Cost-effectiveness of Supplementary Immunization for Measles in India

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Objective: This study aims to estimate the incremental cost effectiveness of a supplementary immunization activity (SIA) for measles in a district of India with measles vaccine coverage equivalent to the National average.

Design: A state transition model is used to estimate the effect of routine vaccination with measles vaccine as well as with measles vaccine during the SIA. The model follows each sub-cohort in the target population at respective age (1-5 years) to five years of age, using age specific incidence rate and vaccination rate to determine the number of cases of measles. Using age specific incidence rates and complication rates for measles; deaths and disability adjusted life year (DALY) averted is estimated.

Results: Using base-case assumptions, an estimated 65479 cases of measles and 1637 deaths due to measles will be prevented in a span of four years from a single supplementary immunization activity in a pediatric population (1-5 years of age) of size 839,473. The cost per measles vaccine dose delivered is INR 30. Using base case analysis the cost to avert a death is INR 15381 and the cost per disability adjusted life year (DALY) averted is INR 430.

Conclusions: Supplementary immunization activity for measles is cost-effective. However, this cannot be considered superior to a second dose of measles in routine immunization.

Key Words: Cost-effectiveness, India, Measles, Vaccine, Supplementary immunization.

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Due to the availability of an efficient vaccine which provides long term immunity, and the fact that measles is generally limited to the pediatric population, measles is considered as the next disease targeted for eradication. The World Health Organization and United Nations Children Fund have come up with a Measles Vaccine Initiative focused towards controlling and eradicating measles in the developing countries. In India, a single dose of measles vaccine is offered to every child at the age of nine months under the National Immunization Program. Several developed countries have national immunization programs offering upto three doses of the measles vaccine. The current strategy for measles mortality reduction in India by two thirds by 2010, focuses on a second opportunity for measles immunization through routine immunization in states where routine measles coverage exceeds 90% and local resources are available to sustain the strategy(1). However, this does not address the question of measles eradication strategy for almost 38% of districts of India with measles coverage less than fifty percent(2).

One of the key activities identified to improve routine immunization coverage rates is Supplementary Immunization activity (SIA) in low coverage states. In the past, countries in the American subcontinent have adopted SIA campaigns which have led to improvements in routine immunization services and surveillance system(3). In India, this strategy has been used successfully for pulse immunization for polio, outbreak control, and crisis management in low coverage areas to rapidly achieve high coverage. United Nations Children Fund (UNICEF), in collaboration with the Ministry of Health and Family Welfare, Government of India has in the past conducted such activities as part of the urban measles control strategy.

This paper presents a cost effectiveness analysis from the provider's perspective. It provides decision makers with evidence to make a case for conducting supplementary immunization activity for measles in low coverage districts in India.

METHODS

The state of health of the theoretical pediatric cohort was modeled using TreeAge Pro and Microsoft Excel software. A Markov model was constructed to estimate the health outcomes in two hypothetical cohorts of children in India. One cohort received second dose of measles vaccine through SIA, whereas the other did not; the cohorts were similar in all other respects.

A simplified decision tree diagram is presented in ***Fig.* 1**. In the model it was assumed that everyone in the age group of 1-5 years is eligible for a dose of measles vaccine during SIA; including children with previous history of measles infection or immunization. The main cohort has been divided into four sub-cohorts according to age groups (1-2yrs, 2-3yrs, 3-4yrs, and 4-5yrs) to determine the actual number of children who would be susceptible to measles according to the age specific transmission rates, measles vaccine coverage and efficacy rates. Children who may have developed immunity following the first dose of vaccine or an episode of measles were not included in the susceptible group. The study of complication rates has been limited to five years of age, beyond which the complication rates due to measles are not well documented. Consequences of disease are considered over the lifetime of individuals in the cohort.

Epidemiologic data

Probability estimates were obtained from articles in peer reviewed journals. Studies were identified through a Medline search and whenever possible the data were collected from published Indian scientific literature. Age specific transmission rates were obtained from pre-vaccine era literature(6).

A cohort of 8,39,473 as reported by the WHO Office for the National Polio Surveillance Program for an Indian district(7)was used to determine total

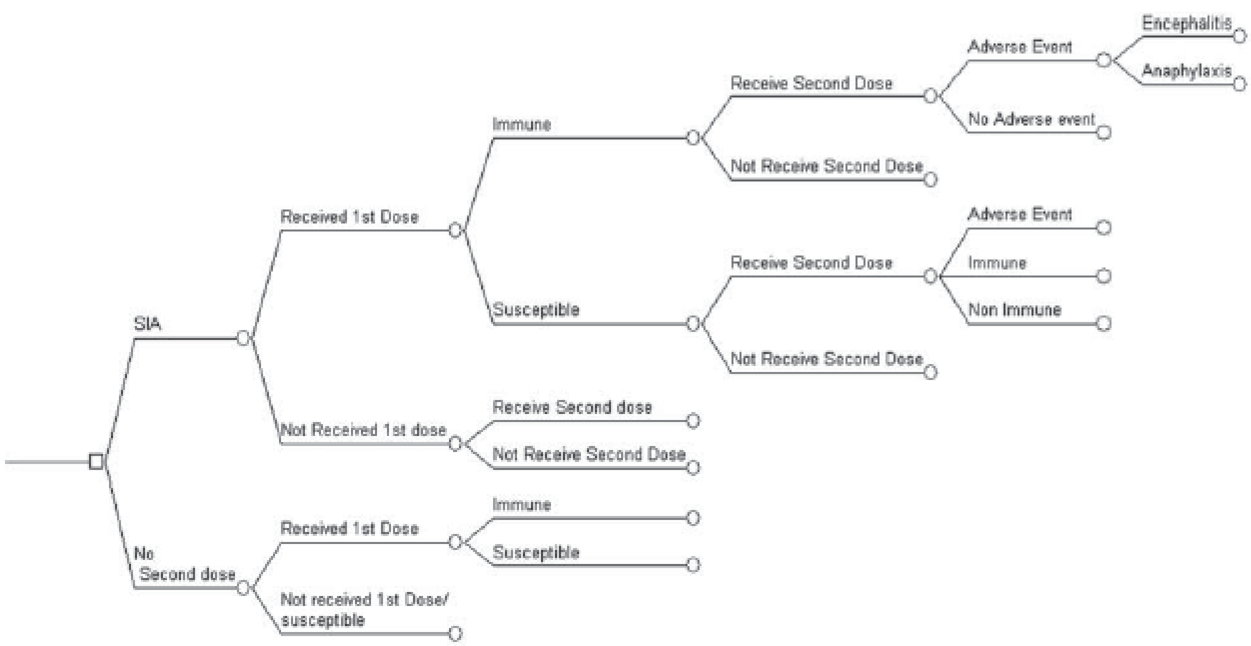

FIG.1 *Simplified decision tree: proximal branches.*

costs of the campaign, disability adjusted life years (DALYs) and cases averted comparing the measles supplementary immunization activity with the status quo of the national pulse polio campaign activity. For routine immunization activity, baseline coverage rate of 58% with variation between 30-90% was used, based on the national average for measles vaccine coverage and state level coverage rates(8). Baseline coverage rate of 75 percent with variation between 69-96% was used for the supplementary immunization activity, based on the level achieved in past mass measles vaccination campaign(1). Case fatality in measles was calculated using median case fatality ratio of 2.5 percent (C.I. 0.2 to 3.7%) from prospective community based studies in India(9). Age specific death rate of 0.4% per annum was used to account for a dynamic population (***Table* I**).

An earlier study shows that adverse reaction to the measles vaccine is more likely to be related to toxic shock syndrome due to the use of unsterile syringes and needles, and perhaps the use of reconstituted vaccines beyond their specified time for administration resulting in contamination(10). Side effects specifically attributable to the measles vaccine are fever (5-15 %), rash (5%), encephalitis (1/1000,000 doses), and anaphylaxis (1/1000,000 doses)(11,12).

Vaccine effectiveness determined by case reference method has been found to be widely varying from as low as 46% to as high as 100%(15), and a median value of 85 % by seropositivity methods(16). Effectiveness for this evaluation was determined at 85% with variation between 45-100%, used in sensitivity analyses.

Cost data

The measles vaccine costs Rs. 41.71 per vial(1). Additional dose wastage, transport cost, handling charges and use of syringes were all factored into the vaccine cost at levels prescribed under the National Policy for Universal Immunization Program(1). Additional costs including time cost, travel cost, surveillance cost, campaign cost and cold chain maintenance cost were taken as equivalent to that in the National pulse polio campaign.

Cost of injection waste disposal plan was assumed to be 1/3rd of procuring syringes and needles. The total cost of the SIA campaign came to INR 2,51,77,095. The cost per measles vaccine dose delivered is INR 30.

Disability Adjusted Life Years

In this study, a 3% discount rate was applied to the calculation of DALYs, and standardized life expectancy according to age has been used as in the Global Burden of Disease Study and the Disease

TABLE I INCIDENCE DATA ON MEASLES RELATED SEQUELAE

Data	Incidence value	Range used in sensitivity analysis	Average Duration (age weighted and discounted at 3%) (assumed)
Case fatality ratio	2.5 %	0.2 - 3.7%(9)	
Diarrhea	30%	20 - 72%(18)	1 week
Pneumonia	20%	10 - 30 %(19)	1 week
Malnutrition (kwashiorkor/marasmus)	3.5%	3 - 4 % (20)	30 days
Keratomalacia	0.1%	0.05 - 0.2(21)	34.8 years
Otitis media	5%	5-15 %(22)	2years
Encephalitis	1/1,000,000 doses; 1-2 cases/1000 cases(20)		34.8 years
Subacute sclerosing pan encephalitis	8.5 cases/million cases(12)		36.7 years

Control Priorities Project(18). Disability weights were apportioned according to the Global Burden of Disease Study. Using base case scenario, 58,638 DALYs will be averted over a span of four years.

Sensitivity analysis

One-way, two-way and three-way sensitivity analyses were conducted on variables associated with the greatest degree of uncertainty including the probability of developing immunity, probability of developing measles and vaccine coverage rates through routine immunization and through supplementary immunization. The overall result was still cost effective, assuming a willingness-to-pay of US $950 per DALY averted. The overall cases averted were most sensitive to changes in probability of developing immunity following measles vaccination, followed by vaccine coverage rates through routine immunization activity (RIA), and followed by the SIA coverage rates (***Fig*.2**).

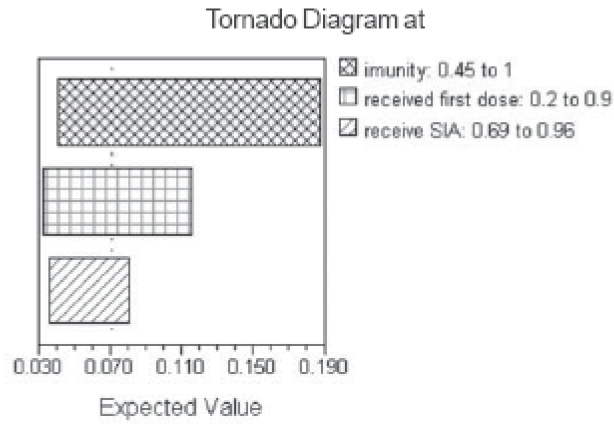

FIG. 2 *Sensitivity analyses for the variables with maximum variability (expected value here is the probability of developing measles for a single person).*

RESULTS

If no supplementary immunization activity is conducted, 1,39,982 children in this cohort are expected to have an episode of measles infection in the next 4 years. 3500 deaths would result due to measles in this cohort. The burden of disease and its sequelae would be 1,25,349 DALYs. A supplementary immunization activity by reducing the number of susceptible in the population would avert 65479 cases and 1637 deaths, and lower the disease burden by 58638 DALYs. The cost of implementing the supplementary immunization activity is approximately INR 25.18 million (Year 2008). The incremental cost-effectiveness ratio (ICER) would be INR 430 per DALY averted (***Table* III**). Requisite formulas and age specific incidence rates are provided as *Annexure.*

DISCUSSION

Measles vaccination in India when administered as a supplementary immunization strategy, is a cost-effective intervention compared to the status quo of measles vaccination by routine immunization alone, assuming a willingness-to-pay of US $950 per DALY averted. At an ICER of INR 430 per DALY averted, the result highly favors program implementation considering that the World Bank has

TABLE III INCREMENTAL COST-EFFECTIVENESS ESTIMATES: BASE- CASE ANALYSIS AND RANGE

Activity	Cost (INR)	Measles Cases (upto 5 yr of age)	Measles Deaths	Discounted DALYs	Costs per case averted	Costs per death averted	Costs per discounted DALY averted
Routine Immunization	Unknown	139982	3500	125349			
Routine plus SIA	Unknown + 25177095	74504	1863	66712			
Incremental Values							
Base Case	25177095	65479	1637	58638	INR 385	INR 15381	INR 430
C.I.		54986-113119	1375-2828	49464-101292	INR 223-406	INR 8903-16212	INR 249-453

WHAT IS ALREADY KNOWN?

- Measles morbidity and mortality rates in India are high due to poor measles vaccine coverage.

WHAT THIS STUDY ADDS?

- A supplementary immunization activity for measles, although costlier than introducing a second dose through routine immunization, is a cost effective option for lowering morbidity and mortality due to measles in districts with coverage lower than the National average.

described any activity which costs less than US$ 100 per DALY saved as highly cost effective for developing nations. The results achieved in this study are comparable to the lowest values in comparative cost effective analysis(17). There are three reasons for the favorable cost effectiveness ratio. First, vaccine coverage rates under routine immunization are low. Second, the incidence of measles in the Indian population is high. Lastly, the vaccination cost per child is quite low.

Estimates used in this study were from studies in settings from all over India and also some studies from other developing countries. To account for imprecision to minimize favoring SIA this paper used conservative estimates, limited the rate of complications due to measles to upto 5 years of age, and applied large ranges of sensitivity around the base estimates for sensitivity analysis. Under conservative assumptions of invasive measles infection, the introduction of supplementary immunization activity appears to be a very good investment, especially in states with lower than national average (Bihar, Jharkhand, Uttar Pradesh, Rajasthan), which are also among the most populated states in India with a combined population in the 0-6 year age group of 160 million (National Census, 2001).

If routine immunization coverage for measles can be expanded to include a second dose of the vaccine as in other developed countries, it will prove to be even more cost effective than SIA in lowering the morbidity due to measles. It would prevent the extra costs of manpower, material, IEC, and community mobilization required for SIA. However, the effectiveness would depend upon the vaccination coverage rate. The coverage rates could vary and a coverage rate for the second dose is more likely to be lower than that for the primary dose, even if it increases the coverage rate for a single dose of the vaccine (given the fact that other vaccines with multiple doses (*e.g.* DPT, OPV) show a similar pattern). In contrast, coverage levels are almost always higher in SIA as compared to the routine immunization coverage, as witnessed in earlier programs. Hence, strengthening of the routine immunization coverage for the first dose should be the primary strategy in dealing with measles morbidity, with the second dose of vaccine being included in the routine immunization program only in districts which have shown consistently high levels of coverage for the first dose and have the resources to sustain the strategy. This is also consistent with the Measles mortality reduction India strategic plan 2005-2010(1). Thus, while second dose through routine immunization would be a good strategy for high coverage districts, SIA can be a good strategy to supplement primary coverage in low coverage districts.

Future initiatives should also be focused on strengthening health systems to improve cold chain maintenance and maintain vaccine efficacy, and increase vaccine coverage levels through routine immunization activity.

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Annexure

Population at risk at a certain age = Total population – (children who have had developed measles + children who have developed immunity following immunization.

Total Cases upto 5 years of age = Σ (Population at risk at a certain age)*(Age specific incidence rate upto 5 years of age).

Total Deaths = Total Cases upto 5 years of age*Probability of death following measles.

Total DALY's = Σ {Probability of developing a complication following measles* disability weight associated with a complication* age weighted duration of a disability/ (1+r) ^n}