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Measles Eradication versus Measles Control: An Economic Analysis

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Abstract

Background: Policy makers choosing whether to eradicate or control measles need to know about the costs of eradication and its alternatives.

Methods: This project used a dynamic age-tiered measles transmission model for 6 countries (Bangladesh, Brazil, Colombia, Ethiopia, Tajikistan, and Uganda), which was extrapolated to a linear model that was applied globally. Policy options were constant vaccine coverage at 2010 levels, eradication by 2020, eradication by 2025, 95% mortality reduction by 2015, and 98% mortality reduction by 2020. We compared cumulative discounted societal costs, caseloads, lives, and disability adjusted life years (DALYS) saved with each policy option from 2010 to 2050. Sensitivity analysis tested robustness to parameters.

Findings: Strategies to eradicate measles in Bangladesh, Ethiopia, and Uganda cost more than twice as much as control strategies, but have similar costs per DALY averted. More generally, in low and middle income countries that have not yet eliminated measles, the incremental cost effectiveness of control at $20 to $25 per measles death averted is similar to eradication at $22 to $24 per measles death averted. For high income countries that have not yet eliminated measles, eradication by 2020 would prevent deaths and save $800 million more than measles control from 2010-2050 due to averted costs of outbreaks.

Interpretation: Measles eradication and measles control are both cost effective. Measles control and eradication have equivalent costs per life saved in low income countries, but high income countries derive savings only if measles is eradicated and imported cases stop.

Keywords: Measles eradication; Measles control; Transmission; Eradication

Introduction

A country can eliminate an infectious disease by bringing incidence to zero. The world can eradicate measles if all countries simultaneously eliminate it. All countries in North and South America have demonstrated the biological feasibility of measles elimination [1]. Nevertheless, measles still kills 139,300 children annually [2]. Whether or not measles can and should be eradicated requires a global consensus supported by an analysis of costs and benefits [3]. This study analyzes the question of whether to eradicate measles or just control it from an economic perspective. Economic analysis can help policy makers define the costs and benefits from a national perspective as well as globally.

In the year 2005, a goal of 90% reduction in measles mortality by 2010 (compared to 2000) was adopted globally [4] . The World Health Organization (WHO) observed worldwide success in reducing measles mortality between 2000-2008 and the establishment of measles elimination goals in 5 of its 6 regions [2]. It consequently has set a global goal of 95% global mortality reduction by 2015, while continuing to evaluate the establishment of a global measles eradication goal [5]. This paper is intended to inform upcoming decisions on whether to eradicate measles.

To provide decision makers with information on the financial and health implications of measles vaccination policy options, these options were translated into vaccination program inputs (i.e. costs) and outputs (i.e. doses delivered and related health impact) in six diverse countries to offer a global perspective on cost-effectiveness that is informed by detailed models of local transmission dynamics. In each of the six countries the models depict the outcomes from six different strategies as follows: 1)Baseline: perpetually maintain the exact same level of routine coverage and supplemental immunization activity (SIA) coverage that was achieved in 2010; 2) Stop SIAs: SIAs cease in 2010 in GAVI eligible countries because of reduction of support from donor community and reprioritization of national resources; 3) 95% mortality reduction by 2015: Increase routine coverage enough to achieve 95% reduction of measles mortality by 2015 compared to mortality in 2000; 4) 98% mortality reduction by 2020: Increase routine coverage enough to achieve 98% reduction of measles mortality by 2020 compared to mortality in 2000. 5) Eradicate 2020: All countries simultaneously eliminate measles by 2020; 6) Eradicate 2025: All countries simultaneously eliminate measles by 2025. The model also examined the option of dropping the second dose of measles vaccine at a routine immunization visit (MCV2) after global eradication was achieved. (If future decision-makers become convinced that health benefits of MCV2 are inconsequential after eradication, they may choose to discontinue it. However, a 2nd dose of mumps vaccine or non-specific health benefits of measles vaccine might be a reason to perpetuate MCV2 after eradication [6-8]). The Stop SIAs scenario is

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Strategy	Description of Strategy
Baseline (B) :	Freeze routine coverage at the 2010 levels that achieved a 90% reduction in mortality relative to 2000*
Stop SIAs (SS):	Freeze routine coverage at 2010. No more SIAs after 2010.
95% Mortality reduction by 2015	Maintain SIAs and increase routine coverage by 3 percentage points per year from 2010 to 2015
98% Mortality reduction by 2020	Maintain SIAs and increase routine coverage by 2 percentage points per year from 2010 to 2020
Eradication 2020 (Erad2020):	Eliminate endogenous transmission measles in every country by 2020. For countries above 70% coverage this is achieved by increasing coverage by 3 percentage points per year until 2020. For failed states and countries below 60% this implies best efforts at improving routine coverage and annual SIAs.
Eradication 2025 (Erad2025):	Eliminate endogenous transmission measles in the country by 2025 by increasing routine measles coverage by 3 percentage points per year till 2025

*India has not yet achieved the 90% mortality reduction and it is an exception. India's baseline scenario would be to advance coverage to 90% mortality reduction levels by around 2013 and then to freeze routine coverage there.

Table 1: Scenarios tested.

examined because funding shortfalls have led some decision makers to question the value of continued donor support of SIAs [9]. The 95% mortality reduction scenario is the current World Health Assembly target. The 98% mortality reduction by 2020 scenario is included as an alternative to illustrate a more intensive measles control strategy. The rationale for studying eradication by both 2020 and 2025 is to illustrate the impact of slower or more rapid scale up plans. Modeling two different intensities for both control and eradication makes the results more generalizable to a broader range of potential strategies that would be ultimately considered. All scenarios are compared against the baseline strategy in terms of incremental costs, incremental lives saved, and Incremental Cost Effectiveness Ratio (ICER).

Methods

Detailed models as a foundation for a global model

This paper strikes a balance between serving both national and global policy decisions in estimating the costs and benefits of measles control policies using mathematical models of disease burden. The heavy data requirements of dynamic disease models rule out producing detailed models of measles for every country in the world, yet a global perspective is necessary for a global decision. The analysis builds a foundation for global inference based on detailed models of measles dynamics and costs in a subset of 6 low and middle income countries to generate cost and disease forecasts from 2010 to 2050. Breadth is achieved by using results from the 6 focal countries to extrapolate estimates of vaccination costs, deaths averted, and life years saved for the globe. Parameters to support the global estimates of costs and lives saved emerge from the detailed work on 6 focal countries.

In depth dynamic model of measles transmission in six focal countries

The focal countries were chosen in consultation with WHO's Quantitative Immunization And Vaccines Related Research expert advisory group (QUIVER) and WHO regional offices to represent two countries that had already eliminated measles (Brazil, Colombia), one that was near elimination (Tajikistan) and three that were actively scaling up coverage (Bangladesh, Ethiopia, and Uganda). Each of these countries supports the establishment of regional measles elimination goals. MCV1 coverage for 2010 in the 6 countries is estimated at: Bangladesh 0.88, Brazil 0.99, Colombia 0.94 , Ethiopia 0.69 , Tajikistan 0.86, Uganda 0.68 [10]. In addition to this routine first dose coverage, each country offers periodic supplemental immunization activities (SIAs) and Brazil, Colombia and Tajikistan have offered routine MCV2 since 1997 or earlier. The frequency of SIA implementation in each country is contingent on how quickly SIAs are needed to fill immunity gaps created by sub-optimal routine vaccination coverage. In the baseline scenario, SIAs are assumed to be implemented every 3 years in Bangladesh, Ethiopia, Tajikistan, and Uganda. While SIAs were implemented regularly in Brazil and Colombia prior to elimination, these countries are assumed to cease nation-wide SIAs and rely on routine immunization over the 2010-2050 time frame of this analysis.

For each of the 6 focal countries the future trajectory of measles is simulated as a discrete time, Markov chain, susceptible, immune, recovered (SIR) model with a time step of 2 weeks [11-13] Our model builds on existing methods of discrete time SIR models of measles [12-14] but adds an age structure. The population is broken into five age groups: 6-12 months, 1-5 years, 6-15 years, 16-45 years, and 45+. The effect of waning maternal measles antibodies prior to 6 months for infants of vaccinated mothers is not depicted in this model, but discussed extensively elsewhere in the literature [15].

Because there are physical limitations on how many people can have epidemiological contact with each other, the model assumed that mixing of the population occurred in populations of 1 million people as of 2010 and case counts were rescaled to the country's total population. Age proportions in each scale model were based on country data for 2008 and projected to 2050 as a function of the UN's future birth and age specific death rates [16]. Population heterogeneity was modeled by distributing the 1 million people into a core population with higher vaccine coverage and a smaller satellite population where coverage is 20 percentage points lower. The fraction of the population in the hard to reach population was approximated based on UNICEF and WHO data on the percent of districts that had achieved poor coverage. Mixing rates between the core and satellite populations are varied in sensitivity analysis. Each country's birth and death rates were based on the medium projection of the United Nations for each age group out to 2050 [16]. Details are in the web appendix.

For Bangladesh, Ethiopia, Tajikistan, and Uganda increasing measles coverage was modeled as a linear ramp of routine vaccine coverage fractions starting in 2010 (Table 1). (Sensitivity testing modeled a 50% slowdown in the rate of coverage growth after 80% had been achieved.) MCV1 administered between 9 and 12 months of age was assumed to produce full protection in 85% of infants [17]. Doses administered at or after 12 months of age were assumed to produce immunity in 95% [17]. Receipt of MCV1 and MCV2 was arbitrarily set to have a covariance of 5% implying that children who missed MCV1 were more likely than average to miss MCV2 as well. (The covariance of MCV1 and MCV2 coverage was varied in sensitivity analysis.) It was assumed that countries that had not yet adopted MCV2 would do so three years after having consistently achieved MCV1 coverage above 80%. Countries that used SIAs in their measles control efforts were assumed to continue these on schedule until MCV1 and MCV2 reached ≥ 90% coverage for three consecutive years, or global eradication was

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Parameter			Bangladesh	Ethiopia	Uganda	Source
Baseline average cost per child vaccinated prior to scale up			$1.04	$1.00	$1.00	[36]
Scale up cost per child for core areas			$27.83	$18.82	$26.93	(See appendix)
Scale up cost per child for satellite areas			$37.93	$27.4	$35.83	
Scale up cost per child for MCV2 in core areas			$8.79	$11.04	$8.79	
Scale up cost per child for MCV2 in satellite			$27.11	$13.99	$27.10	
SIA cost per child			$0.58	$0.58	$0.58	
Monthly force of infection parameters (x 10^{-5})		Jan	7.75	6.392	6.392	(See appendix)
		Feb	8.88	7.325	7.325	
		Mar	1.01	8.090	8.090	
		Apr	8.43	8.57	8.57	
		May	7.55	7.162	7.162	
		Jun	7.37	10.455	10.455	
		Jul	7.19	7.821	7.821	
		Aug	6.98	7.61	7.61	
		Sep	6.89	7.831	7.831	
		Oct	6.83	8.567	8.567	
		Nov	6.77	7.201	7.201	
		Dec	6.87	8.348	8.348	
Initialization of proportion vaccinated			0.65-0.88*	0.12-0.77*	0.59-0.77 *	[39]
Initial measles case fatality rate**	Infant:		0.034	0.06	0.06	[29]
	Toddler:		0.017	0.03	0.03	
	Child:		0.0085	0.015	0.015	
	Adult:		0.0085	0.015	0.015	
Life expectancy (additional years)	Infant:		67.3	62.2	54.8	[40]
	Toddler:		65.3	60.2	52.8	
	Child:		57.9	54.9	47.9	
	Fertile:		39.9	37.2	31.4	
	Post Fertile:		20	20	20	
Fraction of population in hard to reach (satellite) compartment***			17%	32%	25%	[32]
Initial population sizes (Millions)	Infant:		3.3	2.9	1.29	[16]
	Toddler:		10.6	9.5	4.12	
	Child:		29.1	21.1	8.49	
	Fertile:		73.9	31.5	11.60	
	Post Fertile:		47.7	9.4	10.49	

*For the first 20 years of the model, the proportion of adults vaccinated tracks historical coverage rates as they were reported to WHO from 1990 to 2009. After 2025, the model tracks the coverage rates that were depicted in the model's earlier years. The historical coverage of children and toddlers is similarly tracked, but for only 5 and 2 years respectively.
**From 2011 to 2050 CFR declines in parallel with the improvements in U5MR that the UN has projected for each country [16].
***Approximated based on fraction of districts with poor coverage.

Table 2: Typical parameters for low income countries.

achieved. Models for Brazil and Colombia simply retained the current coverage rates of 99% and 94% respectively for all subsequent years. The scenarios of 95 and 98% mortality reduction were not modeled for Brazil and Colombia because measles has already been eliminated in these countries.

The model set baseline values for the number of susceptible, infected, vaccinated, and recovered people in each age group for January 1, 2010. (Methods available in an appendix upon request) These values were updated stochastically for January 14, 2010 and every 2 weeks thereafter till December 31, 2050. The predicted number of infections was based on the standard assumption that the number of new infections is a random draw from a negative binomial distribution depending on the preceding period's numbers of susceptible and infected people who come into contact. The negative binomial distribution is a mainstay in discrete time models of measles because it has shown the capacity to depict rare occurrences of large outbreaks from a gathering of many susceptible and few infected people with cyclic dynamics that fit well to historical time series [13,18,19] .

Separate equations for each age group and compartment modeled the force of infection as $\lambda_t = \beta_M (S_t I_t^{\alpha})$ where β_M is a set of monthly infectiousness parameters that impose seasonality. Unique parameters and base case values were used for each country as shown in Table 2. S_t is the number of susceptibles in biweek t, I_t is the number infected in biweek t, and α is a parameter that adjusts for the heterogeneity in contact and the discretization of the continuous time transmission process. Until eradication was achieved, the population was exposed to a regular influx of 2 immigrant infectious cases per week. The number of new infections was stochastically updated every two weeks using a negative binomial function according to $I_{t+1} \sim NegBin(I_t, \lambda_t)$ [12,13]. These basic equations were modified slightly in order to depict population contact patterns among age groups. The infectiousness parameters, β_M, for Uganda were estimated from monthly district data accounting for vaccination coverage using the method of susceptible reconstruction [12,13]. Bangladesh's β_M parameters were extrapolated from a prior published monthly case series in Matlab district [20]. See web appendix for more details.

The epidemiological model was programmed in Stata 11 and then validated according to its ability to approximate WHO's estimates of annual measles deaths for 2005-2008 within 5%, its ability to match historical age distributions of incident cases in unvaccinated populations, and its ability to replicate the observed negative correlation between vaccine coverage and deaths within 5%. The natural history models predicted measles cycles every 2-3 years, which is consistent with historical populations in Africa [21,22], Asia [20,22,23], and Latin

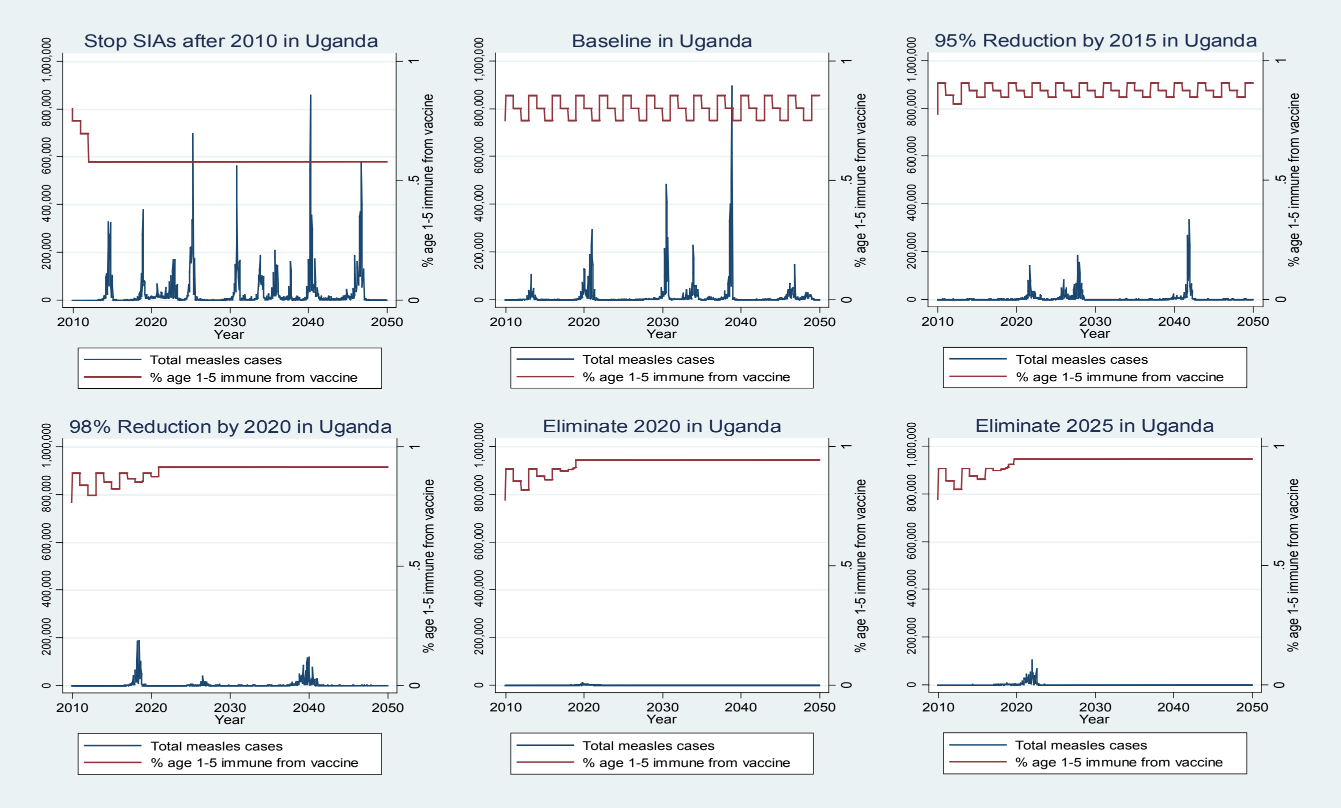

Figure 1: Epidemic curves for natural history and six scenarios for the example of Uganda. Left axis is the number of cases. Right axis is the % of children age 1-5 who have attained immunity due to vaccination.

America [22]. The models can also exhibit annual dynamics observed in developing country settings with higher birth rates [24].

Costs

Costs are expressed in 2010 US dollars and are based on a societal perspective with time horizon of 40 years with discounting at 3% for both costs and DALYs [25]. Total costs include costs of scaling up routine vaccination, conducting SIAs, outbreak control, routine surveillance, health sector costs of treating measles cases, and societal costs of lost productivity for adults whose children were sick and for cases of disability due to measles encephalitis. The incremental costs of the various vaccination strategies were compared to the baseline reference point--a strategy that kept coverage fixed at 2010 levels.

An ingredients based costing approach segmented the population of unreached children into six categories based on (urban/rural/remote) × (core/satellite) area. After stratifying the population of children not yet reached by routine MCV, the coverage increments in each compartment were multiplied by an estimate of the corresponding unit costs to scale up in each location. Separating low cost and high cost populations allows the model to depict non-linear increases in unit costs if policymakers defer covering the high cost populations further into the future. (Deferring the coverage of high cost populations became a consideration in developing polio control policies.) In each of the 6 countries, we found no reports that policy makers were actually planning to defer vaccinations for higher cost regions, so the models presented assume simultaneous scale up in all regions regardless of the unit cost in any particular area.

Estimates of the quantity of resources needed for ramping up coverage in each of the 6 compartments were based on interviews that WHO sponsored with country EPI managers in Bangladesh, Brazil, Colombia, Ethiopia, and Uganda (See web appendix for details on costing parameters). The interviews disclosed that the most likely investments to scale up coverage would echo the “reaching every district” (RED) strategy [26]. Scaling up routine coverage with MCV1 will require more human resources for clinic-based outreach, better supervision, as well as more transport, supplies, and antigen. Most of the costs of the RED strategy are recurrent labor costs to permanently hire new staff to conduct the outreach and supervision as well as an increase in recurrent costs of vaccine acquisition and transport. Scale-up decisions thus lead to permanently higher unit costs per increment in the number of children covered above baseline. Once new costs are allocated to reach previously unreached groups—these costs remain in all subsequent years. The cost of reaching a new unreached child in easier to reach areas of Bangladesh, Ethiopia, and Uganda is estimated at $11, $19, $15, respectively with higher costs assumed for children in hard to reach areas (See web appendix). Cost assumptions stayed conservative and included extra costs for the need to hire additional recruiting staff that was not currently on payroll to reach currently unreached children. The cost per child reached by Supplementary Immunization Activities (SIAs) was estimated based on literature review of 12 studies [27,28] and then extrapolated based on GDP per capita (See web appendix).

Measles Disability Adjusted Life Years (DALYs) were estimated as life years lost relative to each country’s estimated life expectancy at each age. Disease burden due to the acute disability of measles was ignored because it would account for less than 0.5% of the DALYs

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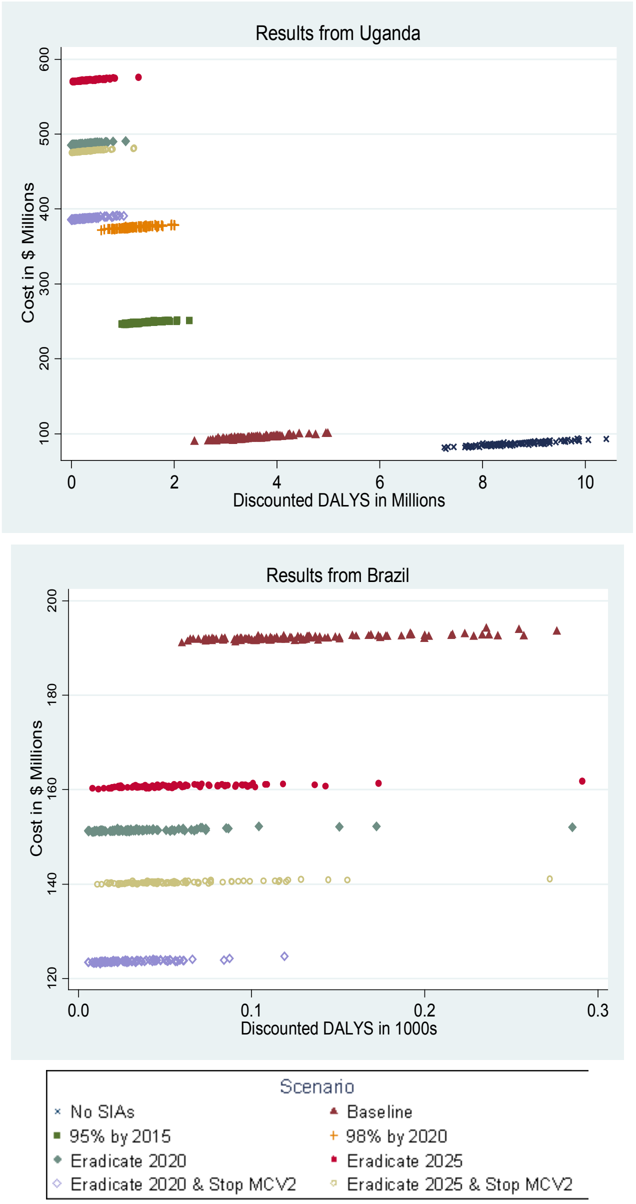

Figure 2: Costs vs. measles DALYS for 8 scenarios in Uganda and Brazil. Each marker plots costs against DALYs emerging from a single iteration of the model. Policy makers prefer to be in bottom left with fewest DALYs and lowest costs. Stop SIAs and 95% and 98% mortality reduction scenarios are not modeled for Brazil, because Brazil has already eliminated measles.

from measles at baseline. Case fatality rates for each country and age group varied based on literature [29]. Case fatality did not vary as a function of incidence. Measles survivors were assumed to have the same survival rates as their vaccinated and never infected counterparts, although literature suggests that mortality may be lower if measles survivors are compared to children who had not been vaccinated [30]. Projected improvements in measles CFR between 2010 and 2050 [31] were assumed to occur at the same rate as UN projections of under five mortality reductions for the next 40 years [16].

In univariate sensitivity analysis parameters in Table 2 were replaced by values that were either 20% lower or higher and the results were compared to baseline. Since few of the parameters have an empirical distribution that could support a confidence interval, maintaining the +/- 20% range for all parameters has the advantage of being set objectively. The length of the bars in the tornado diagrams in Figure 4 show how the incremental DALYs, incremental costs and, ICERs vary when parameters vary.

In multivariate sensitivity analysis of the transmission models, each scenario was run 100 times to establish the range of expected values. In tests of up to 700 iterations, the sensitivity ranges were not different from 100 iterations. Each iteration of the stochastic model is plotted as an XY coordinate in Figure 2 to show how each had different costs and disease burden driven by the negative binomial process of disease transmission.

Global model of measles eradication

The global models of health and cost outcome assumed a simple linear decrease from current measles deaths downward to the policy targets set for 2015, 2020, and 2025. Experience with the six dynamic models showed that the linear assumption was a good approximation in estimating total deaths averted for each country as the difference in the area under these straight lines. The costs in the global model were based on the population in low coverage and high coverage compartments in each country based on their reports to UNICEF and WHO [32]. An ingredient based model of the costs of scaling up routine coverage discussed above was based on detailed study of the 6 focal countries and then extrapolated globally (See web appendix). In some high-income countries, populations resistant to vaccination impede further increases in routine coverage. The efficacy and costs of various strategies to reach these populations remain entirely unknown. It was arbitrarily decided to apply a $200 recruitment cost for each additional child immunized among groups in high income countries that were heretofore resisting vaccination. Policy makers from these affluent countries will have to determine what it would actually cost to improve coverage for populations that are resistant to vaccinating their children.

Role of the funding source

The funding source had no role in the design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and final responsibility to submit for publication.

Results for six focal countries: Bangladesh, Brazil, Colombia, Ethiopia, Uganda, Tajikistan

Figure 1 illustrates the non-linear transition from epidemic caseloads to eradication for the case of Uganda. The scale on the left axis is caseloads. The scale on the right axis is percent of children who acquired immunity from immunization. The rectangular upticks in immunity every 3 years are due to regular SIAs. The scenario of stopping SIAs shown in the upper left panel leads to more frequent epidemics than would occur at baseline.

Figure 2 plots costs against DALYs for each scenario in Uganda and Brazil. Each marker summarizes the 40 year sum of costs on the y-axis and 40 year sum of DALYs on the x-axis that the country would see if it enacted a policy for 40 years. There are 100 iterations of each policy shown. Because it is a stochastic model the markers from the 100 iterations of each policy form a cloud. The size of each cloud conveys the degree of uncertainty due to the underlying random nature of measles epidemics. One can compare the costs and effects of the various policies by examining differences between the average costs and DALYs in the center of each cloud.

	Δ Discounted DALYS relative to baseline		Δ Discounted Costs ($ millions) relative to baseline		Ratio of $ saved (-) or $ spent (+) to DALYs averted or incurred. Positive ratios are Incremental Cost Effectiveness Ratio (ICER) $ per DALY averted.			
Bangladesh	**Mean**	**SD**	**Mean**	**SD**	**Median**	**Interquartile Range**		***Notes***
Stop SIAs (SS)	2.34E+06	9.09E+05	-44	(7)	-$19	(-14:	-28.9)	[1]
95% Reduction by 2015	-1.88E+06	4.71E+05	61	(4)	$34	(26:	44)	
98% Reduction by 2020	-1.78E+06	4.95E+05	74	(5)	$42	(33:	54)	
Eradication 2020 (E2020)	-1.96E+06	4.50E+05	156	(4)	$81	(67:	102)	
Eradication 2025 (E2025)	-1.96E+06	4.52E+05	164	(4)	$85	(70:	108)	
Eradication 2020 & Stop MCV2	-1.97E+06	4.49E+05	71	(4)	$36	(29:	48)	
Eradication 2025 & Stop MCV2	-1.94E+06	4.46E+05	102	(4)	$55	(43:	68)	
Ethiopia								
Stop SIAs (SS)	1.05E+07	1.69E+06	-26	(5)	-$3	(2.0:	3.1)	[1]
95% Reduction by 2015	-4.38E+06	1.14E+06	197	(4)	$43	(38:	56)	
98% Reduction by 2020	-4.63E+06	1.17E+06	394	(4)	$86	(72:	107)	
Eradication 2020 (E2020)	-6.03E+06	1.01E+06	534	(3)	$91	(78:	101)	
Eradication 2025 (E2025)	-5.74E+06	1.20E+06	644	(4)	$112	(96:	132)	
Eradication 2020 & Stop MCV2	-6.07E+06	1.07E+06	376	(4)	$64	(54:	71)	
Eradication 2025 & Stop MCV2	-5.94E+06	9.82E+05	506	(3)	$86	(76:	97)	
Uganda								
Stop SIAs (SS)	5.09E+06	9.00E+05	-7	(4)	-$1	(-2:	-.8)	[1]
95% Reduction by 2015	-2.15E+06	6.48E+05	154	(3)	$72	(59:	90.5)	
98% Reduction by 2020	-2.37E+06	6.49E+05	281	(3)	$119	(100:	147)	
Eradication 2020 (E2020)	-3.34E+06	5.63E+05	393	(3)	$118	(106:	135)	
Eradication 2025 (E2025)	-3.26E+06	5.40E+05	478	(3)	$147	(133:	167)	
Eradication 2020 & Stop MCV2	-3.29E+06	6.08E+05	293	(3)	$89	(78:	103)	
Eradication 2025 & Stop MCV2	-3.25E+06	5.69E+05	383	(3)	$119	(106:	134)	
Brazil								
Eradication 2020 (E2020)	-9.29E+01	6.80E+01	-41	(.6)	-$432,000	(-280,000:	-630,000)	[2]
Eradication 2025 (E2025)	-6.80E+01	7.10E+01	-31	(.6)	-$394,000	(-227,000:	-658,000)	
Eradication 2020 & Stop MCV2	-9.96E+01	5.54E+01	-68	(.6)	-$748,000	(-510,000:	-1,043,000)	
Eradication 2025 & Stop MCV2	-7.54E+01	6.54E+01	-52	(.6)	-$646,000	(-391,000:	-1,175,000)	
Colombia								
Eradication 2020 (E2020)	-3.30E+02	5.41E+02	-12	(3)	-$70,000	(-37,000:	-92,600)	[2]
Eradication 2025 (E2025)	-2.97E+02	5.46E+02	-9	(3)	-$58,000	(-27,100:	-87,100)	
Eradication 2020 & Stop MCV2	-3.28E+02	5.42E+02	-21	(3)	-$122,000	(-62,800:	-169,700)	
Eradication 2025 & Stop MCV2	-3.05E+02	5.46E+02	-16	(3)	-$103,000	(-43,500:	-146,000)	
Tajikistan								
Eradication 2020 (E2020)	-9.63E+03	3.15E+03	14	(1)	$1,500	(1,900:	1,200)	[2]
Eradication 2025 (E2025)	-6.45E+03	3.00E+03	12	(1)	$1,800	(2,800:	1,400)	
Eradication 2020 & Stop MCV2	-9.74E+03	2.71E+03	9	(1)	$1,000	(1,300:	800)	
Eradication 2025 & Stop MCV2	-7.06E+03	2.78E+03	9	(1)	$1,300	(1,800:	900)	
[1] Stop SIAs option is cost saving, but increases the DALY burden								
[2] Eradication options in Brazil, Colombia, and Tajikistan save money and lower DALY burden. ICER column gives ratio in which these benefits accumulate								

Region	Baseline	Eradication 2020	Eradication 2025	Eradication 2020 with no MCV2 after elimination	Eradication 2025 with no MCV2 after elimination	95% Mortality Reduction	98% Mortality Reduction

Baseline Levels	Bangladesh	Ethiopia	Uganda	Brazil	Colombia	Tajikistan
Discounted DALYS	1.9 M	6.3 M	3.5 M	131	325	11.4K
Discounted Costs	$170M	$157M	$94M	$192M	$55M	$15M

Table 3: Δ DALYs Δ Costs ICERS under 6 scenarios.

Decision makers are assumed to prefer points that are lower on the vertical axis because these have lower cost and to prefer points that are more to the left on the horizontal axis because these have fewer DALYs. One can see from Figure 2 that the baseline scenario (Δs) imposes higher costs but saves more lives than stopping SIAs (Xs). For a decision maker at the baseline position (Δ) in Uganda all choices that improve health lead to higher costs. Stopping SIAs (Xs) can save costs but more children die. In contrast, in Brazil, the eradication scenarios result in both better health and lower costs relative to baseline.

If one were to plot trajectories from the center of the cloud of baseline points (Δs) to the center of each cloud of health improving strategies at the upper left of Figure 2 the lines would have similar slopes going upward and to the left. These slopes measure (change in cost)/ (change in DALYs) and are the incremental cost effectiveness ratios (ICERS) that are listed in Table 3. ICERS and their distribution were estimated by examining slopes from samples of 200 random line segments joining a randomly selected point from each alternative scenario to a randomly selected point in the baseline reference scenario.

For all three low income countries in Table 3, each measles control option other than stopping SIAs offers a chance to avert DALYs for less than $200 per DALY. In particular, the eradication scenarios lead to similar $ per DALY averted when compared to either the 95% or 98% reduction scenarios. The substantial overlap between ICER's inter quartile ranges for the scenarios given in Table 3 rejects the conclusion that non-eradication policies represent a statistically significantly better opportunity to avert more DALYs per dollar.

The interquartile ranges (IQR) in the last column of Table 3 can help assess whether 98% reduction, for example, is significantly more cost effective than eradication. For Ethiopia the ICER for 98% reduction is $85.6 (IQR: 72-107) compared to E2020's value of $90.6 (IQR: 78-101). For Uganda, the comparison shows $119.2 (IQR: 100-147) vs. $117.9 (IQR: 106-135). In these cases the interquartile ranges of ICER estimates for eradication and control options substantially overlap. The overlap offers no support for concluding that controlling measles is dramatically more cost effective than eradicating it, under the assumption that countries would continue to offer two doses of vaccine after eradication. The similarity of most of the ICER estimates in Table 3 supports the broad conclusion that all of the ICER estimates of $ per DALY are attractive whether the strategy ultimately leads to disease reduction or eradication. Recall that for the two Latin American countries, the scenarios of 95 and 98% mortality reduction were not modeled because measles has already been eliminated.

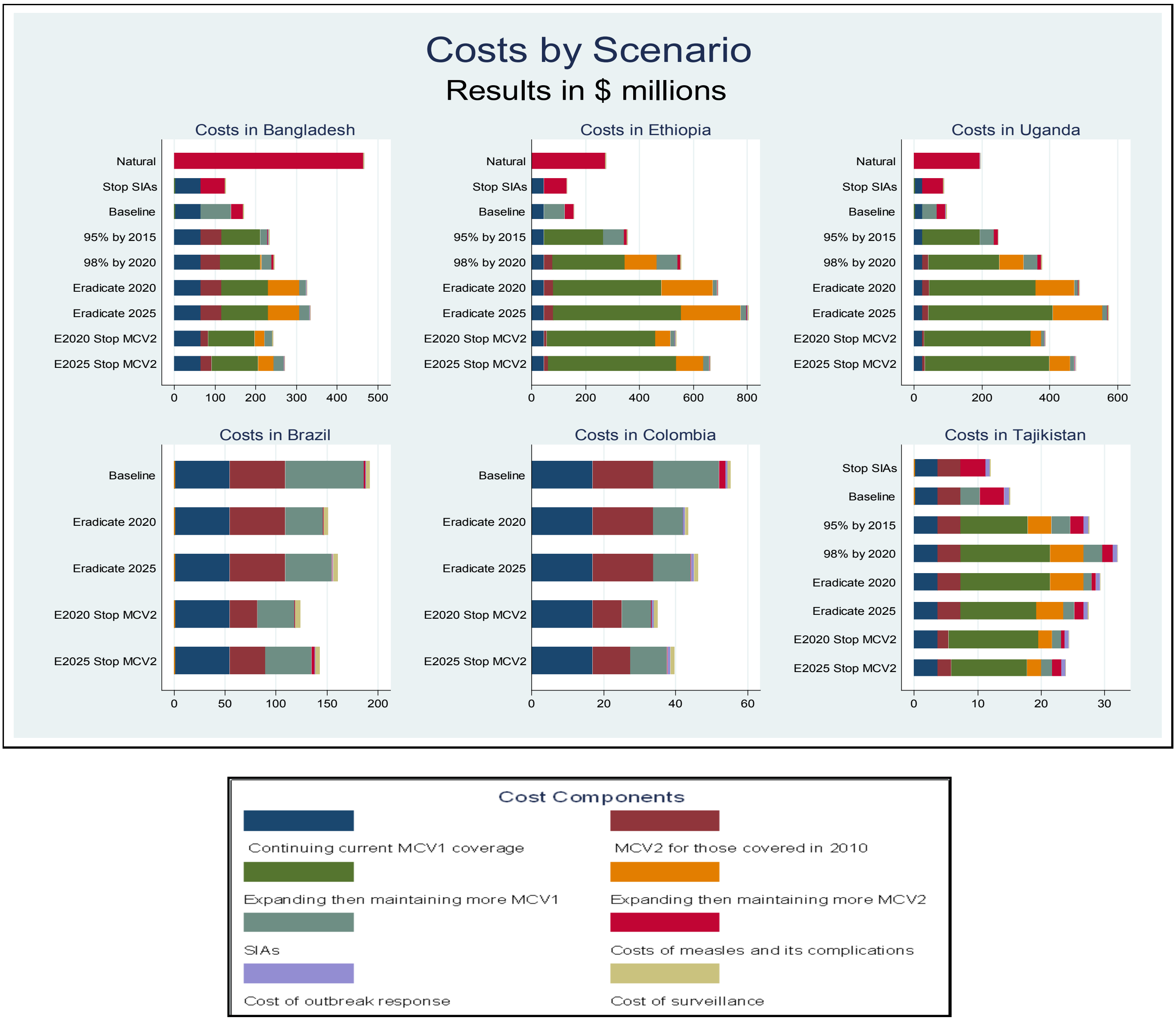

Figure 3: Components of costs in each scenario.

	Cost (Billions)	DALYs (Billions)	IC (M$)	IDA (M)	ICER	IC (M$)	IDA (M)	ICER	IC (M$)	IDA (M)	ICER	IC (M$)	IDA (M)	ICER	IC (M$)	IDA (M)	ICER	IC (M$)	IDA (M)	ICER
Global	23	0.5	13,872	488	28	12,712	465	27	7,753	488	16	8,002	465	17	6,380	209	31	12,243	411	30
WHO Region																				
Africa	2	0.1	9,237	92	101	8,596	88	98	7,447	92	81	7,170	88	81	4,396	39	112	9,993	77	129
America	4	0	-305	0	C/S	-222	0	C/S	-1,316	0	C/S	-1,000	0	C/S	-13	0	N/A	-6	0	N/A
Eastern Mediterranean	1	0	1,298	44	29	1,165	42	28	767	44	17	757	42	18	556	19	29	1073	37	29
Europe	5	0	-370	0	C/S	-316	0	C/S	-1,285	0	C/S	-1,013	0	C/S	-740	0	C/S	-652	0	C/S
Southeast Asia	4	0.4	4,743	333	14	4,175	317	13	3,460	333	10	3,216	317	10	3,217	143	23	3,658	280	13
Western Pacific	5	0	-730	19	C/S	-687	18	C/S	-1,320	19	C/S	-1,128	18	C/S	-1,056	8	C/S	-1,839	16	C/S
By Income and Coverage																				
Current Very Low Coverage	1	0.1	6,506	52	126	6,080	50	122	5,505	52	106	5,284	50	106	3,557	22	161	7,294	44	167
Low-Middle Income, Not Yet Eliminated	9	0.5	10,289	435	24	9,158	415	22	7,285	435	17	6,865	415	17	4,615	186	25	7,514	367	20
Low-Middle Income, Eliminated	1	0	-266	0	C/S	-193	0	C/S	-329	0	C/S	-240	0	C/S	-13	0	N/A	-7	0	N/A
High Income, Not Yet Eliminated	9	0	-2,617	1	C/S	-2,304	1	C/S	-3,721	1	C/S	-3,147	1	C/S	-1,799	0	C/S	-2,576	1	C/S
High Income, Eliminated	3	0	-39	0	C/S	-30	0	C/S	-987	0	C/S	-760	0	C/S	0	0	N/A	1	0	N/A

Region	95% Mortality Reduction			98% Mortality Reduction		
	IC (M$)	I DA (M)	ICER	IC (M$)	I DA (M)	ICER
Global	6,380	209	31	12,243	411	30
WHO Region						
Africa	4,396	39	112	9,993	77	129
America	-13	0	N/A	-6	0	N/A
Eastern Mediterranean	556	19	29	1,073	37	29
Europe	-740	0	C/S	-652	0	C/S
Southeast Asia	3,217	143	23	3,658	280	13
Western Pacific	-1,056	8	C/S	-1,839	16	C/S
By Income and Coverage						
Current Very Low Coverage	3,557	22	161	7,294	44	167
Low-Middle Income, Not Yet Eliminated	4,615	186	25	7,514	367	20
Low-Middle Income, Eliminated	-13	0	N/A	-7	0	N/A
High Income, Not Yet Eliminated	-1,799	0	C/S	-2,576	1	C/S
High Income, Eliminated	0	0	N/A	1	0	N/A

IC: Incremental costs
M$: Millions of dollars
IDA: Incremental DALYS averted
M: Millions
ICER: Incremental cost effectiveness ratio
C/S: Cost saving
N/A: Not applicable
Very Low Coverage: Current MCV1 coverage under 65% and/or the presence of armed conflict within a country
High Income: GDP greater than US$11,906
Low-Middle Income: GDP less than US$11,906
All costs reported in 2010 US$

Table 4: Costs, effects, and cost effectiveness of different scenarios at the global level.

Even though the cost per DALY averted is similar between eradication and control across countries that have not eliminated measles, the total cost of eradication strategies is higher than control. Table 3 shows that the incremental 40 year discounted cost of eradication strategies in Bangladesh is $156-$164 million compared to control strategies running $61-$74 million. The respective comparisons are $534 million (E2020) vs. $197 million (95% by 2015) in Ethiopia and $393 million (E2020) vs. $154 million (95% by 2015) in Uganda.

In the Latin American countries, the eradication scenarios involved only the opportunity to both save money and lives due to fewer imported cases and outbreaks, rather than any changes to immunization activities within the country. For Latin America, eradication involves an intensification of efforts in other countries and the cost of this intensification is borne by other countries. The numbers in the far right column of Table 3 for Colombia and Brazil are not ICERS; they are the ratio in which the dual benefits of financial savings and fewer imported measles DALYS will accrue if eradication is achieved. For Brazil and Colombia the high ratio of financial gain to health gain indicates that these countries will appreciate larger financial gains per health gain from measles eradication. At less than 1000 DALYs gained, the health benefits in either country over the next 40 years are negligible, but the financial savings are between $9 and $68 million, depending on the scenario and whether MCV2 is maintained after eradication.

Figure 3 shows the components of costs in each scenario in each country. In all scenarios that improve measles control the largest cost component is the cost of expanding and maintaining higher routine

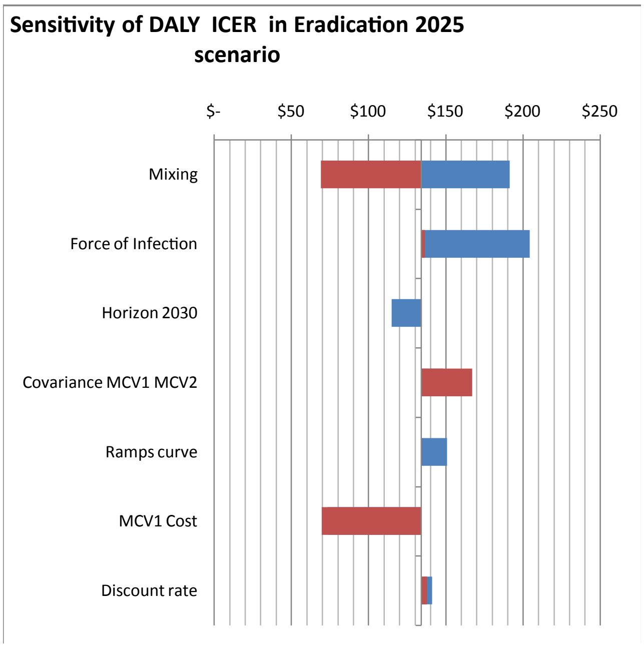

Figure 4: Sensitivity analysis. Tornado diagrams showing impact of parameter changes on ICERs for Uganda. Left side of each bar shows value when parameter set at low bound. Right side when parameter set at highest bound.

measles coverage which roughly doubles the total cost of measles control in eradication scenarios compared to baseline. These new costs are partially offset by savings from lowering the frequency of SIAs which were contributing roughly 1/3 of total costs in baseline models, but much less when coverage scales up. Net savings from eradication for both Brazil and Colombia were primarily from lowered outbreak response SIA expenses, with smaller contributions from lower surveillance and lower costs for case investigation and management.

Figure 4 shows the results of univariate sensitivity analysis in the form of tornado diagrams which were calculated for Uganda. These results show that assumptions about population mixing have the largest impact on cost effectiveness. Other factors that had a large impact on ICERS were assumptions on the force of infection and the degree of overlap between MCV1 and MCV2 coverage.

Results of global model

Table 4 shows the results for the cost-effectiveness analysis on the global level. Depending on the scenario adopted, it is estimated that eradicating measles will cost between $7.8 and $13.9 billion additional US$ and avert between 465 and 488 million discounted DALYs (or roughly 8 to 8.7 million undiscounted deaths) between 2010 and 2050. The most costly scenario was eradication by 2020, costing an additional $13.9 billion more than the $23 billion projected if baseline vaccination levels in 2010 are maintained unchanged for the next 40 years. With eradication in 2020, The Americas, Europe, and Western Pacific regions are projected to make net savings of $305, $370, and $730 million respectively (total $1.4 billion savings). On the global level the $1.4 billion in savings can partially offset the $15.3 billion of total costs required in Africa, Eastern Mediterranean, and Southeast Asia where costs are projected at $9.2, $1.3 and $4.7 billion respectively.

At the global level, the incremental cost-effectiveness of the eradication scenarios averaged around 27 dollars per DALY averted (dropping under $20 per DALY averted if MCV1 is continued while MCV2 vaccination is stopped after eradication), while scenarios with expanding coverage without eradication are around 30 dollars per DALY averted. The closeness of these ICERs indicates that the cost-effectiveness of the different scenarios cannot be distinguished, but all demonstrate that investing in expanding the coverage of measles vaccination is good value for money. The scenario of stopping SIAs in low income countries also shows that SIAs are good value for money; moving from a hypothetical situation without SIAs in GAVI-eligible countries to a situation where there are SIAs (the current situation) has an ICER of only US$34 per DALY averted.

Within this global picture there is considerable heterogeneity (Table 4). The ICERs for elimination tend to be around US$100 per DALY averted in the WHO Africa region, $29 in the Eastern Mediterranean region, under $15 in the Southeast Asia region, and cost saving in the America, European, and Western Pacific regions. Maintaining MCV1 and removing MCV2 after elimination moves the ICER lower in all areas to under $100 per DALY averted.

Discussion

By all metrics for judging cost-effectiveness, scaling up routine measles coverage while maintaining SIAs in countries that have not yet achieved 90% coverage is a very cost-effective investment in health. We estimate that as global average measles eradication would cost $20 to $30 per DALY averted. For reference, celebrated "best buys" in public health include HIV/AIDS prevention, TB control and treating childhood lung infections at $68, $135, and $146 per DALY respectively [33]. Eliminating a disease entails higher direct costs of increased coverage, but permits countries to stop SIAs earlier which offsets the higher direct costs.

For endemic countries, both measles control and measles eradication have similar cost effectiveness, but countries that have already eliminated measles have an economic preference for global eradication of measles. The economic non-inferiority of measles eradication in low income countries is similar to results shown for polio eradication [34]. However, for measles, eradication is actually superior to control from the perspective of high income countries. Our study shows that countries that have already eliminated measles achieve much larger financial savings if measles is eradicated from the planet globally than if it is merely controlled. Their financial savings amount to 9-10% of the global incremental costs of measles eradication. For high income countries that have already eliminated measles, if the world eradicates measles it will lead to large financial savings by enabling them to potentially stop MCV2, outbreak response, and lab testing for measles among rash-fever illnesses. There is a $1 to 1.3 billion dollar financial difference for the Americas between measles eradication and measles control strategies, mostly savings realized if MCV2 is discontinued. In contrast, there is a much smaller difference in Africa between mortality reduction scenarios and measles elimination. For Africa, 98% mortality reduction by 2020 would cost an additional $10 billion, whereas eradication by 2020 would cost $9.2 billion or $7.4 billion depending on whether MCV2 is retained or abandoned after 2023 respectively (Table 4). The costs of mortality reduction are higher than eradication in this region because routine coverage was not projected to increase enough in some countries by 2020 to warrant discontinuation of SIAs if the slower scale up of a mortality reduction approach was chosen

An independent parallel study of the cost-effectiveness of measles eradication by Levin and others focused on the same 6 countries and prepared global estimates as well [35]. Like our study, the Levin et al.

study found that eradication by 2020 would be cost effective with a cost per DALY averted that was less than GDP per capita. However, unlike our study, the Levin et al. study stated that eradication by 2020 would be preferred to measles control in each country that had not yet eliminated measles, and on a global basis. The incremental cost effectiveness of measles eradication for Bangladesh, Ethiopia, and Uganda by 2020 was respectively estimated at $16, $134, and $804 per DALY (compared to our estimates of $81, $91, and $118). The 95% RM strategies in their model cost 1.4 to 16 times as much per DALY averted in the focal countries and twice as much in low and upper-middle income countries in global models.

In contrast to the Levin et al. study's conclusion that measles eradication has superior cost-effectiveness, our analysis concludes that the cost effectiveness of measles eradication is not inferior to control strategies. Our more circumspect conclusion can be attributed to differences in the way variation in measles transmission was modeled and how variation in costs and effects were analyzed. The Levin study used a deterministic model with an added Gaussian noise term. Our study used a stochastic transmission process based on biweekly draws from a negative binomial force of infection. Furthermore the Levin study produced point estimates of cost-effectiveness ratios based on differences in means emerging from 10 runs of the model. Our study's cost-effectiveness ratios and confidence intervals summarize the distribution of differences emerging from 700 runs of the model.

As one can see from the width of scatter plots in Figure 2 the number of DALYs can vary widely due to stochastic variation in outbreak size in populations whose vaccine coverage scenarios are kept exactly comparable. Standard deviations in our model were estimated at between 17% and 39% of the mean DALY burdens in Ethiopia, Bangladesh, and Uganda and between 55% and 160% in Brazil and Colombia (Table 3). Rather than hinging claims about cost-effectiveness on one single point per scenario, our Monte Carlo analysis can show the range of possible outcomes. Stochastic analysis guards against the chance that the cost-effectiveness ratio is being derived from a particularly fortuitous eradication run that has happened to be compared to a particularly unfortunate instance of a non-eradication scenario. Our model also goes beyond the Levin (2011) paper to show how the cost effectiveness of measles eradication would be altered if it were delayed to 2025 and if the second dose of measles was discontinued after eradication.

The strategy we used to estimate the costs of all measles scale up policies is more likely to overestimate than underestimate costs. We assumed that even though low income countries have been able to achieve their current levels of MCV1 coverage at an average cost of $1.00 per child [36], efforts to expand coverage would require new and recurring investments in supervision, outreach, logistics, and cold chain that would cost $10 to $40 per newly covered child per year in core areas of low income countries and $12 to $38 per newly covered child in outlying satellite areas. In high income countries the incremental cost to advance measles coverage among heretofore unvaccinated subgroups was assumed ad hoc to be $200 per child. Estimates of the incremental cost savings of eradication in high income countries that have not yet eliminated measles are sensitive to this ad-hoc parameter, but the true costs of overcoming resistance to vaccination in these countries are not known. Health planners in high income countries planning to cooperate with global efforts to eradicate measles urgently need to identify effective strategies to reach their unreached population and what these strategies cost.

Global perspectives on measles eradication

The global models of measles eradication locate the largest financial gains from eradication among the high income countries which stand to save $2.3 to $2.6 billion if measles is eradicated and save $3.1 to $3.7 billion if after eradication they decide to drop administering MCV2 (Table 4). The largest financial requirements will be in low and middle income countries which can be classified into 2 groups. The countries with very low coverage will require additional spending of $5.3 to $6.5 billion between now and 2050, discounted at 3%, to eradicate measles. Other low and middle income countries will require $6.8 to $10.3 billion between now and 2050, discounted at 3%, to eradicate measles. Countries that currently have very low coverage are assumed to need to spend much more in total to bring their coverage up to eradication thresholds and this spending makes the cost effectiveness less attractive, ranging from $106 to $126 per DALY averted. In the global picture, the amount of money saved by the countries that do realize net savings from measles eradication is sufficient to offset 10% of the incremental global costs of measles eradication from now till 2050. Both the public and private health sectors of high income countries would realize the savings. Only the public sector and civil societies of high income countries are configured to make investments in global eradication efforts through bilateral and multilateral aid.

Future priorities in measles research for decision-making

Although the point estimates of deaths, DALYs, and costs shift somewhat as parameters are altered, the fundamental conclusions discussed above do not change during sensitivity analysis for a wide range of assumptions about the behavior of measles dynamics and the nature of the costs of measles control. The incremental cost-effectiveness ratios at the global level remain below $100 per DALY for eradication across the ranges of parameter values assessed. Better measurement is unlikely to reverse any of the above conclusions. Based on the experience with other disease eradication efforts, the key unknowns are the magnitude and location of social and political obstacles to measles control.

The project can be summarized as follows. For low income countries that do not yet have high routine measles vaccination coverage it would be a cost-effective investment to spend up to $20 to $30 per new child reached to improve measles coverage. The Reaching Every District (RED) strategy which involves new and recurrent investments in outreach, supervision, and logistics forms a good template for these efforts to scale up. The RED investments will complement the strength of primary care systems because they improve core capacity in data, logistics, supervision, and community liaison. Better routine coverage has spillover effects that can improve health system performance through record keeping, logistics, and outreach. SIAs have more complex effects on health systems [37].

A low income country that commits to measles elimination instead of measles control is not wasting resources when one calculates dollars per life year saved. However, such a commitment requires potentially finite resources of political will and the ability to sustain consistent policies to expand vaccine coverage into the future. Although the Americas were able to create and sustain demand for vaccination to the point at which measles could be eliminated [38], it remains to be seen whether social obstacles can be overcome in other regions. In contrast to the indifference of low income countries, the high income countries of the world would achieve dramatically higher financial gains if measles is eradicated from the planet than if it is merely kept under control. The direct financial savings of the high income countries from reducing the frequency of SIAs, potentially stopping MCV2, surveillance, and outbreak control after eradication does not offset the total global cost of eradication. Nevertheless, investments in better measles vaccine coverage remain an extremely low-cost opportunity to save more lives. Humanitarian concerns would justify the interest of high income countries to save lives at low cost by improving routine vaccination whether or not it leads to eradication. If the commitment to a global eradication goal can mobilize additional enthusiasm for coverage scale up there is no economic reason to object.

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Contributors

DB led the project, designed the models, wrote the code for the measles transmission model, analyzed the output, wrote and edited the manuscript and co-wrote all of the appendices. BJ prepared the costing parameters, wrote the code for global models, analyzed the output, and co-wrote the manuscript and methodological appendices. DN prepared the demographic parameters, analyzed the output and co-wrote country appendices and the manuscript. AL checked all of the costing models, analyzed output, co-wrote the manuscript and appendices. ES helped acquire cost and epidemiological parameters, analyzed output and co-wrote the appendices and manuscript. AD oversaw the technical feedback to the project from WHO and its technical review team, helped design policy scenarios, analyzed output, and co-wrote appendices and manuscript.

Competing Interest Statement

David Bishai has consulted for Becton Dickinson which manufactures syringes and needles. There are no conflicts of interest for all others.

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