THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet* 2012; published online April 24. DOI:10.1016/S0140-6736(12)60522-4.

Supplementary appendix

Supplement to: Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, Strebel A. Has the 2010 global measles mortality reduction goal been achieved? Results from a model using surveillance data

Input data

All input data used to estimate measles mortality, described in the table 1, is publicly available online, in published studies, or in the tables below. Data on routine and supplemental immunization activities and reported measles cases are submitted to WHO annually through the WHO/UNICEF Joint Reporting Form (JRF.) Details on the form and reporting process are available at http://www.who.int/immunization_monitoring/routine/joint_reporting/en/index.html.

Coverage for the first routine dose measles vaccine is derived from a variety of data sources, including coverage reported by national authorities and results from national household or community surveys. Computional logic is used to select the most reliable coverage information by applying a set of rules to the data conditions, such as the sample size of surveys, reports of vaccine supply shortages, or changes in immunization policies.(1) Currently, insufficient survey information is available to derive coverage estimates for the second routine dose of measles vaccine or SIAs.

Information on SIAs, such as coverage, target population size, doses administered, age range, antigen combination used, and extent (sub-national or national) of the campaign is available at the link in Table 1. The SIA information from the JRF is verified and supplemented through annual updates from WHO regional offices on measles activity implementation. SIAs may target a variety of age ranges, depending on the objective of the campaign. We included all measles SIAs except for those targeting only adults for the purposes of rubella control (often referred to as "speed-up" SIAs.) To generate the measles model input, we converted data on doses administered to a proportion of the national cohort in the target age range, capped at 99%, that was reportedly vaccinated.

Incidence was estimated using aggregate annual reported case data, which were extracted from the JRF and sent to national immunization program managers to identify updates. In addition to annual data on reported cases provided by the JRF, case-based surveillance data is also available for most WHO member states. By 2010, 179 countries were implementing case-based surveillance, which is up from 120 countries in 2004 (see Progress in global measles control, 2000–2010. Weekly Epidemiologic Record No. 5, 2012, 87, 45–52 for additional details.). Case-based surveillance data disaggregated by age at infection was requested from WHO regional offices to support the analysis of the age distribution of measles cases and is summarized in tables 2A and 2B.

Interpretation of surveillance data is complex and many changes to surveillance norms and staff capacity can affect reporting completeness. As the first effort to objectively interpret surveillance data at the global level, our modeling was able to identify and quantify only one consistent trend affecting reporting completeness, which was that reporting completeness was likely to increase in years with extremely high numbers of reported cases.

The remaining factors we identified that could affect reporting completeness were not characterized well enough to allow quantitative assessment of their impact on surveillance sensitivity. These included the following changes in surveillance norms: a) the introduction of case-based reporting, b) beginning lab confirmation of cases, c) broadening the measles case definition to "fever and rash" in order to increase surveillance sensitivity for countries moving towards elimination, and d) changing the operational definition of a "confirmed case" to only lab-confirmed cases rather than any case with clinical, epidemiologic linkage, or lab confirmation. Through country consultation, we found no consistent impact of documented changes in norms on the reporting completeness of aggregate annual data. Drawing conclusions on the impact of changes in surveillance norms was complicated by the fact that countries often implemented an SIA in the same year that surveillance standards changed. In these cases, a decrease in reported cases could reflect a true drop in incidence, or could equally likely be an artifact of data

management as data managers adjusted to the new system and perhaps did not have the capacity to enter in all case reports received.

We also compared data on lab-confirmed cases from the global measles/rubella lab network to aggregate surveillance data, which allowed us to identify when some countries began to rely exclusively on lab confirmation. Again, we found no universal trend. Reporting completeness was not affected for many countries, but if lab capacity was limited or specimen collection materials were not widely available at the health facility level, reporting completeness was negatively impacted by requiring lab confirmation to qualify a suspected case as "confirmed."

For further discussion on reporting completeness, please refer to:

1. Harpaz R. Completeness of measles case reporting: Review of estimates for the United States. J Infect Dis 2004; 189: S185-S190.
2. Jani JV, Jani IV, Araújo C, Sahay S, Barreto J, Bjune G. Assessment of routine surveillance data as a tool to investigate measles outbreaks in Mozambique. BMC Infectious Diseases 2006, 6:29

Table 1: Sources for input data and key parameters

Data element	Source and public access site
Vital registration data	WHO Mortality Database, available at: http://www.who.int/whosis/database/mort/table1.cfm Vital registration data was used for the following countries that had >85% of child deaths registered: Antigua and Barbuda, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belgium, Belize, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Dominica, Estonia, Finland, France, Germany, Greece, Grenada, Guyana, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Mauritius, Mexico, Montenegro, Netherlands, New Zealand, Norway, Panama, Poland, Republic of Korea, Republic of Moldova, Romania, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, San Marino, Serbia, Singapore, Slovakia, Slovenia, Spain, Suriname, Sweden, Switzerland, Trinidad and Tobago, United Kingdom, United States, Uruguay, Venezuela
MCV1 estimated coverage	WHO/UNICEF coverage estimates, available at: http://www.who.int/entity/immunization_monitoring/data/coverage_estimates_series.xls
MCV2 reported coverage	WHO/UNICEF Joint Reporting Form, available at: http://www.who.int/entity/immunization_monitoring/data/coverage_series.xls
Measles SIA coverage	WHO SIA database, available at: http://www.who.int/entity/immunization_monitoring/data/Summary_Measles_SIAs_2000_2010.xls
Reported cases	WHO/UNICEF Joint Reporting Form, available at: http://www.who.int/entity/immunization_monitoring/data/incidence_series.xls
Under-five background mortality	UN Inter-agency Group for Child Mortality Estimation. 2010 report, available at: http://www.childmortality.org
Number of births	World Population Prospects, 2010 revision, available at: http://esa.un.org/wpp/Excel-Data/DB01_Period_Indicators/WPP2010_DB1_F04_BIRTHS_BOTH_SEXES.XLS
Total population	World Population Prospects, 2010 revision, available at: http://esa.un.org/wpp/Excel-Data/DB04_Population_ByAgeSex_Annual/WPP2010_DB4_F1A_POPULATION_BY_AGE_BOTH_SEXES_ANNUAL_1950-2010.XLS
Age distribution	Regression of WHO case-based surveillance by age and MCV1 coverage level. The observed data is presenting in table 2A below.
Vaccine effectiveness	Literature review(2)
Case-fatality ratios	Literature review (3) updated to include (4;5). The CFRs for outliers identified by a regression of CFR vs. child mortality rate were re-assessed. See table 3 below.

Table 2A: Observed age distribution of reported measles cases from 121 countries reporting case-based surveillance, 2000-2009

Region	MCV1 coverage estimate level	Number of case reports	Percent of measles cases by age group				
			<1 year	1-4 years	5-9 years	10-14 years	>15 years
Asia Pacific and Australia	<60	0	-	-	-	-	-
	60-84	197	6	27	15	18	35
	85-100	8017	6	13	9	12	60
Eastern Europe and Central Asia	<60	0	-	-	-	-	-
	60-84	262	4	12	13	21	50
	85-100	10746	7	6	5	9	73
North Africa and the Middle East	<60	1142	13	45	28	5	8
	60-84	13821	19	47	14	5	14
	85-100	11651	14	26	27	12	21
South Asia	<60	5352	12	62	19	4	3
	60-84	28754	11	39	33	11	6
	85-100	0	-	-	-	-	-
South East Asia and Oceania	<60	376	36	21	21	14	9
	60-84	8756	8	37	33	18	4
	85-100	10241	22	18	16	9	35
Sub-Saharan Africa	<60	24399	30	45	13	3	8
	60-84	21875	31	32	16	5	16
	85-100	2685	33	26	18	8	15
West and Central Europe	<60	0	-	-	-	-	-
	60-84	6058	9	26	21	14	29
	85-100	17859	15	28	15	8	34

*Age distribution for East Asia assumed to be average age distribution reported for 2000-2009 in (6)

Table 2B: Region assignments for evaluating age distribution of reported measles cases

Region name (abbreviation)	Countries
Asia Pacific and Australia (AsiaPac/AUS)	Australia, Brunei Darussalam, Japan, Republic of Korea, New Zealand, Singapore
East Asia (EAsia)	China, Democratic People's Republic of Korea
Eastern Europe and Central Asia (EEuro/CAsia)	Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Lithuania, Latvia, Republic of Moldova, Mongolia, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
North Africa and the Middle East (NAfr/MEast)	United Arab Emirates, Bahrain, Algeria, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, Yemen
South Asia (SAsia)	Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan
South East Asia and Oceania	Cook Islands, Fiji, Micronesia (Federated States of), Indonesia, Cambodia, Kiribati, Lao People's Democratic Republic, Sri Lanka, Maldives, Marshall Islands, Myanmar, Mauritius, Malaysia, Niue, Nauru, Philippines, Palau, Papua New Guinea, Solomon

(SEAsia)	Islands, Seychelles, Thailand, Timor-Leste, Tonga, Tuvalu, Viet Nam, Vanuatu, Samoa
Sub-Saharan Africa (SSAfr)	Angola, Burundi, Benin, Burkina Faso, Botswana, Central African Republic, Côte d'Ivoire, Cameroon, Democratic Republic of the Congo, Congo, Comoros, Cape Verde, Djibouti, Eritrea, Ethiopia, Gabon, Ghana, Guinea, Gambia, Guinea-Bissau, Equatorial Guinea, Kenya, Liberia, Lesotho, Madagascar, Mali, Mozambique, Mauritania, Malawi, Namibia, Niger, Nigeria, Rwanda, Sudan, Senegal, Sierra Leone, Somalia, Sao Tome and Principe, Swaziland, Chad, Togo, United Republic of Tanzania, Uganda, South Africa, Zambia, Zimbabwe
West and Central Europe (WCEuro)	Albania, Andorra, Austria, Belgium, Bulgaria, Bosnia and Herzegovina, Switzerland, Cyprus, Czech Republic, Germany, Denmark, Spain, Finland, France, United Kingdom of Great Britain and Northern Ireland, Greece, Croatia, Hungary, Ireland, Iceland, Israel, Italy, Luxembourg, Monaco, The former Yugoslav Republic of Macedonia, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Sweden

Table 3: Revised measles CFRs for children under five years of age by country (3-5)

CFR	Countries
<.002	All remaining countries
0.002-<.01	China, Cook Islands, Egypt, Fiji, Jordan, Kiribati, Marshall Islands, Micronesia, Nauru, Niue, Palau, Samoa, Solomon Islands, Swaziland, Tonga, Tuvalu, Vanuatu
.01-<.02	Bangladesh, Bhutan, India, Iraq, Mongolia, Pakistan, Philippines, Sri Lanka
.02-<.03	Algeria, Botswana, Cambodia, Cape Verde, Djibouti, Indonesia, Malawi, Namibia, Nepal, South Africa, Timor-Leste, Viet Nam, Yemen
.03-<.04	Angola, Cameroon, Ethiopia, Kenya, Lao People's Democratic Republic, Madagascar, Papua New Guinea, Sudan, Uganda, United Republic of Tanzania
.04-<.05	Burundi, Central African Republic , Chad, Comoros , Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Lesotho, Mozambique, Myanmar, Niger, Nigeria, Rwanda, Sao Tome and Principe, Zamia
0.06	Benin, Gambia, Guinea, Guinea-Bissau, Liberia, Mauritania, Sierra Leone, Togo, Zimbabwe

Estimation process and technical details of the state-space model

The estimation process using the state-space model, which was applied to all countries expected to have appreciable measles mortality, is presented in Figure 1. State-space models are valuable tools for disease burden estimation because they provide a probabilistic framework to predict the unobserved outcome of a dynamic process, such as true measles incidence, given observed elements of that dynamic process, such as reported measles cases and vaccination coverage. In addition to providing an objective method for interpreting surveillance data, the state-space model offers a formal method for estimating uncertainty in the unobserved burden that is derived directly from the observed surveillance data, rather than from *ad hoc* bounds on model parameters as has been done previously.(7) Below we present an overview of the state-space model for measles burden estimation. The full technical details of state-space models are beyond the scope of this work, however we refer the reader to (8-12) for further information.

State-space models are characterized by two inter-related sets of equations with unknown parameters; a "process model" that represents the evolution of a dynamic process through time (i.e. the true disease incidence through time as a function of infection risk and immunization coverage) and an "observation model" that represents the observation of that process (i.e. the cases reported through the national measles surveillance system.)

The process model describes the trend in measles cases in a country over time as a function of transmission, births, deaths, and vaccination. In equation [1], susceptibles at year t are equivalent to the pool of susceptibles in the previous year that have not been protected by an SIA plus births in year t, adjusted for background mortality, than do not receive MCV1 or MCV2. This is an annualized, linear approximation to a dynamic susceptible, infected, recovered (SIR) model of disease transmission, in which births adjusted for immunization add to the pool of susceptibles and cases and background mortality subtract from the pool of susceptibles. The annual measles infection rate (term between first and third instances of the S_{t-1} variable) is assumed to increase from 0 in a completely immune population to 100% in a completely susceptible population, which approximates the high basic reproductive ratio for measles.

Process equation:

$$S_t = \left[S_{t-1} - \left(1 - e^{-\theta_1 \left(\frac{S_{t-1}}{N_{t-1}} \right)} \right) S_{t-1} + X_t \right] \left(1 - Y_{t-1}\right) + \theta_4 \qquad [1]$$

θ_1=infectiousness
θ_4= process variance
X_t= births in year t, minus background deaths and routine immunization
Y_{t-1}=coverage of SIA in year t-1

The observation model is a set of equations that describe the relationship between the expected number of measles cases estimated by the process model (equation 1) and the number of reported measles cases. Measles cases are assumed to be under-reported at a baseline rate θ_2 that is independent for each country: i.e. reported cases in year *t* are θ_2 * true incidence in year *t*. To reflect the assumed increase in the reporting rate due to outbreaks when awareness of measles is likely to increase (see manuscript for details), we assumed that the reporting rate in outbreak years was $\theta_2+\theta_3$, where θ_3 reflects the improvement in reporting (equation 2.)

$$C_t = (\theta_2)\left(1 - e^{-\theta_1\left(\frac{S_{t-1}}{N_{t-1}}\right)}\right)S_{t-1} + \theta_5 \quad \text{if year t is not an outbreak year}$$

Observation equation: $C_t = (\theta_2 + \theta_3)\left(1 - e^{-\theta_1\left(\frac{S_{t-1}}{N_{t-1}}\right)}\right)S_{t-1} + \theta_5$ if year t is an outbreak year [2]

C_t= cases at year t
S_{t-1}= susceptibles at year t-1
N_{t-1}= population at year t-1
θ_1=infectiousness
θ_2=base reporting rate
θ_3= increase in reporting rate in outbreak years
θ_5=observation variance

To solve for thetas 1-5, we used an algorithm called the Extended Kalman Filter (EKF). Below we provide a basic statement of the likelihood function for the linear Kalman Filter and we refer readers to (8) for a full treatment of the EKF. While we employ an extension of the linear Kalman Filter algorithm for non-linear models to estimate measles burden, the following outline for linear models provides the basic algorithm that applies to both varieties. The corresponding calculations for an EKF yields an approximation to the true likelihood for the model.

Assume a linear model for the state equation (in our case the state equation is the time-series progression of the population through the susceptible-infected-removed states),

$$S_t = fS_{t-1} + \eta_t$$

where η_t, t=1, . . .,T, are zero mean, independent Gaussian random variables with variance σ_η^2. Note that the number of measles cases, I_t, is simply a linear transformation of the number of susceptibles.
The observation equation (the number of cases reported, C, given the true number susceptibles, S_t) is

$$C_t = gS_t + \varepsilon_t$$

where ε_t, t=1, . . .,T, are zero mean, independent Gaussian random variables with variance σ_ε^2. (Note that we are using different notation here than in the equations specific to the measles model. σ_η^2 and σ_ε^2 are analogous to θ_4 and θ_5 in the measles model.)

Assume that we know the conditional distribution of S_{t-1} given the past observations is Gaussian with mean $\hat{S}_{t-1}$ and variance P_{t-1}. Then the distribution of S_t given S_{t-1}, $S_{t|t-1}$, is Gaussian with mean $f\hat{S}_{t-1}$ and variance $f^2P_{t-1} + \sigma_\eta^2$.

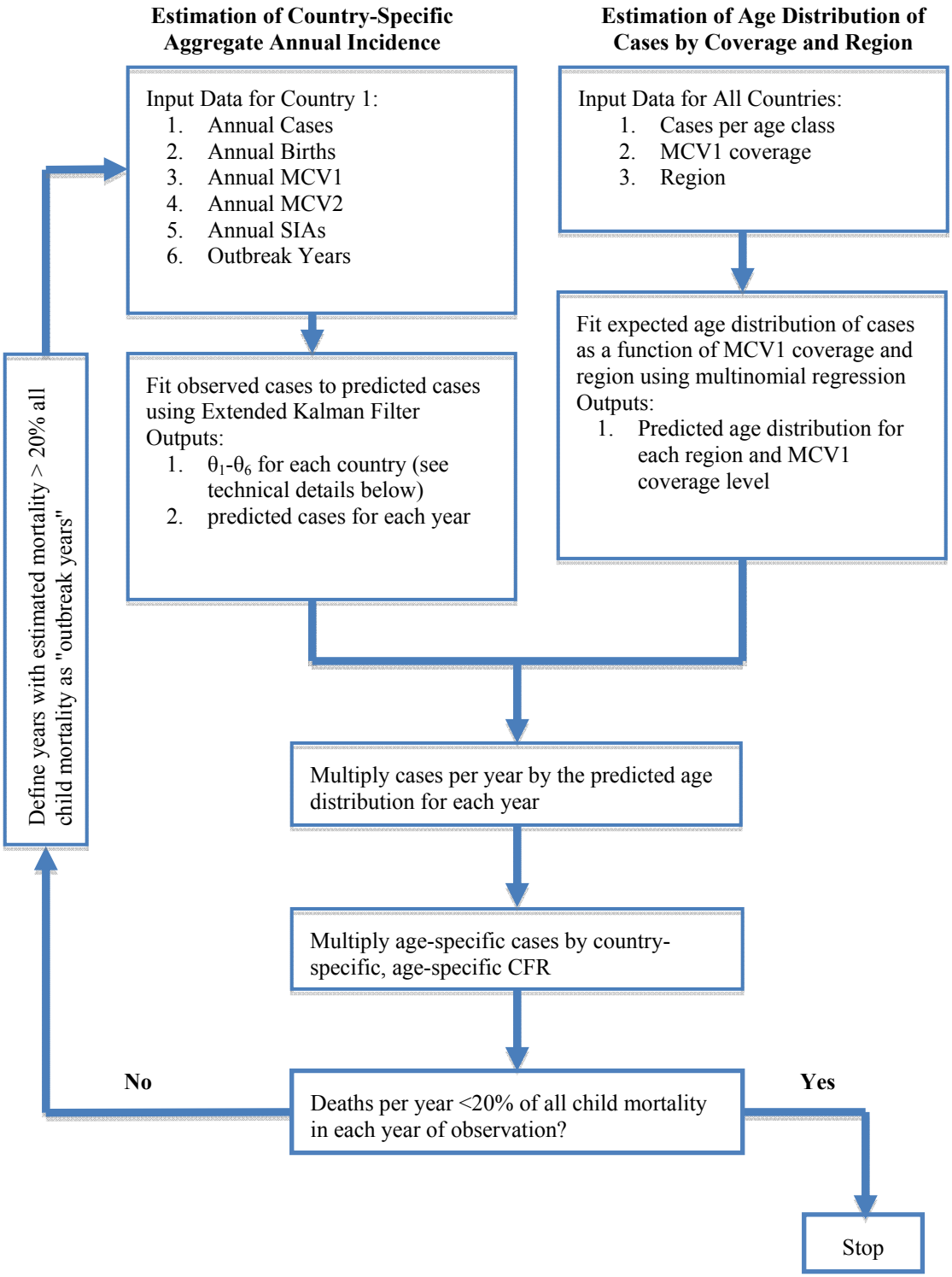
The distribution of the observed cases at time t, C_t, depends only on the past through the number of susceptibles at time t, S_t. Thus, the distribution of $C_{t|t-1}$ is Gaussian with mean $gf\hat{S}_{t-1}$ and variance $g^2f^2P_{t-1} + g^2\sigma_\eta^2 + \sigma_\varepsilon^2$. Employing this notation we can write the joint distribution of the vector $[C_t,S_t]'$ as a multivariate normal random variable. From the properties of multivariate normal distribution we can write the negative log-likelihood (excluding constants) of the observed cases, C_t, as

$$\frac{1}{2}\sum_{t=1}^{T}\log\left(g^2f^2P_{t-1} + g^2\sigma_\eta^2 + \sigma_\varepsilon^2\right) + \sum_{t=1}^{T}\frac{\left(C_i - fg\hat{S}_t\right)^2}{2\left(g^2f^2P_{t-1} + g^2\sigma_\eta^2 + \sigma_\varepsilon^2\right)}.$$

We can then minimize this negative log-likelihood using standard numerical methods to find maximum likelihood estimates of the associated parameters.

In practice, the model that we have presented in the main text is not linear, as in the example above. In essence, the Extended Kalman Filter algorithm overcomes this by first approximating the non-linear state and observation equations (here in terms of the parameters θ_1-θ_5 for each country) using Taylor series expansions to handle the variance calculations and applying the above method on the approximating equations.

Figure 1: Process for estimating measles mortality with a state-space model.



Sensitivity analyses

To test the robustness of the results to parameter assumptions, we evaluated measles mortality under a range of alternative assumptions and compared the results to base case estimates (i.e., univariate sensitivity analysis.) Given the number of data points involved, we focused on parameters that were either supported by inadequate data or were known to have a large influence on mortality estimates in prior modeling exercises. The parameters tested included: temporal changes in CFRs, vaccine effectiveness, age distribution (reverting back to assumptions from prior efforts to estimate measles mortality(7)), outbreak threshold, reporting efficiency assumed for low mortality countries, and the threshold used to define low mortality countries. All alternative scenarios require that the state-space model (and the associated parameters) be re-fit for each country.

A key concern regarding interpretation of CFR data is that CFRs should intuitively be expected to decline over time given the improvement in child health intervention coverage and the decline in overall child mortality in the past several decades. However, recent studies do not consistently indicate a decline in age-specific measles case-fatality ratios compared to earlier data. For an epidemic disease that tends to target the most marginalized populations, it remains unclear whether access to and quality of care for complicated measles cases has improved significantly.

For the ten-year period that this study focused on, we assumed that age-specific CFRs in the base case analysis do not decline over time. Instead, we incorporate a trend documented in surveillance data that the distribution of measles cases shifts to older ages as vaccination coverage among children improves. Because the risk of dying from measles drops significantly beyond the age of 5, the coverage-dependent age-distribution and age-specific CFRs used in this model result in a net decline in death-to-case ratio over time. Over the period 2000-2010, the global crude death-to-case ratio decreased from 1.7% to 1.1%. Compared to broad assumptions on age distribution that were generalized from data in literature in previous estimates of global measles mortality(13), the more specific age distribution predicted from case-based surveillance data for this work produced lower mortality estimates (see "alternate age distribution" in Table 4).

Table 4: Summary of univariate sensitivity analyses of global measles mortality

Parameter variation (see appendix for full description)	Estimated measles deaths (1000s)		Measles mortality reduction between 2000 and 2010
	2000	2010	
Base case (confidence interval)	535 (347-976)	139 (71-448)	74%
CFR indexed to U5MR	550 (359-1045)	101 (55-358)	82%
Alternate age distribution	381 (266-957)	128 (70-442)	66%
Low vaccine effectiveness	681 (441-1182)	229 (131-576)	66%
High vaccine effectiveness	527 (345-957)	153 (81-442)	71%
Low outbreak threshold	575 (400-1044)	191 (128-498)	67%
High outbreak threshold	486 (312-887)	144 (75-397)	70%

Notes:
CFR indexed to U5MR in 2000: CFRs adjusted in proportion to the year-on-year change in under-five mortality rates, using 2000 as the year to anchor base CFRs(14).
Alternate age distribution: estimated cases distributed across age groups using the distributions reported by Stein and others (13) prior to applying CFRs
Low vaccine effectiveness: 72% when given at 9 months and 84.8% when given at 12+ months(15)
High vaccine effectiveness: 95%, when given at 9 months and 97% when given at 12+ months(15)
Low outbreak threshold: outbreaks identified as years when >=10% of all-cause mortality was attributed to measles during initial model runs.(14)
High outbreak threshold: outbreaks identified as years when >=30% of all-cause mortality was attributed to measles during initial model runs.(14)

In the absence of published data on the potential secular decline in the age-specific risk of dying from measles, we evaluated measles mortality using year-on-year change in under-five mortality rates (U5MR)

anchored in 2000, given that the CFR data set was developed to depict analytical work largely completed in 2003-2005. A temporal decline naturally increases the estimated mortality reduction between 2000 and 2010, but even with this additional decline, measles mortality reduction remains below target. To maintain a conservative bias regarding measles mortality reduction, we retained static age-specific CFRs as the base case.

Most variations in parameter assumptions resulted in lower mortality estimates than the base case, except for low vaccine effectiveness and low outbreak thresholds (see Table 4.) At the global level, low vaccine effectiveness led to 33% more measles deaths over 2000-2010 and a low outbreak threshold increased total mortality by 16% over 2000-2010.

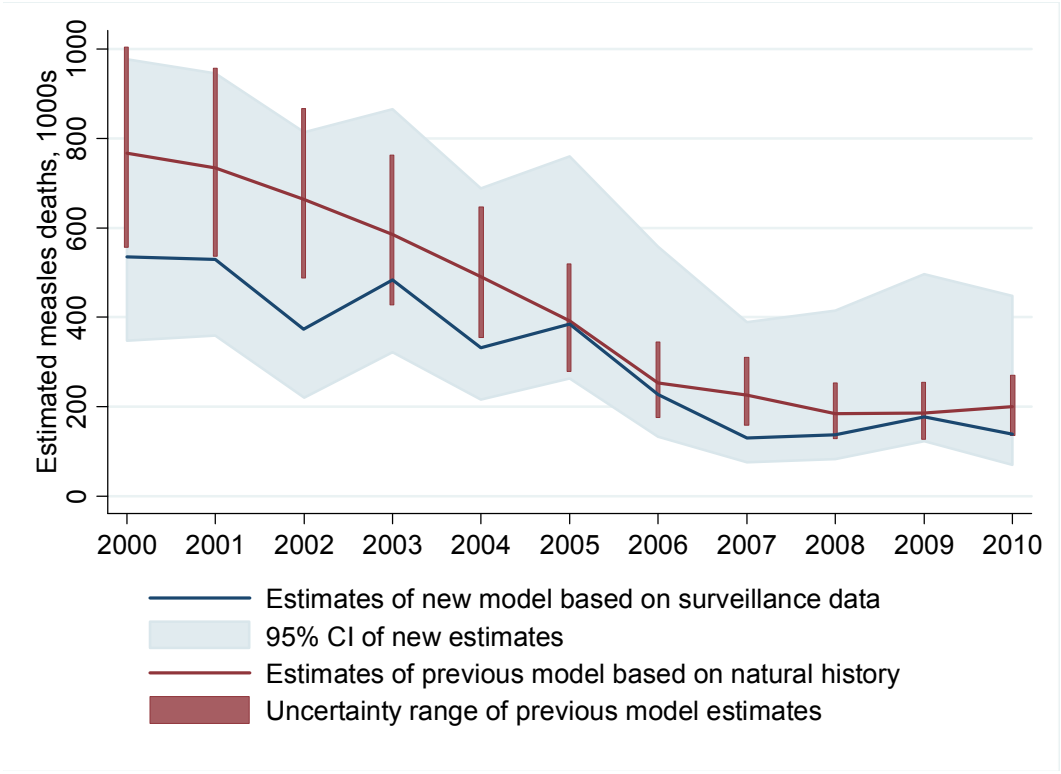
At the regional level, low vaccine effectiveness affected estimates for South East Asia most dramatically, resulting in 76% greater mortality in 2000 and doubling mortality in 2010. The sensitivity of estimates for South East Asia to underlying assumptions is driven by trends in India, where the greatest proportion of the global population susceptible to measles is concentrated. In the absence of reliable surveillance data, the estimates for India are driven by the natural history portion of the model and thus rely more heavily upon assumptions on vaccine effectiveness and CFRs than estimates for countries where reported case data reflects a large portion of true cases.

Countries that were excluded from the state-space framework account for <1% of measles mortality at the regional and global levels for 2000-2009, thus varying the reporting efficiency (5%-40%) yielded mortality estimates that varied by 0 to 1% from base case values at the regional and global levels. The threshold in child mortality rates used to identify countries to exclude from the model (<10, range <7 to <14.5, child deaths per 1000 live births), caused less than 0.1% variation in mortality estimates from the base case values.

Comparison with previous mortality estimates

The state-space model presents a number of advancements over past efforts(7) to estimate measles mortality, including: use of case-based surveillance data to estimate age distribution of cases, use of aggregated surveillance data to estimate incidence, incorporation of herd immunity, and robust statistical methods to estimate uncertainty. As shown in figure 2, the new estimates are significantly lower than previous estimates, though the previous estimates do lie within the margin of uncertainty of the new estimates. The decrease in mortality is largely due to: downward revision of estimated population and number of child deaths, reduction of CFRs for infants (the previous model assumed that infant CFRs were twice as high), and constraining measles mortality to <20% of total child mortality.

Figure 2: Measles mortality estimated using the previous measles burden model(7) and current model



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