Strategic Planning for Measles Control: Using Data to Inform Optimal Vaccination Strategies

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Background. In response to repeated requests for assistance in evaluating the health benefit and cost implications of adjustments to national measles immunization strategies, the World Health Organization (WHO) has developed the Measles Strategic Planning (MSP) tool to harness routinely available data to estimate effectiveness and cost effectiveness of vaccination strategies.

Method. The MSP tool estimates measles incidence and mortality through a country-specific cohort model, using a probability of infection dependent on population immunity levels. This method approximates measles transmission dynamics without requiring detailed data that would prohibit use in low- and middle-income countries. Coupled with cost data, the tool estimates incremental costs and cost effectiveness of user-defined vaccination strategies over 5–10 year planning periods.

Results. The MSP tool produces valid estimates of measles incidence in settings with low to moderate vaccination coverage. Early adopters report that the tool facilitates decision making by minimizing the amount of time required to assess the impact of vaccination strategies on population immunity.

Conclusions. By clearly illustrating what vaccination strategies can effectively protect against measles at the least cost to immunization programs, the MSP tool supports evidence-based decision making for effective and comprehensive measles control.

Measles is among the most highly infectious diseases known, affecting >95% of exposed populations in the absence of vaccination. With measles case-fatality ratios (CFRs) among children ranging from <0.1% in high-income countries to 6% in high-mortality settings, measles vaccination prevented an estimated 12 million deaths over the period 2000–2008 among children under the age of 10 [1, 2]. The large preventable disease burden attributable to measles infection, combined with an inexpensive and highly effective vaccine, makes measles vaccination one of the most cost-effective health interventions worldwide [3]. Although considerable progress in measles control has been made with average global measles vaccination coverage reaching 82% in 2009, many countries continue to face challenges optimizing resources to effectively protect children and achieve or maintain regional measles control goals.

Tradeoffs in choosing an optimal vaccination strategy relate to the timing of routine doses and need for supplemental immunization activities (SIAs) to fill immunity gaps. Immunization program managers must choose between protecting infants as early as possible when the risk of mortality is greatest by giving the first routine dose of measles containing vaccine (MCV1) at 9 months, and achieving 85% vaccine effectiveness at this age, or delaying MCV1 to 12 months and achieving ≥95% vaccine effectiveness [4, 5]. SIAs can greatly enhance the equity of vaccination by reaching more zero-dose children than routine vaccination alone [6], but follow-up campaigns are needed every 2–4 years to

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prevent outbreaks until routine coverage reaches at least 90% [7]. Where school enrollment is high, a second routine dose (MCV2) can reach more children if given through a school-based program, although earlier administration, typically in the second year of life, may prevent more deaths from measles. These vaccination strategy choices differentially impact the rate of accumulation of susceptible individuals within a given country, thereby informing the risk of measles outbreaks and expected number of measles cases and deaths. In addition, these choices have cost implications that are not easily managed despite the affordability of measles vaccine in many low- and middle-income countries.

In response to repeated requests for assistance in evaluating the expected level of health benefit and cost implications of adjustments to national measles vaccination strategies, in 2004 the World Health Organization (WHO) began working with member states to develop a tool to facilitate analysis of national immunization and surveillance data and cost effectiveness of different vaccination strategies. Here we describe the information routinely available to guide the design of immunization program strategies and how the Excel-based Measles Strategic Planning tool (MSP tool, which can be accessed at https://extranet.who.int/aim_elearning/en/measles/index.html) harnesses this information through a natural history model of measles infection and cost-effectiveness analyses. We provide a country example of use of the MSP tool for evaluating measles vaccination strategies and conclude by reviewing preliminary user experience and lessons learned on disease intervention planning tools.

Data and Natural History Models

The types of information on measles that are routinely collected at the national level and reported annually to WHO include the following:

- Scheduled age and vaccination coverage for MCV1 and, where administered, MCV2;
- Dates, target age range, and vaccination coverage of measles SIAs;
- Number of reported measles cases.

To examine the protection provided by vaccination across a population, a single year cohort approach can be used that tracks birth cohorts over time, subtracting out protection due to vaccination (incorporating the vaccine effectiveness at age of administration) and removing all-cause background mortality on an annual basis, as illustrated in Figure 1 [8]. This approach produces a matrix of the level of protection provided by the intervention in each age group, as shown in Table 1. In this example for Kenya over 1983–1986, birth cohorts born after vaccine introduction in 1984 are protected in proportion to coverage multiplied by effectiveness. To incorporate the impact of vaccination on disease burden, a mathematical model of year-specific risk of infection and age-specific risk of death from infection is superimposed on the basic cohort approach, which

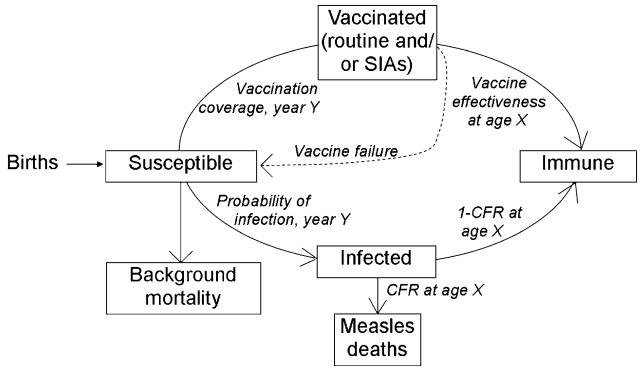

Figure 1. Natural history model of measles infection for single birth cohort in single year. Individuals are removed each year from the pool of susceptibles in each birth cohort by effective vaccination, infection, or background mortality.

results in the matrix shown in the lower half of Table 1. By age 3, unvaccinated cohort susceptibility drops to 44% due to immunity from prior infection.

If the population immunity profile indicates insufficient protection against outbreaks, immunization program managers can use a tool like the MSP to project what adjustments would have the greatest impact on reducing measles incidence or mortality while minimally affecting immunization program costs. Adjustments to vaccination program strategies include improving routine vaccination coverage (mechanisms for improving routine coverage, in conjunction with the health system, include regular outreach services, supportive supervision, establishing community links with service delivery, monitoring data for action, and better planning of resources [9]); modifying the frequency, age range, or coverage of SIAs; introducing a second routine dose; and changing the scheduled age for routine doses.

METHODS

MSP Natural History Model

A series of algebraic equations, (1)–(3) below, calculates the movement of children through the susceptible, infected, and removed states in proportion to vaccination coverage, probability of infection, and case-fatality ratio [8]. To remove individuals from the pool of susceptibles in a given year, they must become either effectively vaccinated through MCV1, MCV2, and/or SIAs (eq. 1) or infected (eq. 2). Herd immunity effects are incorporated by drawing the annual probability of infection (*POI*) from a curve (see Figure 2) that was derived specifically for this tool.

$$S_{X,Y} = S_{X-1,Y-1} \times (1 - I_{X-1,Y-1}) \times VE_X \times (1 - MCV1_{X,Y})(1 - MCV2_{X,Y} \times D_X)(1 - SIA_{X,Y}) \quad (1)$$

Table 1. Proportion of Cohorts 0–3 Years of Age That Remain Unprotected From Measles, by Either Vaccination Only or Both Vaccination and Prior Infection, Over 1983–1987 in Kenya

	Year				
	1983	1984	1985	1986	1987
	MCV1 coverage (%)				
	0	55	63	65	69
Age (years)	Proportion of cohort unprotected by vaccination (%)				
<1[a]	*50*	**77**	73	72	71
1	*100*	*100*	**53**	46	45
2	*100*	*100*	*100*	**53**	46
3	*100*	*100*	*100*	*100*	**53**
Age (years)	Proportion of cohort unprotected by vaccination or prior infection (%)				
<1[a]	*50*	**77**	73	72	71
1	*90*	*90*	**48**	42	41
2	*63*	*63*	*63*	**34**	31
3	*44*	*44*	*44*	*44*	**25**

NOTE. Values in bold indicate the progressive decline in susceptibility of a single birth cohort over time. Italicized values indicate children born before vaccine introduction.

[a] Infants assumed to be protected from infection by maternal antibodies during the first six months of life.

$$I_{X,Y}=S_{X,Y}\times POI_Y,\ \text{where}\ POI_Y=POI_i\times\left(\frac{\log(S_{Y-1})}{\log(10.5)}\right)^{\left(3.5-\frac{S_{Y-1}}{3.5}\right)} \quad 2$$

*the values 3.5 and 10.5 are the results of least-squares estimation of POI from dynamic simulations

$$R_{X,Y}=S_{X-1,Y-1}-S_{X,Y}-I_{X,Y}\times CFR_X \quad 3$$

where X denotes age and Y denotes year

S= % susceptible

I= % infected

R= % removed from susceptible pool

VE = vaccine effectiveness (85% for ages <1 year, 95% for ages ≥1 year)

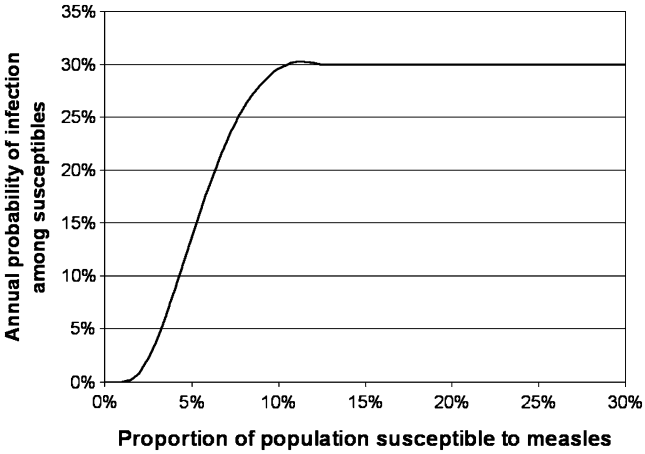

Figure 2. Annual probability of measles infection among unprotected population as a function of proportion of population susceptible to measles.

$$D=\begin{cases} .75\times MCV1\times(1-VE1) & \text{if MCV2 given at}<3\text{years of age} \\ .25\times MCV1\times(1-VE1) & \text{if MCV2 given at}\geq 3\text{ years of age} \end{cases}$$

POI_i=0.3

Many models of measles transmission have been developed over the past several decades, and more complex methods exist that are capable of producing more nuanced estimates of measles incidence and mortality (see, eg, [10–13]). These often use a dynamic transmission function based on contact patterns between susceptible and infected individuals in different age groups and may incorporate effects of age structure. Such models require local data on contact patterns, surveillance data in 2–4 week time steps, and substantial processor speed to run the computationally intensive systems of equations. Few national immunization programs in low- and middle-income countries have the information and resources available to meet the needs of complex dynamic transmission models [14], so we adopted the simplified approach of a uniform year-specific probability of infection.

The initial probability of infection (POI_i) among susceptibles was obtained from the cumulative POI by age observed in developing countries in the prevaccine era, when about half of children had been infected by age 2 and all children had been infected by age 15 [15]. For subsequent years, the POI among susceptibles was modeled as a function of population susceptibility (see Figure 3), derived using least-squares estimation of simulated data. The simulations were produced with a dynamic susceptible-exposed-infected-removed (SEIR) model with homogeneous mixing across age groups that was run on a variety of scenarios in which population, coverage, and the basic reproductive number (R_0) for measles were varied.

As an approximation to a fully dynamic transmission function, the POI curve can be considered "quasi-dynamic" in the sense that the overall probability of a susceptible getting measles

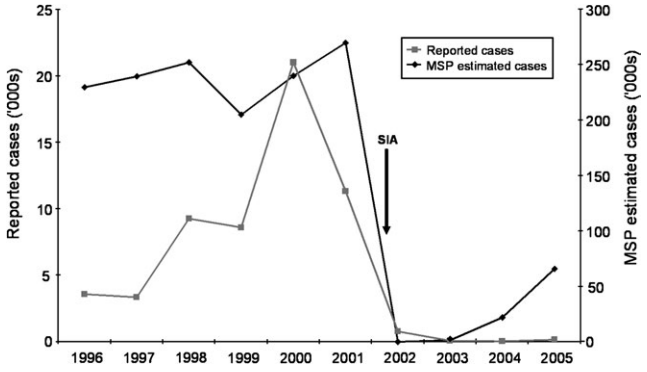

Figure 3. Measles cases reported nationally and estimated by the MSP tool, 1996–2005 in Kenya.

in year $i + 1$ is informed by the number of susceptibles in year i, but is not informed by the number of infections in year i, as shown in equation (2).

Deaths are calculated by applying an age and country-specific CFR to infections [1]. Disability-adjusted life years (DALYs) are also computed for the purposes of cost-effectiveness analyses using methods described by Murray et al [16], with the following adjustable specifications: 3% discount rate, ideal (82 year) life expectancy at birth, equal distribution of cases across genders, and disability weight of 0.152 for measles cases.

Results of the MSP tool were found to be highly sensitive to the fraction of MCV2 doses, defined as a parameter D above, which were recorded as MCV2 because they are given at the age scheduled for the second routine dose, but actually reach children who missed routine vaccination at the first scheduled age. Unfortunately, the quality of data on MCV2 is often inadequate, and most immunization programs do not track whether doses recorded as MCV2 are a child's first or second dose of MCV. Using the following proxy developed through consultation with immunization program experts, we assumed the fraction D allows MCV2 to reach (a) 25% of children who missed MCV1 if the age scheduled for MCV2 is <3 years, based on the assumption that these doses are administered through the same immunization system that delivers MCV1, or (b) 75% of children who missed MCV1 if the age scheduled for MCV2 is >3 years, based on the assumption that these doses are delivered through a school-based approach. Countries that have low enough measles transmission to warrant delaying MCV2 to school entry tend to have high school enrollment rates, which allow school-entry vaccination to reach children that did not have access to primary health services at the age scheduled for MCV1. SIAs are assumed to reach children indiscriminant of vaccination history, due to the ability of SIAs to achieve uniformly high coverage [6].

Costs

Costs were incorporated in the MSP tool in response to requests during in-country workshops for cost-effectiveness data on measles vaccination strategies. Country-specific costs per dose were computed using the ingredients approach, which costs each input to deliver a dose of vaccine, based upon cost data extracted from the WHO Financial Sustainability Plans (FSPs) submitted over 2000–2004 by low-income countries. Additional details on the costing method are described elsewhere [17]. When adjusted to 2008 US dollars, the bundled cost of delivering a dose of measles vaccine through SIAs and routine services ranged \$0.26–\$2.77 and \$0.96–\$37.17, respectively, in low-income countries. In the absence of data from middle-income countries, we assumed that delivering a dose of measles vaccine through SIAs and routine services cost \$7 and \$100, respectively, in middle-income countries [18]. High-income countries are not included in the MSP tool due to the unrealistically high estimates of measles incidence the tool produces for these low-incidence settings where infections become very sporadic and difficult to predict, which was a limitation identified during validation.

Costs are applied to each vaccination strategy that the user defines using a linear cost function that multiples the number of doses delivered by the country-specific cost per dose, which is held constant across immunization coverage levels. In reality, we expect that the marginal cost per new child vaccinated would increase as coverage improves. As the size of the unvaccinated population decreases, the per-child cost of reaching remaining uncovered children may increase in an exponential manner because unvaccinated children become progressively more difficult and expensive to locate and vaccinate. This nonlinear increase in per-child costs, however, has not been built into the model because it has not been well defined. The approach adopted is expected to provide sufficient accuracy for incremental costs over a 5–10 year program planning period. In large countries, instructions were given for how to populate the tool with state or province level data to provide a more tailored approached.

Cost Effectiveness

Incremental cost-effectiveness ratios (ICERs), comparing the incremental cost per additional case, death, and DALY averted over baseline, are presented for each scenario next to the incremental costs and health outcomes averted, discounted at 3% to reflect preference for immediate benefit over future benefit. These data allow users to identify which scenarios are the most efficient, effective, and/or cost minimizing with respect to measles control over the time period analyzed. However, users should exercise caution when comparing the ICERs with cost-effectiveness information for other interventions because MSP tool is not a generalized cost-effectiveness analysis and some key assumptions will differ from those of other cost-effectiveness analyses.

Validation of Natural History Model Against Simulated Data

The MSP tool was reviewed by WHO's Quantitative Immunization and Vaccine-Related Research advisory group, which subsequently selected a team of experts on disease transmission

dynamics to validate the natural history model. The team validated the MSP tool against a method referred to as realistic age structured (RAS) modeling, which has previously been shown to reproduce measles transmission dynamics with accuracy [19, 20]. The RAS model specifications were set as close to the MSP tool as possible, including assumptions of homogeneous mixing, and then identical scenarios were run with the 2 models and output compared. Overall, the reviewers found that the MSP tool produced reliable estimates of measles incidence over longer periods of time (at least 5 years) and when demographics and vaccination coverage were not highly variable. However, mortality was consistently overestimated compared with RAS results, particularly in scenarios with high or rapidly increasing vaccination coverage. The drop in incidence usually observed in years following SIAs was also not sustained as long as in the MSP tool as in RAS model, which was not surprising given that the POI function in the MSP tool is not fully dynamic [21]. User instructions were modified to reflect these limitations.

Validation of Natural History Model Against Reported Data

The natural history model in the MSP tool was further validated by a vaccine-preventable disease surveillance officer by comparing MSP projections of incidence for 9 countries with low to moderate coverage to national measles surveillance data. While surveillance data do not reliably indicate the true incidence of measles, we expect the change over time in reported cases to reflect changes in true incidence. When comparing the average incidence over 6 years before an SIA to average incidence over 3 years after the SIA, the MSP tool projected incidence reductions that were within 10%–15% of reductions in reported cases for 7 of 9 countries. For example, following a high-coverage SIA in 2002 in Kenya, the MSP tool estimated that incidence decreased by 88% compared with a 98% drop in reported cases over the same time period (see Figure 3.) The 2 conditions under which the tool did not estimate similar incidence reductions in comparison to surveillance data were low coverage SIAs or multiyear phased SIAs. Corroborating findings from validation with simulated data, comparisons to reported data also showed that the rates of infection estimated by the MSP tool did not remain suppressed following SIAs as long as would be expected, as shown in Figure 3 over 2003–2005.

Using the MSP Tool

After selecting a country to evaluate, the first step in using the MSP tool is reviewing and updating the data on vaccination, population, and surveillance that has been preloaded from WHO databases to facilitate use [22, 23]. Once information is corrected, users are prompted to review the current population immunity profile produced by these data. An example of the population immunity profile produced for Kenya in 2008, when routine coverage reached 76% and SIAs had last been conducted in 2006 and 2002, is shown in Figure 4. To provide a complete population immunity profile through adult cohorts, the model begins calculations in 1960 but presents the immunity profile only for the year the user specifies as baseline. The 2008 population immunity profile for Kenya indicates that almost a quarter of under-5-year-old children were projected to be susceptible, indicating a very high risk of outbreaks.

After reviewing the current immunity profile, the MSP tool interface allows users to define strategies for up to 4 vaccination scenarios at a time. For Kenya in 2008, some key strategies to assess might be (*a*) improve routine coverage at an achievable rate, in this case 1%–2% per year; (*b*) conduct an immediate follow-up SIA in 2009, and again in 2013; (*c*) introduce MCV2; and *d*) continue MCV1 at current coverage. The impact of these strategies on measles incidence and mortality are instantaneously computed, while taking into account factors such as the enhanced equity but limited sustainability of SIAs and the tradeoffs in timing of routine doses described earlier. For each scenario, the number of cases, deaths, and costs are estimated over the planning period chosen and presented in a series of tables and graphs for side-by-side comparison, which can be exported for use in other programs. Figure 5 presents one of these graphs: the predicted number of cases under each strategy projected to 2015, which indicates that conducting SIAs in 2009 and 2013 would offer the greatest protection against measles over this time period. In reality, a follow-up campaign was conducted in 2009 and no major outbreaks were reported in the following year.

Preliminary User Experience

The WHO MSP tool was pretested remotely with country-level staff in Ghana and Mali, followed by workshops with country staff in China and India and in the WHO regions of the Eastern Mediterranean and Southeast Asia. In general, country staff (EPI managers and surveillance officers) found this to be a useful tool that promotes better understanding of measles epidemiology and vaccination strategies, but the users faced a number of challenges due to the design limitations. The tool was subsequently modified, based on users' feedback, to include expanded age ranges with adults, costs and cost-effectiveness, preloaded data, and an export function to facilitate sharing and presentation of results.

Many users also found they needed further training on measles epidemiology and vaccination program costing to be able to interpret the incidence and cost-effectiveness estimates the tool provides. In conjunction with PATH and the US Centers for Disease Control and Prevention, WHO developed an interactive e-learning module that provides essential background information on measles epidemiology, control strategies, immunization program costing, and how to maximize the MSP tool's use at the national-level. The Strategic Planning for Measles Control e-learning module was released online in 2009.

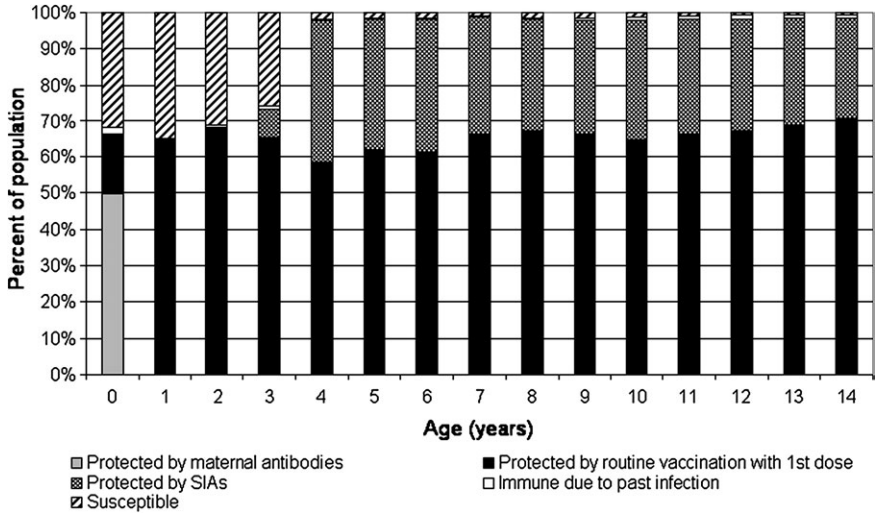

Figure 4. Population immunity and infection profile for children 0–14 years in 2008 in Kenya.

DISCUSSION

While measles vaccination has continually been shown to be a best buy in public health, a large resurgence in 2010 [2] corroborates concerns that decisions on health spending allocation frequently are not based on evidence of disease control costs and benefits. Effective and comprehensive national plans for disease control can also be impeded by lack of accessible and interpretable data on what strategies are capable of reaching control goals. By clearly illustrating what strategies can improve population immunity against measles at the least cost to immunization programs, the MSP tool facilitates evidence-based decision-making for measles control.

Use of the MSP tool is restricted to planning purposes only, however, and the results are only as reliable as the vaccination coverage, CFR, and demographic data allow. Given these limitations, users are repeatedly prompted to replace pre-loaded data with the most accurate data available at the time of use and are warned not to use the tool to estimate true incidence in a single year or predict when outbreaks will occur. Rather, the MSP tool provides general guidance on the most appropriate strategies for a given country.

Eight months after release of the MSP tool and e-learning module package, an electronic survey on user satisfaction was sent to 152 immunization focal points in Ministries of Health and WHO country offices. Twenty-three responses were received within a 2-week period, mostly from Ministry of Health staff in countries with low levels of measles disease burden. While these responses may be limited, several observations bear mentioning. First, the majority of respondents agreed or

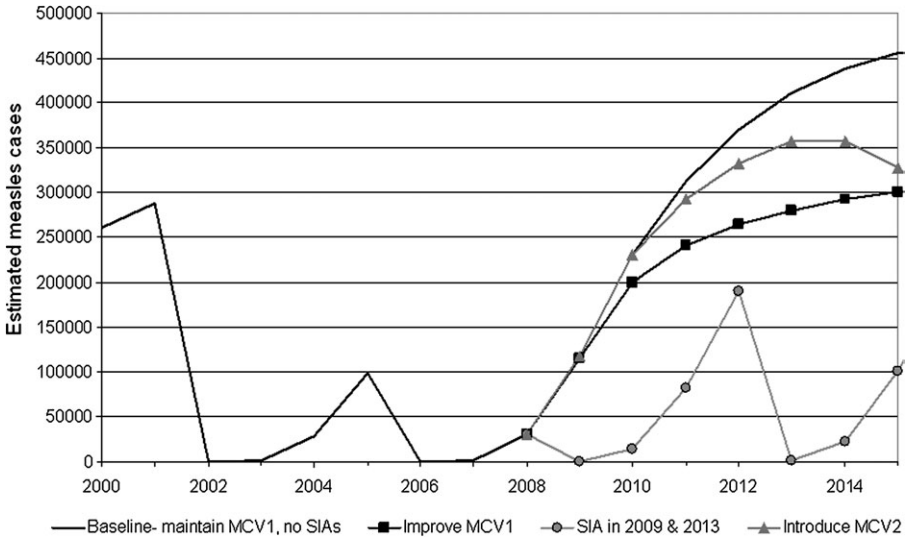

Figure 5. Predicted measles cases in Kenya for 4 vaccination strategies, 2000–2015.

strongly agreed that they liked using the e-learning module and MSP tool and that the tool makes decision-making easier by minimizing the amount of data entry and analysis normally required to assess the impact of vaccination strategies on measles mortality and program costs. We believe the iterative development process through country-level workshops was critical to this indicator of success.

Second, when asked the likelihood of using the e-learning module and the WHO MSP tool in their work, the majority of respondents reported that they would definitely or probably use the MSP tool to evaluate different vaccination strategies and use the e-learning module to train their staff. We believe the bottom-up development process, which began with requests for assistance from immunization program managers, has been critical to ensure that the tool serves country-level purposes effectively.

The majority of survey responses, webpage visits, and user requests for support submitted to WHO in the first year originated from Europe and the Western Pacific, indicating that adoption may be limited in developing countries. Increased support from the developers and expert users is needed to encourage utilization where warranted and cultivate the tool as immunization program needs and types of available data change over time. For example, when the tool was used during a WHO regional workshop in the Eastern Mediterranean including country-led discussion on the implications of the workshop findings, adoption levels were higher than in other regions.

A number of tools have been developed to demonstrate the impact of disease control interventions (eg, Spectrum PMTCT and LiST modules, TEHIP), primarily focusing on issues of prioritization. The MSP tool is unique in its capability to assess how an intervention can be delivered most efficiently (the MSP tool can be accessed at: https://extranet.who.int/aim_elearning/en/measles/index.html). As we move toward measles elimination in more countries and regions, the central question for immunization managers is not whether to invest in improving measles vaccination, but rather how to ensure this investment will produce the best possible outcome.

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