility to and severity of other infectious diseases. Thus, malaria contributes to child mortality beyond the direct fatal consequences of malaria infection, which means that the analysis underestimates the DALYs averted by effective malaria prevention and treatment.

Challenges

Diagnosis of malarial cases

Diagnostic medical services in malaria endemic countries are limited, poor in quality, or expensive, resulting in malaria treatment being administered on the basis of either clinical or self-diagnosis, or microscopy which is generally limited to larger clinics and does not reach remote endemic areas since it is resource-intensive. The non-specific symptoms of malaria make it particularly difficult to diagnose malaria syndromically. As a consequence, antimalarial drugs are usually prescribed presumptively and indiscriminately to treat all patients with fever or history of fever. A significant number of these treated cases may not have malarial parasites, which leads to a waste of considerable amount of drugs. Moreover, this also causes under-diagnosis and mistreatment of other febrile illnesses. Other parasite-based diagnostic laboratory techniques besides microscopy to accurately detect malaria cases are commercially available; however, they are rarely used in low-resource settings either because they are too complicated, expensive, or less sensitive in the diagnosis of human malaria infections other than falciparum malaria. There is rising evidence that rapid diagnostic tests (RDTs)for malaria have the potential to be highly cost effective across most of Africa if they are accurate and are used to guide treatment decisions (Shillcutt et al. 2008; Jonkman et al. 1999; Goodman 1999; Rolland et al. 2006). RDTs provide quick results, require no capital investment, are simple to use and easy to interpret. They have achieved greater than 95% sensitivity for P. falciparum malaria, although they are less

sensitive for non-falciparum parasites (Wongsrichanalai et al. 2007). Shillcutt and colleagues' model evaluates cost-effectiveness of RDTs and microscopy relative to presumptive treatment in rural health facilities in Africa and finds that RDTs could save many costly and unnecessary ACT treatments and improve treatment of non-malarial febrile infections, thus making RDTs highly cost-effective (Shillcutt et al. 2008). Accurate use of RDTs in the field, use of the tests to guide treatment, and improved clinician adherence to treatment protocol are vital to the successful use of RDTs.

Affordability of ACTs

Most patients in the malaria-endemic areas of Africa (50-75%) seek treatment through the private sector, which is often unregulated. In the wake of poor diagnostic infrastructure and presumptive treatment of febrile illnesses in endemic areas with antimalarial drugs, quality-assured treatment with an ACTs has emerged as the most cost-effective malaria intervention as explained earlier. And yet, treatment with ACTs is relatively more expensive compared to other antimalarial drugs. .

In 2004, an Institute of Medicine (IOM) committee recommended establishing an international fund to purchase artemisinin combinations at producer cost and resell them to distributors (government or private wholesalers) at a subsidized cost. If ACTs drugs enter the supply chain at a low price and the supply chain is adequate, the price to consumers is expected to be similar to the price of chloroquine. This centralized procurement of ACTs drugs at the international level would assure quality standards, remove artemisinin shortage by encouraging drug manufacturers to enter the market in lieu of guaranteed purchase of drugs on behalf of countries, and ease the delivery of foreign aid by reducing administrative bottlenecks within country governments (Arrow et al. 2005). In 2009, the first phase of the Affordable Medicines Facility-malaria (AMFm) was piloted in response to the recommendation of IoM committee in seven countries that together share 25% of the malaria disease burden in the world. It was hosted by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and was funded by DfID, UNITAID, and the Bill and Melinda Gates Foundation. An independent evaluation of an 18-month AMFm pilot revealed that AMFm met or exceeded the benchmarks for availability, price and market share of quality-assured ACTs (Arrow et al. 2012). In November 2012, the Global Fund Board decided to modify the existing AMFm by integrating it into the regular Global Fund model called the Private Sector Co-payment Mechanism (PSCM) whereby countries would choose how much of their country budgets would be reallocated to AMFm and mobilize resources for the copayment. Arrow et al. (2012) argue that such an approach will destabilize artemisinin demand, increase ACTs prices, discourage ACTs manufacturers, and deprive access to ACTs drugs. Since the transition, of the seven participating countries, Cambodia, Niger and Zanzibar stopped AMFm implementation after the first phase and Ghana, Madagascar, and Tanzania have integrated the PSCM into existing Global Fund grants. While it remains to be seen if the transition of AMFm into PSCM proves to be successful, providing subsidized access to effective antimalarial drugs, especially in the private sector, poses a considerable challenge in the face of growing spread of antimalarial drug resistance to older drugs and artemisinin monotherapies.

Policy considerations

In general, reducing malaria incidence requires substantial scale up of treatment coverage. However, incremental costs of scaling up coverage can be expected to be much higher than, say, switching treatment since scale up involves additional infrastructural costs, staff salaries, training and supervision costs, and costs incurred by patients. The estimated incremental cost of scaling up treatment coverage with ACTs is approximately Int$20 per patient while DALYs averted per patient would be 0.22 DALYs (Mills and Shillcutt 2004). A combination of nationwide distribution of ACTs and LLITNs to all under-five children has been associated with reductions in inpatient morbidity and deaths in Rwanda and Ethiopia (Otten et al. 2010). Substantially high coverage of ACTs (and correspondingly, low coverage of component drugs' monotherapy) is required if additional cost of ACTs is to be matched by the benefits of reduction in drug resistance. Besides improvements in public sector services, this also requires addressing private sector dispensing and home-based case management practices such as drug packaging, retailer training, and consumer education (Mills and Shillcut 2004).

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This paper was written for the Post-2015 Consensus Project by Neha Raykar, Lead Economist at Public Health Foundation of India and by Ramanan Laxminarayan, Vice President for Research and Policy at Public Health Foundation of India and director at Center for Disease Dynamics, Economics & Policy. The project brings together 60 teams of economists with NGOs, international agencies and businesses to identify the targets with the greatest benefit-to-cost ratio for the UN's post-2015 development goals.

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