

Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data



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Summary

Background In 2008 all WHO member states endorsed a target of 90% reduction in measles mortality by 2010 over 2000 levels. We developed a model to estimate progress made towards this goal.

Methods We constructed a state-space model with population and immunisation coverage estimates and reported surveillance data to estimate annual national measles cases, distributed across age classes. We estimated deaths by applying age-specific and country-specific case-fatality ratios to estimated cases in each age-country class.

Findings Estimated global measles mortality decreased 74% from 535 300 deaths (95% CI 347 200–976 400) in 2000 to 139 300 (71 200–447 800) in 2010. Measles mortality was reduced by more than three-quarters in all WHO regions except the WHO southeast Asia region. India accounted for 47% of estimated measles mortality in 2010, and the WHO African region accounted for 36%.

Interpretation Despite rapid progress in measles control from 2000 to 2007, delayed implementation of accelerated disease control in India and continued outbreaks in Africa stalled momentum towards the 2010 global measles mortality reduction goal. Intensified control measures and renewed political and financial commitment are needed to achieve mortality reduction targets and lay the foundation for future global eradication of measles.

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Introduction

In 2007, investigators reported that the global goal to reduce measles deaths by 50% by 2005, compared with 1999, had been achieved.¹ Building on this accomplishment, in 2008 the World Health Assembly endorsed a target of 90% reduction in measles mortality by 2010, compared with 2000. Endemic transmission of measles virus was interrupted in the Americas in 2002, and four of the remaining five WHO regions (all except southeast Asia) have set target dates for measles elimination by 2020 or earlier.² The establishment of a global measles eradication goal has been extensively discussed by the World Health Assembly and advisory committees to WHO and now hinges on progress towards regional elimination outside the Americas.³

Monitoring measles mortality is relevant for all partners involved in child survival. The fourth Millennium Development Goal (MDG4) aims to reduce deaths of children by two thirds by 2015 compared with 1990. The proportion of children vaccinated against measles was adopted as an indicator to measure progress towards MDG4; a rebound in measles deaths would pose a substantial threat to achieving this goal.^{4,5}

The rapid progress in measles control from 2000 to 2007 was based on implementation of recommended measles mortality reduction strategies, including increasing routine immunisation coverage, periodic supplemental immunisation activities (SIAs—ie, mass vaccination campaigns aimed at immunising 100% of a predefined population within several days or weeks), laboratory-supported surveillance, and appropriate

management of measles cases.⁶ Countries that have fully implemented and sustained these strategies have experienced reductions in measles cases of greater than 90%.⁷ However, not all countries have managed to do so, and several of the largest recorded outbreaks of the past decade were during 2009–10.⁸

Because most measles deaths are in countries where vital registration systems cannot provide reliable information on cause-specific mortality, WHO has relied on mathematical models to estimate the global burden of measles.^{1,9} Previous models have not objectively incorporated measles surveillance data and instead relied on vaccination coverage data as the primary indicator of local disease burden. Consequently, these models could neither consistently capture the effects of large outbreaks on measles mortality where high vaccination coverage was reported, nor show periods of low mortality between outbreaks when low vaccination coverage was reported. To assess progress towards the 2010 global measles mortality reduction goal, we developed a new model that, unlike previous models, uses surveillance data objectively to estimate both incidence and the age distribution of cases, accounts for herd immunity, and uses robust statistical methods to estimate uncertainty.

Methods

Estimating annual measles incidence

For 65 countries with adequate vital registration data ($\geq 85\%$ of estimated deaths of children younger than 5 years registered and coded), we used the reported number of measles deaths. These deaths accounted for

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less than 0.01% of global measles mortality, according to vital registration data and estimated mortality.¹⁰

For 128 remaining countries with inadequate vital registration data, we estimated country-specific measles deaths through a three-step process. We estimated annual measles incidence on the basis of reported measles cases for each country, then we distributed estimated incidence across age groups, and finally we calculated the number of deaths in each age class by applying age-specific and country-specific measles case-fatality ratios (CFRs).

Measles cases and vaccination coverage are reported annually to WHO by all member states through the WHO/UNICEF Joint Reporting Form.¹¹ WHO derived coverage estimates for the first routine dose of measles-containing vaccine (MCV1) from reported coverage data and survey results by use of computational logic.¹² We sent input data (full list in the appendix) to national immunisation programme managers to identify updates and corrections.

Measles cases reported through surveillance systems typically represent a fraction of the true number of cases because many children do not present for medical attention and, when medical care is sought, cases can be misdiagnosed or not reported to central authorities.¹³ However, national measles surveillance data can show underlying measles incidence trends over time.

State-space models provide a probabilistic framework to predict the unobserved elements of a dynamic process, such as true measles incidence, when provided with observed elements of the dynamic process, such as reported measles cases and vaccination coverage.^{14–17} Our state-space model is characterised by two inter-related sets of equations with unknown parameters: a process model that represents the evolution of true disease incidence through time as a function of infection risk and vaccination coverage and an observation model that represents the observation, or reporting, of cases through the national measles surveillance system.

The technical aspects of the state-space model are described elsewhere.¹⁵ In general, the process model describes the trend in measles cases in a country over time as a function of births, deaths, measles virus transmission, and vaccination. This is an annualised, linear approximation to a dynamic susceptible, infected, recovered (SIR) model of disease transmission.¹⁸ In a particular year, we added infants that are born and neither die from other causes of death nor are immunised through routine vaccination services to a pool of susceptibles. The pool of susceptibles was then depleted by SIAs and infection, which might result in death or recovery and immunity. We assumed the first vaccination was 84% effective if given before age 12 months and 93% effective at or beyond 12 months, the second vaccination was 99% effective irrespective of age at administration,¹⁹ and vaccine-induced immunity was lifelong.²⁰

We assumed the annualised rate of infection increases from zero in a completely immune population to 100% in a completely susceptible population, which is consistent

with the findings that greater than 90% of a completely susceptible population is likely to become infected if exposed to measles.¹⁸ Although we did not include a non-zero threshold of population susceptibility below which transmission ceases, the reduction of the annualised infection rate with increasing population immunity is compatible with herd immunity. In accordance with the equation below, population susceptibility reduces the annualised rate of infection:

$$\text{Percentage of susceptibles infected annually} = 1 - e^{-\theta_1 \left(\frac{S}{N}\right)}$$

θ_1 is the transmissibility estimated from the surveillance data separately for each country (estimation method described below), S is the number of susceptibles, and N is the total population. The median estimated value for θ_1 across all countries was 3.8 (IQR 1.3–8.0). With a θ_1 of 3.8, the percentage of susceptibles that would be infected at 10%, 50%, and 90% population susceptibility would be 26%, 77%, and 93%, respectively.

The observation model describes the relation between the expected number of measles cases estimated by the process model (with the infection rate above) and the number of reported measles cases. Measles cases are estimated to be under-reported at a baseline rate θ_2 that is independent for each country: reported cases in year $t = \theta_2 * \text{true incidence in year } t$.

Because measles surveillance sensitivity can increase when measles outbreaks happen,²¹ we assumed that years with large outbreaks had more complete reporting. We defined years with outbreaks as those with documented outbreaks, annual case reports that had a large effect on a linear regression of reported measles incidence against time ($d\beta > 0.37$), or when estimated measles mortality exceeded 20% of all child mortality with the baseline reporting rate (θ_3). We assumed that the years defined as outbreaks had an increased reporting rate of $\theta_2 + \theta_3$. We then fitted the model to all countries, with θ_2 and $\theta_2 + \theta_3$ estimated according to the applicable country-years of surveillance data.

We used a recursive algorithm called an extended Kalman filter,²² which has shown valid approximations of unobserved measles virus transmission dynamics,¹⁵ to estimate the parameters $\theta_1 - \theta_3$ ($\theta_1 - \theta_3$ described above, θ_4 and θ_3 are variance parameters described in the appendix), which resulted in a predicted number of cases with the highest likelihood in view of the observed surveillance data. The extended Kalman filter provides point estimates of the unobserved incidence in each year, I_t , and SEs of those estimates, SE_{I_t} .

During validation exercises we noted that model accuracy was low in two circumstances: consistently high population immunity to measles and low levels of all-cause child mortality. We consequently did not use the state-space model to estimate reporting rates for countries where measles was eliminated, where 95% or greater coverage with two routine doses of measles vaccine was

See Online for appendix

reported for 5 years or longer, or where child mortality fell in the lowest quartile of 2009 national child-mortality rates (27 countries). Instead, we estimated measles incidence by applying a 20% (with 5–40% upper and lower bounds) reporting rate to reported cases, based on published reporting rates in high-performing surveillance systems.¹³

Case characteristics

We extracted data from WHO's measles case-based reporting system for age at infection for 172 191 measles cases reported from 121 countries from 2000 to 2009. Age was expressed as a categorical variable (<1, 1–4, 5–9, 10–14, and ≥15 years) and predicted as a function of two explanatory variables with multinomial logistic regression. The explanatory variables were the 5 year moving average of estimated MCV1 coverage, in categories of less than 60%, 60–84%, and 85–100%; and geographical region based on a modification of the classification used by the Global Burden of Disease project.²³ To account for the clustering of cases within country-years we used the Taylor series method of variance estimation.²⁴

We took country-specific measles CFRs for children aged 1–4 years from a published review of community-based studies,²⁵ which identified 58 publications providing 102 different measles CFR estimates in 29 countries during the period 1974–2007. The investigators of the review noted that models of CFRs, attempted with several covariates, led to implausible results for many countries, because of low predictive value of the variables available for all member states. Consequently, expert opinion was used to develop a set of country-specific CFRs for children

aged 1–4 years.²⁵ We revised this set of CFRs to include new data from India and Nepal (appendix).^{26,27} Relative to the CFRs for children aged 1–4 years, we assumed that CFRs were equal for infants, half for children aged 5–9 years, and zero for children older than 10 years.

Estimated mortality

With a Monte Carlo algorithm, we derived 1000 values of the annual cases for each country from a normal distribution with mean I , and variance SE_I . Next, we derived 1000 age distributions from the multivariate normal distribution with mean equal to the point estimate and variance equal to the estimated variance-covariance matrix. The product of estimated cases, age distribution, and the age-specific CFRs resulted in 1000 values of measles deaths in each country-year. We took the 2.5th and 97.5th quantiles of this distribution as the lower and upper bounds of the estimated number of measles deaths.

To test the robustness of the results to variable assumptions, we assessed measles mortality under various alternative assumptions and compared the results with base-case estimates (ie, univariate sensitivity analysis). The variables we tested were vaccine effectiveness, temporal change in CFRs, threshold for defining outbreaks in reported case data, and age distribution of cases.

Role of the funding source

The sponsor of the study had no role in study design, data collection, or data interpretation. Two authors are employees of the sponsor institution and were involved in data analysis and reviewing the report, but were not

	2000					2010					Mortality reduction 2000–10	Number of doses given through SIAs, 2000–10 (millions)*
	Reported measles cases	MCV1 estimated coverage	Estimated measles deaths (95% upper and lower bounds)	Percentage of global measles deaths	Deaths averted	Reported measles cases	MCV1 estimated coverage	Estimated measles deaths (95% upper and lower bounds)	Global measles deaths per region	Deaths averted		
Africa	520 102	56%	337 000 (216 600–653 000)	63%	197 900	186 675	76%	50 000 (8900–258 100)	36%	569 300	85%	527
Americas	1755	92%	<100	0	3600	208	93%	<100	0	3500	..†	341
Eastern Mediterranean	38 592	73%	48 600 (29 400–82 300)	9%	86 300	10 072	85%	10 100 (3500–39 000)	7%	132 500	79%	273
Europe	37 421	91%	400 (200–2300)	0%	2700	30 625	95%	100 (0–1300)	0	2900	87%	52
Southeast Asia excluding India	39 723	76%	48 200 (25 700–84 900)	9%	59 900	20 457	79%	10 500 (4700–38 000)	8%	96 600	78%	169
India	38 835	55%	88 000 (70 700–107 800)	16%	224 600	29 808	74%	65 500 (53 600–78 800)	47%	208 800	26%	12
Western Pacific	177 052	85%	13 100 (4700–46 100)	2%	48 000	49 460	97%	3100 (500–32 500)	2%	53 300	76%	382
Worldwide total	853 480	72%	535 300 (347 200–976 400)	100%	623 100	327 305	85%	139 300 (71 200–447 800)	100%	1 066 900	74%	1756

SIAs=supplemental immunisation activities. *Not all SIAs are reported to WHO. †We estimated that measles mortality in the Americas was too low to allow reliable measurement of mortality reduction between 2000 and 2010.

Table: Reported measles cases, measles vaccination coverage, estimated measles deaths, and children reached by SIAs by WHO region

involved in the decision to fund this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The state-space model and adjusted surveillance data suggested that, from 2000 to 2010, annual estimated measles incidence aggregated across all countries fell 66% from 4.6 to 1.6 cases per 1000 total global population. During the same period, global MCV1 coverage increased from 72% to 85% and the reported number of measles cases declined 62% from 853 480 (140 per million total population) to 327 305 (48 per million total population; table).

In developing countries in the prevaccine era, roughly 70% of children were infected with measles virus by age 5 years.²⁸ Results from the multinomial regression model suggest that children younger than 5 years account for greater than 60% of cases in most countries with less than 60% MCV1 coverage (figure 1). However, at 85% or greater MCV1 coverage, cases were predicted to be predominantly in children older than 5 years and adults. The shift in age distribution was most noticeable for regions with the longest history of high coverage, such as eastern Europe, central Asia, and Asia Pacific, where the proportion of cases before age 5 years was predicted to be 38–51% at low MCV1 coverage and 13–20% at high MCV1 coverage (figure 1).

Global measles mortality was estimated to have decreased 74%, from 535 300 deaths (95% CI 347 200–976 400) in 2000 to 139 300 (71 200–447 800) in 2010 (figure 2). Compared with estimated mortality assuming the complete absence of measles vaccination, 9.6 million deaths were averted by measles vaccination during 2000–10.

We estimated that most measles deaths (79%) were in Africa and India during 2000–10. Measles mortality decreased by 85% in Africa, from 337 000 to 50 000, during 2000–10 (table). Large scale SIAs began in the southern African countries of Botswana, Lesotho, Malawi, Namibia, South Africa, Swaziland, and Zimbabwe during 1996–99 and in remaining countries of the WHO African region during 2000–06. Estimated mortality had already decreased by more than 90% before 2000 in southern African countries compared with mortality before the implementation of SIAs and then decreased by more than 90% during 2000–07 in remaining countries of the African region. The estimated reductions in mortality by 2007 were largely maintained, but mortality did not decrease further thereafter. As a whole, the African region accounted for 36% of global measles mortality in 2010, down from 63% in 2000. India's small decline in measles mortality (26%) led to an increase in the country's share of global measles mortality from 16% in 2000 to 47% in 2010. We estimated that measles mortality decreased by 78% during 2000–10 in the remaining ten countries in the WHO southeast Asia region.

The WHO eastern Mediterranean and western Pacific regions accounted for 9–11% of estimated global measles mortality during 2000–10, and we estimated that measles mortality fell 79% in the eastern Mediterranean and 76% in the western Pacific region. Although the WHO European region continues to have large outbreaks of

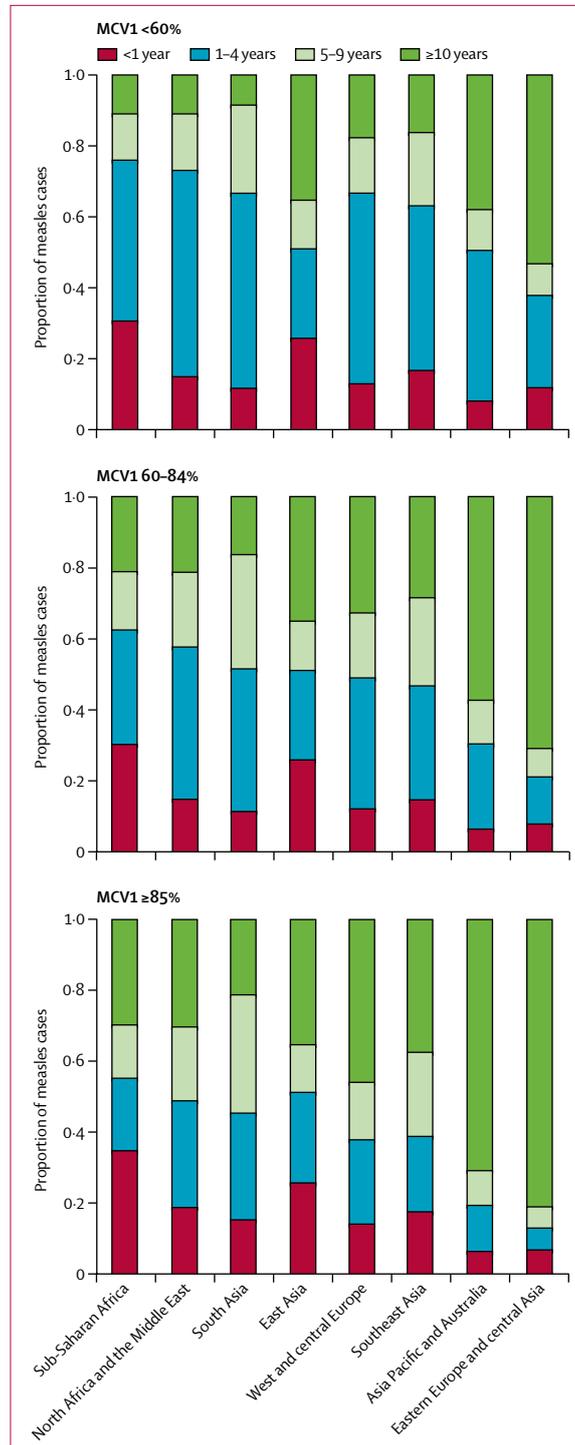


Figure 1: Predicted age distribution of measles cases by MCV1 coverage and region, 2000–09
 MCV1=first routine dose of measles-containing vaccine.

measles, because of very low CFRs, the region accounted for less than 1% of global measles mortality.

Of the alternative variable assumptions we tested by univariate sensitivity analysis, low vaccine effectiveness and low outbreak threshold resulted in higher mortality estimates compared with the base case, whereas indexing CFRs to under-five mortality rates, an alternative age distribution of cases, high vaccine effectiveness, and high outbreak threshold resulted in lower mortality estimates (figure 3). All the sensitivity analyses led to annual mortality estimates lying within the uncertainty bounds of the base-case scenario and none resulted in a 90% or greater reduction in measles mortality over 2000–10 (appendix).

Discussion

Our findings suggest that the goal of reducing measles mortality by 90% from 2000 to 2010 has not yet been met. Our conclusion was sustained under all alternative scenarios we assessed. Estimated global measles mortality declined substantially from 2000 to 2007, associated with increases in routine MCV1 coverage as well as the delivery of more than a billion doses of measles vaccine through SIAs. However, from 2008 to 2010, estimated global measles mortality did not diminish further and large outbreaks in southern Africa in 2009 and 2010 resulted in a small increase in estimated mortality for the WHO African region. Although SIAs substantially affected measles mortality, the highly infectious nature of measles virus requires maintenance of very high levels of population immunity through high routine coverage and timely implementation of SIAs to address immunity gaps.

Measles remains widespread in India because of delayed implementation of SIAs and restricted improvement in MCV1 coverage. We expect planned SIAs targeting 134 million children and the introduction of a routine second dose in some states of India during 2011–13 to substantially reduce measles mortality by 2015.²⁹ The decrease in estimated mortality (78%) during 2000–10 in the remaining ten countries in the WHO southeast Asia region is attributable to comprehensive improvements in immunisation: roughly 169 million children were vaccinated in SIAs, MCV1 coverage rose by 11 percentage points, and six of the ten countries introduced routine MCV2.

To our knowledge, our work presents the first use of a state-space framework to assess the global burden of a disease (panel). The key advantage of this approach for estimating measles mortality is the objective and comprehensive integration of surveillance data in the estimation process, which allows the results to show the episodic nature of measles outbreaks and periods of low virus transmission between outbreaks. A model that tracks fluctuations in measles incidence is better suited than basic natural history^{1,9} or proportionate mortality³⁰ approaches to monitor progress as measles mortality declines to low levels.

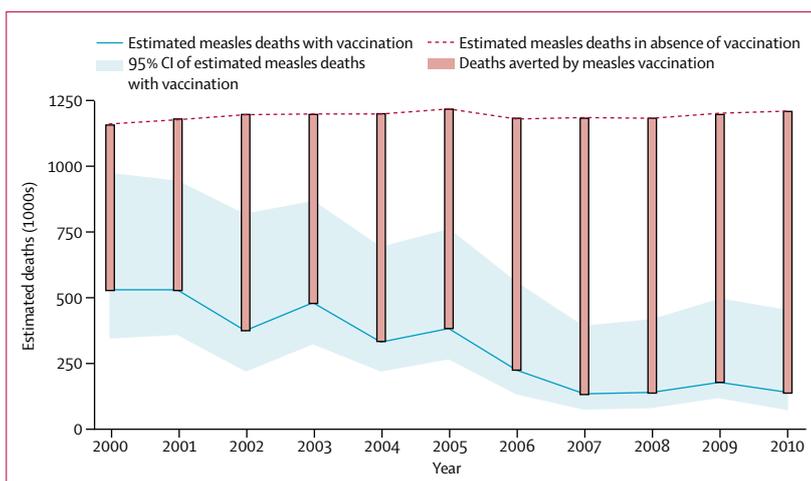


Figure 2: Global estimated measles mortality and measles deaths averted

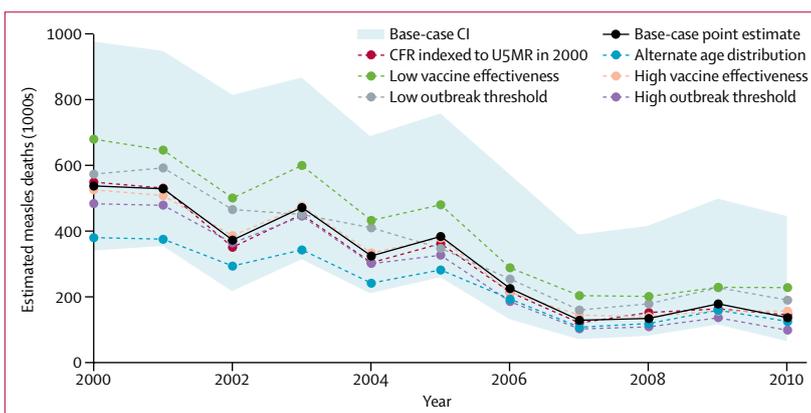


Figure 3: Global measles mortality re-estimated with alternative variable assumptions

The appendix provides details on assumptions. CFR=case-fatality ratio. U5MR=under-five mortality rate.

Panel: Research in context

Systematic review

We searched for country-level information on annual measles incidence through annual surveillance reports, monthly case-based measles reporting, and a process of country consultation with WHO member states. To develop age distributions, we analysed the largest available global dataset of line-listed reported measles cases.¹¹ We systematically searched for the new information on case-fatality rates published after the latest systematic review of case-fatality ratios^{25–27} and used the most comprehensive global set of vital registration data available,¹⁰ which we used in place of modelled estimates for countries that registered more than 85% of estimated deaths. We used sampling methods to combine variables and estimate uncertainty.

Interpretation

Compared with past efforts to model measles burden, we estimated fewer measles deaths, but similar rates of mortality reduction, since 2000 because of advancements in methods and updated input data. Unlike past efforts to model measles burden, our study accounts for herd immunity, uses robust statistical methods to estimate uncertainty, and uses case-based surveillance data to estimate age distribution of cases, and aggregate surveillance data to estimate incidence. As the first attempt to objectively incorporate surveillance data in modelling the global burden of measles, our study provides a basis for more in-depth research to understand the complexities and importance of disease surveillance data.

The estimates we present are lower than previous estimates of measles mortality,¹ although the previous estimates lie within the 95% CI of the new estimates (appendix). The decrease in mortality is largely due to downward revision of population and child-death estimates, reduction of CFRs for infants, and constraining measles mortality to less than 20% of total child mortality.

We did not incorporate several aspects of measles virus transmission dynamics in our state-space framework because of restricted data availability, restricted effects of these refinements on broad patterns in annual measles incidence, or both. These transmission dynamics include the effect of population age-structure on age-specific incidence, generation of infections in one time step from cases in the previous time step, likelihood of importations or interruption of transmission, and contact rates between subpopulations with differing levels of immunity. Within very populous countries, such as China and India, measles burden could be more accurately estimated with subnational data showing local, within-country variation in measles incidence.

Our work has highlighted a crucial lack of information on the measurement and interpretation of changes in surveillance system performance over time. We were unable to develop a simple and yet reliable quantitative indicator of how changes in surveillance practices (eg, introduction of case-based reporting or modification of case definitions), funding, and staffing affect surveillance sensitivity; we instead settled on the algorithm described earlier. The development of clear assessment criteria for surveillance sensitivity would aid routine interpretation of surveillance data for monitoring immunisation programme performance, which will only become more important as measles control efforts move towards global eradication.

Contributors

ES drafted the report, analysed and interpreted data, and contributed to study design. MF was involved in the model development, data analysis, and review of the report. JF was involved in the model development and programming. KW was involved in data analysis and review of the report. AA was involved in data analysis and review of the report. AB contributed to the model design. PS coordinated the project, analysed and interpreted results, and reviewed the report.

Conflicts of interest

We declare that we have no conflict of interest.

Acknowledgments

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References

- Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. *Lancet* 2007; **369**: 191–200.
- Strebel PM, Cochi SL, Hoekstra E, et al. A World Without Measles. *J Infect Dis* 2011; **204** (suppl 1): S1–3.
- WHO. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010—summary, conclusions and recommendations. *Wkly Epidemiol Rec* 2011; **86**: 1–16.
- UN. Road map towards the implementation of the United Nations Millennium Declaration: report of the Secretary-General. New York, NY: United Nations, 2001.
- van den Ent MM, Brown DW, Hoekstra EJ, Christie A, Cochi SL. Measles mortality reduction contributes substantially to reduction of all cause mortality among children less than five years of age, 1990–2008. *J Infect Dis* 2011; **204** (suppl 1): S18–23.
- WHO. Progress in global measles control and mortality reduction, 2000–2007. *Wkly Epidemiol Rec* 2008; **83**: 441–48.
- Otten M, Kezaala R, Fall A, et al. Public-health impact of accelerated measles control in the WHO African Region 2000–03. *Lancet* 2005; **366**: 832–39.
- WHO. Measles outbreaks and progress towards meeting measles pre-elimination goals: WHO African Region, 2009–2010. *Wkly Epidemiol Rec* 2011; **86**: 129–36.
- Stein CE, Birmingham M, Kurian M, Duclos P, Strebel P. The global burden of measles in the year 2000—a model that uses country-specific indicators. *J Infect Dis* 2003; **187** (suppl 1): S8–14.
- Department of Health Statistics and Informatics. WHO mortality data base. Geneva: World Health Organization, 2011.
- WHO. WHO vaccine-preventable diseases: monitoring system. Geneva: World Health Organization, 2010.
- Burton A, Gacic-Dobo M, Karimov R, Kowalski R. A computational logic-based representation of the WHO and UNICEF estimates of national immunization coverage. <http://www.doc.ic.ac.uk/~rak/papers/wuenic.pdf> (accessed April 14, 2012).
- Harpaz R. Completeness of measles case reporting: review of estimates for the United States. *J Infect Dis* 2004; **189** (suppl 1): S185–90.
- Breto C, He DH, Ionides EL, King AA. Time series analysis via mechanistic models. *Ann Appl Stat* 2009; **3**: 319–48.
- Chen S, Fricks J, Ferrari MJ. Tracking measles infection through non-linear state space models. *J R Stat Soc Ser C Appl Stat* 2011; **61**: 117–34.
- Ionides EL, Bretó C, King AA. Inference for nonlinear dynamical systems. *Proc Natl Acad Sci USA* 2006; **103**: 18438–43.
- Shumway RH, Stoffer DS. Time series analysis and its applications. New York, NY: Springer, 2000.
- Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press, 1991.
- Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. *J Infect Dis* 2011; **204** (suppl 1): S133–48.
- Moss WJ, Scott S. The immunological basis for immunization series—module 7: measles update 2009. Geneva: World Health Organization, 2009.
- Mette A, Reuss AM, Feig M, et al. Under-reporting of measles an evaluation based on data from North Rhine-Westphalia. *Dtsch Arztebl Int* 2011; **108**: 191–96.
- Elliott R, Aggoun L, Moore J. Hidden Markov models: estimation and control. Berlin: Springer, 1995.
- Harvard University. Global burden of disease study operations manual. http://www.globalburden.org/GBD_Study_Operations_Manual_Jan_20_2009.pdf (accessed Sept 1, 2010).
- Binder DA. On the variances of asymptotically normal estimators from complex surveys. *Int Stat Rev* 1983; **51**: 279–92.
- Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009; **38**: 192–205.
- Joshi AB, Luman ET, Nandy R, Subedi BK, Liyanage JBL, Wierzbza TF. Measles deaths in Nepal: estimating the national case-fatality ratio. *Bull World Health Organ* 2009; **87**: 456–65.
- Sudfeld CR, Halsey NA. Measles case fatality ratio in India: a review of community based studies. *Indian Pediatr* 2009; **46**: 983–89.
- Black FL. Measles antibody prevalence in diverse populations. *Am J Dis Child* 1962; **103**: 242–49.
- WHO. Progress in implementing measles mortality reduction strategies, India 2010–2011. *Wkly Epidemiol Rec* 2011; **86**: 439–44.
- Morris SS, Black RE, Tomaskovic L. Predicting the distribution of under-five deaths by cause in countries without adequate vital registration systems. *Int J Epidemiol* 2003; **32**: 1041–51.

Measles: the burden of preventable deaths



Measles has been, and remains, a major killer of children around the world. Despite the introduction of the measles vaccine in 1963, measles caused an estimated 2.6 million deaths in a single year as recently as 1980.¹ In *The Lancet*, Emily Simons and colleagues² estimate that, after more than 45 years of measles vaccine availability, the disease caused nearly 140 000 deaths in 2010.

Even in industrialised countries, complications, including pneumonia, diarrhoea, encephalitis, and sub-acute sclerosing panencephalitis, lead to substantial morbidity and mortality.^{3,4} However, it is in developing countries where measles exacts its greatest health burden. A review of community-based measles studies⁵ showed a median case-fatality ratio of 3.91% (mean 7.40%, range 0–40.15%).

Through global measles prevention efforts, great progress has been made in measles control. Elimination of indigenous transmission of disease has been achieved in the WHO Americas region.¹ Five of the six WHO regions have set goals to eliminate measles by 2020. At present, there is a worldwide goal of a 95% reduction in measles mortality by 2015 compared with 2000 estimates. Measles eradication is biologically feasible and, although no formal eradication goal has yet been set, progress toward the mortality reduction goal will lead to consideration of an eradication goal.^{1,6}

Measles is one of the most contagious vaccine-preventable diseases,⁷ and is one of the best indicators for problems in vaccination programmes because of its high communicability and recognisable rash. Outbreaks of measles with complications and deaths can be a greater motivating force for change than immunisation coverage data gaps and the theoretical potential for outbreaks.⁸ This was the case in the USA, where a resurgence of measles in 1989–91 led to major investments in, and strengthening of, the overall National Immunization Program.

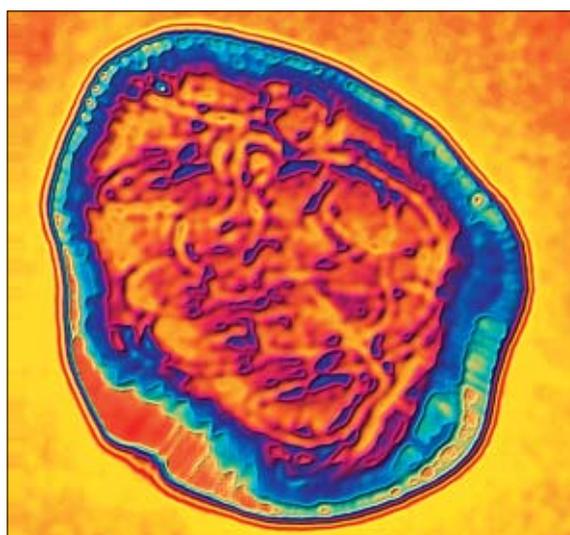
If immunisation programmes fail to immunise new susceptibles added to the population daily through births and migration, enough susceptibles will accumulate to fuel another measles outbreak. For example, since 2008, after substantial reductions in measles mortality, measles has resurged in Africa.⁹ It is crucial to maintain high immunity levels and immunise all children at recommended ages.

How can we best monitor the progress of global immunisation programmes to guide corrective actions if needed? Measuring measles vaccine coverage provides some information but does not directly translate into effects on health burden. Global disease surveillance systems are at present unable to capture measles case numbers accurately enough to monitor deaths directly. Instead, progress has been assessed through changes in estimated annual measles-attributed deaths. As noted by Simons and colleagues,² 65 countries have adequate vital registration data, which allow the measurement of actual deaths. However, for the remaining 128 countries where most deaths from measles occur, vital registration data are inadequate and necessitate the estimation of those deaths.

The accuracy of estimates depends on the assumptions and data used in modelling exercises. Traditionally, it was assumed that all susceptible people acquired measles, so the number of cases depended on vaccine coverage and effectiveness. Once cases were estimated, age distributions were inferred on the basis of coverage, and age-specific case-fatality ratios for a particular region were estimated and applied to the number of cases to estimate the number of deaths.¹⁰ Although this approach has been useful for monitoring the progress of measles mortality reduction efforts, there is a potential bias toward overestimating deaths since it does not account for herd immunity, which

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Measles virus

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is likely to decrease incidence of measles and deaths indirectly. Simons and colleagues² attempt to take this into account by incorporating a decrease in the rate of infection among susceptibles as population immunity rises, and by using actual surveillance data to modify the estimates of cases and mortality (along with other adjustments).² In so doing, they estimated that that there were 535 300 deaths from measles in 2000, 27% lower than the previous estimate of 733 000.¹¹ Although substantially lower, this estimate still highlights that far too many children are dying from this readily preventable disease. And, in 2010, they estimate 139 300 deaths (382 deaths per day) despite substantial improvements in immunisation coverage.

Most importantly, perhaps, Simons and colleagues' report highlights crucial gaps in available data to guide prevention programmes—surveillance and vital record registrations are inadequate in much of the world. What is most needed is not more advanced ways to estimate mortality, but the direct measurement of mortality. As measles is considered for eradication, it will be crucial to improve surveillance to the point that deaths and cases will actually be measured, not estimated.

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- 1 Strebel PM, Cochi SL, Hoekstra E, et al. A world without measles. *J Infect Dis* 2011; **204** (suppl 1): S1–3.
- 2 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.
- 3 Strebel PM, Papania MJ, Dayan GH, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*, 5th edn. Philadelphia: Saunders Elsevier, 2008: 353–98.
- 4 Orenstein WA, Papania MJ, Wharton ME. Measles elimination in the United States. *J Infect Dis* 2004; **189** (suppl 1): S1–3.
- 5 Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. *Lancet* 2007; **369**: 191–200.
- 6 Bellini WJ, Rota PA. Biological feasibility of measles eradication. *Virus Res* 2011; **162**: 72–79.
- 7 Fine PEM, Mulholland K. Community Immunity. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*, 5th edn. Philadelphia: Saunders Elsevier, 2008: 1573–92.
- 8 Orenstein WA. The role of measles elimination in development of a national immunization program. *Pediatr Infect Dis J* 2006; **25**: 1093–101.
- 9 Moss WJ, Griffin DE. Measles. *Lancet* 2011; **379**: 153–64.
- 10 Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009; **38**: 192–205.
- 11 Centers for Disease Control and Prevention. Global measles mortality, 2000–2008. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 1321–26.