Supplement to *Maintaining High Rates of Measles Immunization in Africa*

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Supplemental Tables and Figures

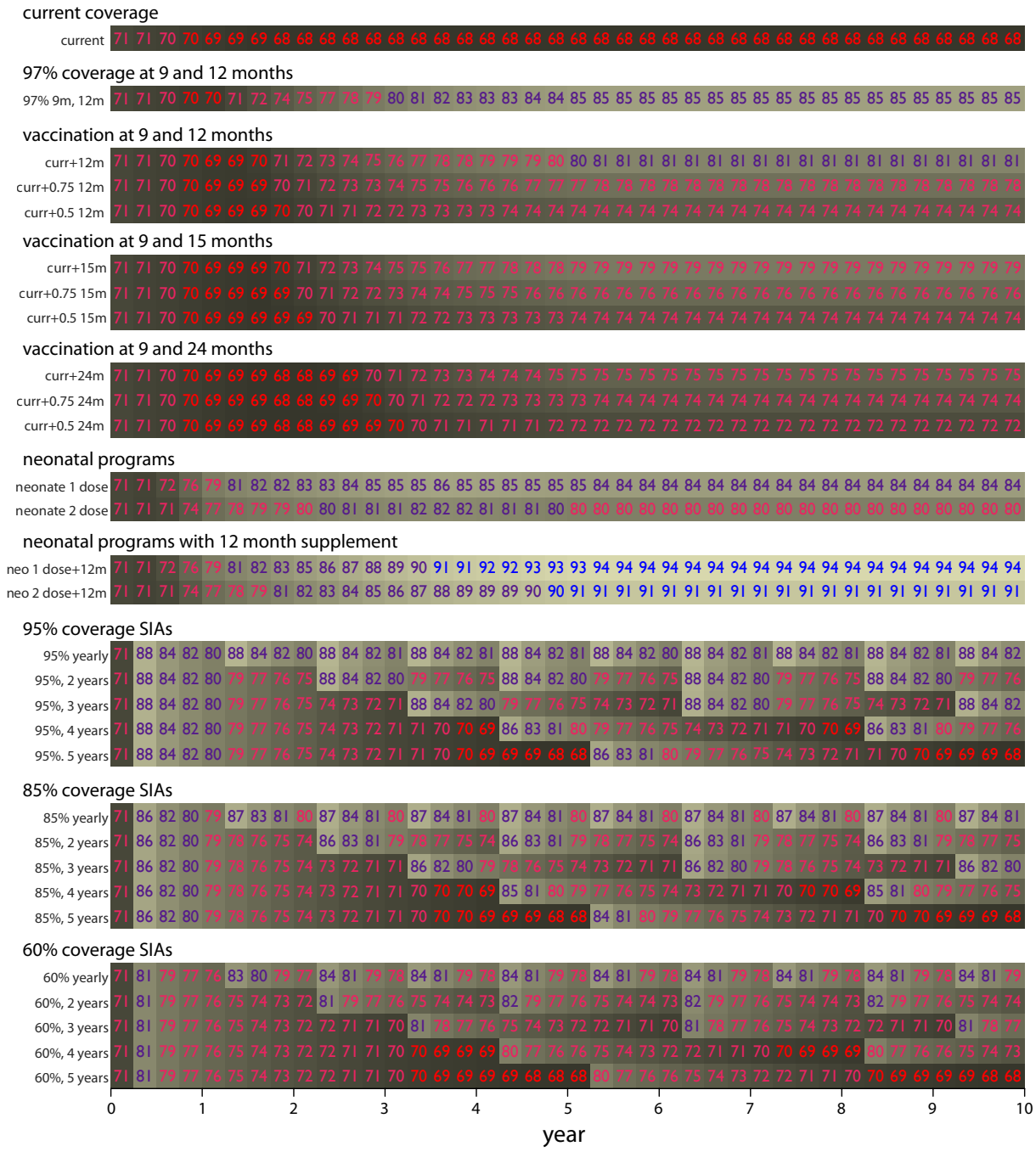


Figure S1: : Quarterly projected measles population immunity in children younger than 5 years of age using different measles vaccination schedules. Darker shades indicate lower coverage. The color of the text indicates coverage, with dark red indicating <70% and dark blue indicating >90%.

Table S1: Projected population immunity to measles virus in children younger than 5 years of age and for the entire population. Y designates the number of years after implementation that the vaccination program reaches a stable state using projections for June 2006 as the baseline.

	Projected Immunity in Children < 5 years of age*						p(immune) at 5 years	Projected Immunity in Entire Population					
			% immune		% time at level			0-5 years after start			5-10 years after start		
	Y	min	mean	max	≥80%	≥85%		range	≥93%	≥95%	range	≥93%	≥95%
Routine Vaccination													
Current Coverage													
current	2	68	68	68	0	0	90	93-94	100	0	92-93	8	0
97% Coverage at 9 and 12 Months													
97% 9m,12m	5	85	85	85	100	100	99	94-96	100	65	96-96	100	100
Vaccination at 9 and 12 Months													
curr+12m	5	81	81	81	100	0	99	94-95	100	38	95-95	100	100
curr+0.75 12m	5	78	78	78	0	0	97	94-95	100	0	94-95	100	0
curr+0.5 12m	5	74	74	74	0	0	95	94-94	100	0	94-94	100	0
Vaccination at 9 and 15 Months													
curr+15m	5	79	79	79	0	0	99	94-95	100	0	95-95	100	47
curr+0.75 15m	5	76	76	76	0	0	97	94-94	100	0	94-94	100	0
curr+0.5 15m	5	74	74	74	0	0	95	94-94	100	0	93-94	100	0
Vaccination at 9 and 24 Months													
curr+24m	5	75	75	75	0	0	99	94-94	100	0	94-94	100	0
curr+0.75 24m	5	74	74	74	0	0	97	94-94	100	0	94-94	100	0
curr+0.5 24m	5	72	72	72	0	0	95	94-94	100	0	93-94	100	0
Neonatal Programs													
neonate 1 dose	5	84	84	84	100	0	86	94-96	100	90	94-96	100	45
neonate 2 dose	5	80	80	80	0	0	84	94-96	100	87	93-95	100	2
Neonatal with 12 Month Supplement													
neo 1 dose+12m	5	94	94	94	100	100	99	94-97	100	90	97-97	100	100
neo 2 dose+12m	5	91	91	91	100	100	99	94-97	100	87	97-97	100	100
SIAs													
95% Coverage SIAs													
95% yearly	2	80	84	90	100	33	100	96-98	100	100	96-98	100	100
95%, 2 years	4	74	80	89	46	17	100	95-98	100	100	95-98	100	100
95%, 3 years	6	71	78	89	32	8	99	94-97	100	80	94-97	100	63
95%, 4 years	8	69	75	88	21	6	99	94-97	100	60	94-97	100	50
95%, 5 years	10	68	74	87	17	3	99/90**	94-97	100	40	93-97	100	30
85% Coverage SIAs													
85% yearly	2	79	83	89	83	25	100	96-97	100	100	96-98	100	100
85%, 2 years	4	74	79	88	38	8	100	95-97	100	95	95-97	100	95
85%, 3 years	6	71	77	87	23	5	98	94-97	100	72	94-97	100	55
85%, 4 years	8	69	75	86	15	2	98	94-97	100	57	94-97	100	35
85%, 5 years	10	68	73	85	12	2	98/90*	94-97	100	37	94-97	100	25
60% Coverage SIAs													
60% yearly	2	77	80	85	50	0	99	95-97	100	100	95-97	100	100
60%, 2 years	4	72	76	83	12	0	98	94-96	100	55	94-96	100	20
60%, 3 years	6	70	74	82	5	0	96	94-96	100	33	93-95	100	7
60%, 4 years	8	69	73	81	2	0	96	93-96	100	27	93-95	82	0
60%, 5 years	10	68	72	80	2	0	96/90**	93-96	98	22	92-95	48	0

* - all results in under 5 year olds are reported for the vaccination program after it reaches stability

** - for SIAs covering 6-48 month olds every 5 years there will be a one year cohort that the SIA misses completely

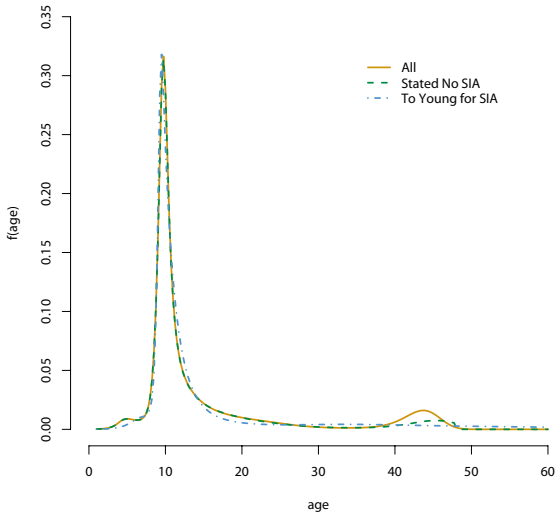


Figure S2: Age specific probabability of vaccination based on models of measles vaccination fit to: all data, data considering those only vaccinated in the 2003 SIA as unvaccinated, and excluding those too young to have been included in the 2003 SIA.

Age Specific Probability of Vaccination

The `oldlogspline` function in R was used to estimate the probability density function (pdf) for vaccination by age, $f(t)$, using events, left and right censored data, as described in [1]. The pdf was estimated using three separate data sets:

1. All individuals for whom a vaccination status was available, using stated vaccination status.

2. All individuals for whom a vaccination status was available, using stated vaccination status and treating those vaccinated only in an SIA as unvaccinated.

3. All individuals younger than 42 months for whom vaccination status was available.

The latter two estimates are used in an attempt to estimate the age specific probability of vaccination in the absence of the national supplemental immunization activity. The resulting pdfs are shown in figure S2.

Note the bump around 42 months of age in both the "All" and "Stated No SIA" cases. This is an aberration due to the attempt to fit left censored data that is reflecting vaccination during the 2003 SIA. This suggests that some who report not being vaccinated during the 2003 SIA actually were, or possibly that there were elevated vaccination rates in this period apart form the SIA.

Three probability models were constructed that incorporated the chance of vaccination during the SIA, using coverage data reported in [2]:

1. The unmodified full data distribution
2. The "Stated No SIA" distribution combined with a 96.9% chance of being vaccinated in the 2003 SIA if 6 months or older as of June 2003.
3. The "To Young for SIA" distribution combined with a 96.9% chance of being vaccinated in the 2003 SIA if 6 months or older as of June 2003.

Under models 2 and 3, the probability of vaccination by a particular age, $F(a)$, is:

$$F(t) = F'(t) + \mathbf{1}(t \geq 42) \cdot 0.969 - \mathbf{1}(t \geq 42) \cdot 0.969 \cdot F'(t)$$

where $F'(t)$ is the probability of normal vaccination by age t, and $\mathbf{1}(t \geq 42)$ is an indicator function of if the child is over 42 months of age (i.e., was ≥ 6 months of age at the time of the 2003 SIA).

A comparison of the projections of these data with the observed percent vaccinated is shown in figure S3.

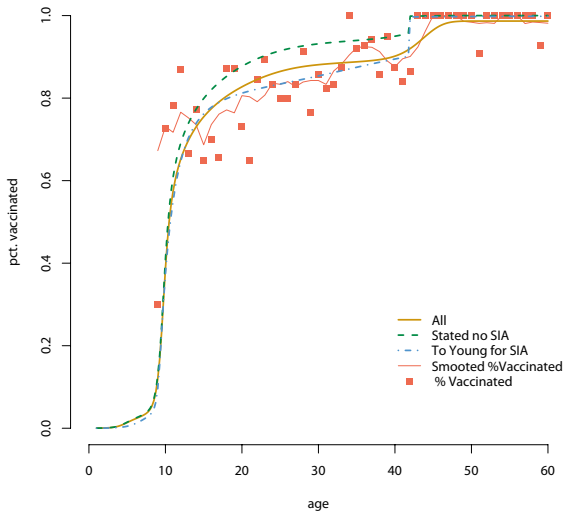


Figure S3: Probability of having been vaccinated by a given age under three different models of the age specific probability of vaccination.

Examining the performance of these models shows that all models are substantially outperformed by the "saturated" model that has a unique probability of having been vaccinated for children at each age, and that the "To Young" model is the best of the two models that explicitly model the SIA. The figure S4 shows the LR of individual points comparing the given model to the saturated model.

The Table S2 and S3 describe the models and show likelihoods with and without the four influential points above 40.

The "To Young" model appears to be the best of the three models.

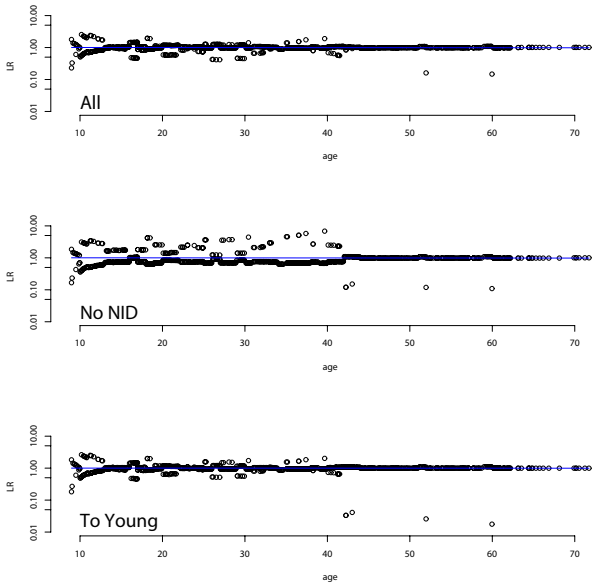


Figure S4: Likelihood-ration of vaccination by a given age under the given vaccination model compared to the probability under the saturated model.

Table S1: Data used to fit a semi-parametric probability density function of the age-specific risk of routine measles vaccination using uncensored (reported on vaccination card), left censored (oral report of having been vaccinated) and right censored (unvaccinated) vaccination data. These models were extended to account for the 2003 SIA. The extended models were compared by the log-likelihood of producing the observed individual vaccination status at the time of interview and visual inspection.

Model	Routine PDF Inclusion Criteria	N	Vaccinated		Unvaccinated	SIA Model*	Log Likelihood
			Card	Report			
1	reported vaccination status	969	376	457	136	included in distribution	-340.7
2	reported vaccination status*	969	376	447	146	independent 96.9% prob.	-418.6
3	children with a reported vaccination status and under 42 months of age	688	277	280	131	independent 96.9% prob.	-333.1

* Children vaccinated against measles only during the 2003 SIA were considered unvaccinated.

prob. – probability

PDF – probability density function

SIA – supplemental immunization activity

Table S2: Likelihood of the data under the three different models and the saturated model.

Model	LL	$L(All)/L(model)$	LL w/o points	$L(All)/L(model)$ w/o points
All	-355.2	1	-338.8	1
No NID	-441.3	$> 10^{37}$	-418.6	$> 10^{34}$
To Young	-363.1	2,5267	-333.1	0.0033
Saturated	-327.6	$< 10^{-12}$	-315.3	$< 10^{-11}$

Maternal Antibodies and the Probability of Vaccine Failure

The probability of vaccine success and protection from measles pre-vaccination are two conflated issues, as the presence of maternal antibodies is the chief reason the measles vaccines fail. Based on data from Kenya we use an estimate of the half life of maternal antibodies of 46.1 days [3]. Assuming that the percentage of the population protected from measles declines at the same rate and that the rate of decay is exponential, this leads to the estimate:

$$\Pr(immune|t) = e^{-0.4511t}$$

where t is the age of the person being vaccinated in months.

There are several different estimates on the effect of age on vaccination success, with variation due to base population and divergent methodologies. Data from [4] and others suggests that vaccination success is not wholly dependent on the presence of maternal antibodies but also on the development of the child's humeral immune system over the first year of life [5]. Using data from Gans et al., 1998, we constructed estimates for a conservative and optimistic age specific success rate for measles vaccination. We assumed that the rate of vaccine success followed a logistic distribution, which both fit the data better than an exponential failure rate model, and makes some biological sense[1]. Hence, the probability of vaccine success is estimated to be:

$$\Pr(success|t) = \min\left(\frac{1}{1+e^{-\alpha+\beta t}}, s_{max}\right)$$

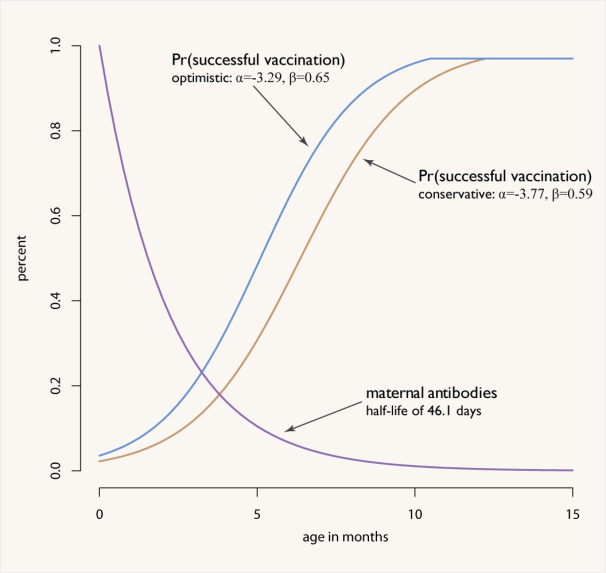
where t is the age in months and s_{max} is the maximum probability of vaccine success, assumed to be 97% in all cases. The conservative estimate (based on seroprotection levels in Gans et al. 1998) and the optimistic level (based on seroconversion levels in Gans et al. [4]) are presented in Table S4 and Figure S5.

We used the conservative estimate in all of our reported analyses.

[1]Over the first 5 months of life the combination of maternal antibodies and an immature immune system prevents seroconversion. After 5 months of age, maternal antibodies are largely absent, but the humeral immune response is still building, and there is a corresponding rapid increase in response to measles vaccination.

Table S3: Estimated rate of successful measles vaccination at 6, 9 and 12 months of age.

	Conservative Success Rate		Optimistic Success Rate	
Age	Gans 1998.	Model	Gans 1998	Model
6 mo	43%(10/23)	45%	65%(15/23)	64%
9 mo	85%(17/20)	82%	90%(18/20)	92%
12 mo	95%(21/22)	97%	100%(22/22)	97% (99% w/o cap)
	$\alpha = -3.77$, $\beta = 0.59$		$\alpha = -3.29$, $\beta = 0.65$	



$$\Pr(success \mid t) = \min\left(\frac{1}{1+e^{-(\alpha+\beta t)}}, 0.97\right)$$

Figure S5: Probability of successful measles vaccination by age in months under optimistic and conservative assumptions.

Age Specific Estimates of Immunity

Assuming no circulation of measles in the population, the above models can give us an estimate of the distribution of immunity in the population. Assuming independent chances of being covered in an SIA and being vaccinated at some other time, the chance of being successfully vaccinated at a particular age can be calculated using the basic rules of probability. Let the event A be successful vaccination, the event R be vaccination by routine coverage, and the event S be successful vaccination during an SIA:

$$\Pr(A|age) = \Pr(R|age) + \Pr(S|age) - \Pr(R|age)\Pr(S|age)$$

Hence, the probability of being immune (I) at a given age is:

$$\Pr(I|age) = \Pr(A|age) + \Pr(M|age) - \Pr(A|age)\Pr(M|age)$$

Where M is the event of being protected by maternal antibodies.

Given the pdf routine vaccination, $f(t)$, and a age specific vaccine success rate, $g(t)$, the probability of being successfully vaccinated in the routine program is:

$$\Pr(R|age) = \int_0^{age} f(t)g(t)dt$$

Assuming that a child is only covered by the routine vaccination program only once. There may be cases (such as when we are considering a recommendation of two doses of vaccine at two separate ages) where we want to calculate the probability of success from multiple doses of vaccine. For the two dose case this becomes:

$$\Pr(R|age) = \Pr(R_1|age) + \Pr(R_2|age) - \Pr(R_1|age) * \Pr(R_2|age)$$

where R_1 and R_2 can represent either the separate or the same vaccination hazard function (i.e., two recommendations or the probability of double coverage under the same program). This assumes that both the probability of vaccine success and vaccine coverage are independent across programs.

The probability of successful vaccination during an SIA covering ages a to b is:

$$Pr(S|age) = \mathbf{1}(a < age' < b)(\text{SIA coverage})(g(age'))$$

where age' is the age the child was at the time of the SIA.

Applying these formulas to the population covered by the 2006 survey leads a prediction of the distribution of immunity, compared in figure S6 with the percentage antibody positive by oral fluid immunoassay (adjusted for the sensitivity and specificity of the test).

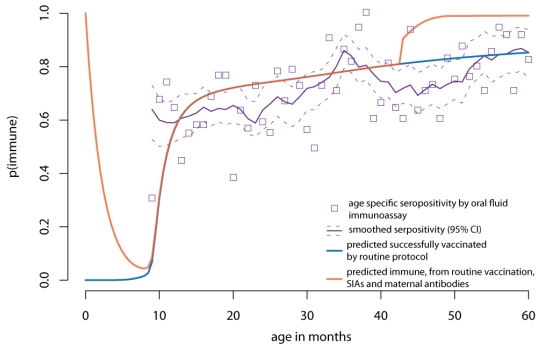


Figure S6: Age specific probability of being immune under model assumptions compared to percentage with protective antibodies to measles by oral-fluid sero-survey.

Table S4: Age specific mortality rates in Zambia.

Age Group	Mortality Statistic	Monthly Mortality Rate	Proportion Surviving To
0-1 mo.	37 per 1,000 live births	37/1,000	1
1-12 mo.	58 per 1,000 living to 1 mo.	5.27/1,000	964/1,000
12-60 mo.	81 per 1,000 living to 1 yr.	1.69/1,000	909/1,000
60+ mo.	4.3 per 1,000 py.[2]	0.35/1,000	838/1,000

Age Structure

Mortality data from the 2001/02 Zambia Demographic Health Survey (DHS) [6] was used to estimate the population distribution of Zambians under the age of 5 years old. Because data on the mortality rate of 5-15 year olds is not available, the death rate in this category is assumed to be the same as among 15-19 year olds (4.3 per 1,000 person years). The reported statistics and implied monthly mortality rates are reported in table S5.

If this model is extended out using death rates for further age groups and applied to a population with an annual growth rate of 2.4%, we predict an age distribution comparable with that stated by the US census bureau for the year 2000. Discrepancies in the trend can be accounted for by the fact that the model does not take into account variability in the birth rate over time. For our simulations we assume a growth rate of 2.1%, based on data for the year 2000 from the DHS [6] (Figure S7).

Using this age structure, the proportion of the population that is immune between ages a and b can be calculated as:

$$p = \frac{1}{H(b) - H(a)} \int_a^b \Pr(I|x)h(x)dx \tag{1}$$

where $h(x)$ is the age distribution of the population, and $H(x)$ is the cumulative distribution function of population ages.

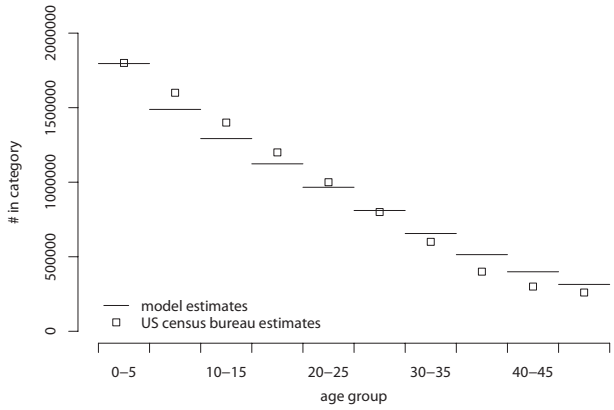


Figure S7: Model estimates of Zambian population structure compared with US census bureau estimates.

Model Predictions

Model predictions were made using equation 1 above. The population state at time 0 was considered to be that predicted for the 2006 population, assuming there had been no circulation of measles between the 2003 SIA and the 2006 survey. This is probably an underestimate of the true population immunity.

At monthly intervals going forward for 15 years, the immune profile of the population was calculated using the assumptions of the vaccination program being considered.

References

[1] W. N. Venables and B.D. Ripley. *Modern Applied Statistics with S-PLUS*. Springer, 3rd edition, 1999.

[2] World Health Organization. Progress in measles control: Zambia, 1999-2004. *Weekly epidemiological record*, 24:213–220, 2005.

[3] V. M. Caceres, P. M. Strebel, and R. W. Sutter. Factors determining prevalence of maternal antibody to measles virus throughout infancy: a review. *Clin Infect Dis*, 31(1):110–9, 2000. Journal Article Review United states an official publication of the Infectious Diseases Society of America.

[4] H. A. Gans, A. M. Arvin, J. Galinus, L. Logan, R. DeHovitz, and Y. Maldonado. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *Jama*, 280(6):527–32, 1998. AI37127/AI/United States NIAID Journal Article Research Support, U.S. Gov't, P.H.S. United states the journal of the American Medical Association.

[5] Stanley A. Plotkin, Walter A. Orenstein, and Paul A. Offit. *Vaccines*. Saunders, 5th edition, 2008.

[6] Zambia CSO Lusaka, Zambia CBH Lusaka, and USA ORC Macro Calverton, Maryland. Zambia demographic and health survey. Technical report, Central Statistical Office Lusaka, Zambia Central Board of Health Lusaka, Zambia ORC Macro Calverton, Maryland, USA, 2003.